NRG ONCOLOGY
RTOG 1203

A RANDOMIZED PHASE III STUDY OF STANDARD VS. IMRT PELVIC RADIATION FOR POST-OPERATIVE TREATMENT OF ENDOMETRIAL AND CERVICAL CANCER (TIME-C)

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology, ECOG-ACRIN Medical Research Foundation Inc., and SWOG.

Study Team (3/16/15)

Principal Investigator/Radiation Oncology
Ann Klopp M.D, PhD
UT MD Anderson Cancer Center
Department of Radiation Oncology
1515 Holcombe Blvd. Suite 1202
Houston, Texas 77030
Phone: 713-563-2444/Fax:713-563-6940
E-mail Address: aklopp@mdanderson.org

Anamaria Yeung, MD
University of Florida
Department of Radiation Oncology
2000 SW Archer Rd, Gainesville, FL 32610
Phone:352-265-0287/Fax:352-265-0759
E-mail Address: areyna@ufl.edu

Quality of Life Co-Chairs
Karen Gil, PhD
Summa Health System
525 East Market Street
Akron, OH 44304
Phone: 330-375-3083/Fax:330-375-3012
E-mail Address: gilk@summahealth.org

Lari Wenzel, PhD
University of California, Irvine
100 Theory, Suite 110
Mail Code: 5800
Irvine, CA 92697
Phone: 949-824-3926/Fax:949-824-3388
Email Address: lwenzel@uci.edu

Gynecological Oncologist Co-Chair
Shannon N. Westin, MD, MPH
UT MD Anderson Cancer Center
Department of Gynecologic Oncology and Reproductive Medicine
1155 Hermann Pressler Blvd, Unit 1362
Houston, Texas 77030
Phone: 713-794-4314/Fax: 713-792-7586
E-mail Address: swestin@mdanderson.org

Cost Analysis Co-Chair
Andre Konkski, MD, MBA, MA, FACR
University of Pennsylvania
Department of Radiation Oncology
The Chester County Hospital
701 E Marshall St
West Chester, PA 19380
Phone: 610 431 5530/Fax: 610 431 5144
E-mail Address: andre.konkski@uphs.upenn.edu

Translational Research Co-Chair
Joanne Weidhaas, MD, PhD
University of California at Los Angeles
10833 Le Conte Ave., B3-109 CHS
Los Angeles, CA 90085
Phone: 203-671-1308/Fax: 310-206-1260
Email Address: jweidhaas@mednet.ucla.net

Medical Physics Co-Chair
Kent Gifford, PhD
UT MD Anderson Cancer Center
Department of Radiation Oncology
1515 Holcombe Blvd. Suite 1202
Houston, Texas 77030
Phone: 713-563-2596/Fax:713-563-6940
E-mail Address: kagifford@mdanderson.org

Senior Statistician
Stephanie Pugh, PhD
Department of Statistics
NRG Oncology
1818 Market Street, Suite 1720
Philadelphia, PA 19103
Phone: 215-717-0850/Fax:215-928-0153
E-mail Address: pugh@nrgoncology.org
NRG ONCOLOGY

RTOG 1203

A RANDOMIZED PHASE III STUDY OF STANDARD VS. IMRT PELVIC RADIATION FOR POST-OPERATIVE TREATMENT OF ENDOMETRIAL AND CERVICAL CANCER (TIME-C)

Title Page (Continued)

Protocol Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Supply</th>
<th>NSC #</th>
<th>IND #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>Commercial</td>
<td>N/A</td>
<td>Exempt</td>
</tr>
</tbody>
</table>

Participating Sites

☐ US Only
☐ Canada Only
☒ US and Canada
☒ Approved International Member Sites

Document History

<table>
<thead>
<tr>
<th>Amendment</th>
<th>Version/Update Date</th>
<th>Broadcast Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amendment 4</td>
<td>March 16, 2015</td>
<td>March 30, 2015</td>
</tr>
<tr>
<td>Amendment 3</td>
<td>August 4, 2014</td>
<td>August 11, 2014</td>
</tr>
<tr>
<td>Update</td>
<td>April 29, 2014</td>
<td>April 29, 2014</td>
</tr>
<tr>
<td>Amendment 2</td>
<td>September 16, 2013</td>
<td>October 2, 2013</td>
</tr>
<tr>
<td>Amendment 1</td>
<td>August 7, 2013</td>
<td>October 2, 2013</td>
</tr>
<tr>
<td>Activation</td>
<td>November 28, 2012</td>
<td>November 28, 2012</td>
</tr>
<tr>
<td>Update</td>
<td>October 4, 2012</td>
<td>October 4, 2012</td>
</tr>
<tr>
<td>Group Activation</td>
<td>September 6, 2012</td>
<td>October 4, 2012</td>
</tr>
</tbody>
</table>

NRG Oncology
1-800-227-5463, ext. 4189

This protocol was designed and developed by NRG Oncology. It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by NRG Oncology nor does NRG Oncology assume any responsibility for unauthorized use of this protocol.
NRG ONCOLOGY
RTOG 1203

A RANDOMIZED PHASE III STUDY OF STANDARD VS. IMRT PELVIC RADIATION FOR POST-OPERATIVE TREATMENT OF ENDOMETRIAL AND CERVICAL CANCER (TIME-C)

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION (3/16/15)

<table>
<thead>
<tr>
<th>To submit site registration documents:</th>
<th>For patient enrollments:</th>
<th>Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTSU Regulatory Office</td>
<td></td>
<td>NRG Oncology</td>
</tr>
<tr>
<td>1818 Market Street, Suite 1100</td>
<td>Please refer to Section</td>
<td>1818 Market Street, Suite 1720</td>
</tr>
<tr>
<td>Philadelphia, PA 19103</td>
<td>5.0 of the protocol for</td>
<td>Philadelphia, PA 19103</td>
</tr>
<tr>
<td>Phone – 1-866-651-CTSU</td>
<td>instructions on using the</td>
<td>Do not submit study data or forms to CTSU Data</td>
</tr>
<tr>
<td>Fax – 215-569-0206</td>
<td>OPEN system which can</td>
<td>Operations. Do not copy the CTSU on data</td>
</tr>
<tr>
<td>Email: <a href="mailto:CTSURegulatory@ctsu.coccg.org">CTSURegulatory@ctsu.coccg.org</a></td>
<td>be accessed at</td>
<td>submissions.</td>
</tr>
<tr>
<td>(for submitting regulatory</td>
<td><a href="https://www.ctsu.org/OPE">https://www.ctsu.org/OPE</a></td>
<td></td>
</tr>
<tr>
<td>documents only)</td>
<td>NTERN_SYSTEM/ or</td>
<td></td>
</tr>
<tr>
<td></td>
<td><a href="https://OPEN.ctsu.org">https://OPEN.ctsu.org</a></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Contact the CTSU Help</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Desk with any OPEN-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>related questions at</td>
<td></td>
</tr>
<tr>
<td></td>
<td><a href="mailto:ctsucontact@westat.com">ctsucontact@westat.com</a></td>
<td></td>
</tr>
</tbody>
</table>

The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific web page of the CTSU Member Web site located at [https://www.ctsu.org](https://www.ctsu.org). Access to the CTSU members’ web site is managed through the Cancer Therapy and Evaluation Program – Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.

For clinical questions (i.e. related to patient eligibility or treatment-related): Contact the Study PI of the Lead Protocol Organization.

For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members’ website [https://www.ctsu.org> education and resources tab > CTSU Operations Information >CTSU Regulatory and Monitoring Policy](https://www.ctsu.org> education and resources tab > CTSU Operations Information >CTSU Regulatory and Monitoring Policy).

The CTSU web site is located at [https://www.ctsu.org](https://www.ctsu.org)
INDEX

Schema
Eligibility Checklist

1.0 Introduction
2.0 Objectives
3.0 Patient Selection
4.0 Pretreatment Evaluations/Management
5.0 Registration Procedures
6.0 Radiation Therapy
7.0 Drug Therapy
8.0 Surgery
9.0 Other Therapy
10.0 Tissue/Specimen Submission
11.0 Patient Assessments
12.0 Data Collection
13.0 Statistical Considerations

References

Appendix I - Sample Consent Form
Appendix II - Study Parameters
Appendix III - Performance Status Scoring
Appendix IV - Staging System
Appendix V - Biospecimen Collection Instructions
Appendix VI - Definition of Bladder and Rectal Points
**NRG ONCOLOGY**

**RTOG 1203**

A RANDOMIZED PHASE III STUDY OF STANDARD VS. IMRT PELVIC RADIATION FOR POST-OPERATIVE TREATMENT OF ENDOMETRIAL AND CERVICAL CANCER (TIME-C)

**SCHEMA**

<table>
<thead>
<tr>
<th>STRATIFY</th>
<th>XRT Dose</th>
<th>RANDOMIZE</th>
<th>Arm 1</th>
<th>Arm 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. 45 Gy</td>
<td></td>
<td>IMRT pelvic radiation treatment</td>
<td>4-field pelvic radiation treatment</td>
</tr>
<tr>
<td></td>
<td>2. 50.4 Gy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>1. No Chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. 5 cycles of weekly cisplatin at 40mg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease Site</td>
<td>1. Endometrial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Cervix</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

See Section 5.0 for pre-registration requirements, Section 6.0 for details of radiation therapy, and Section 7.0 for details of drug therapy.

**Patient Population:** (See Section 3.0 for Eligibility)
Pathologically proven diagnosis of endometrial and cervical cancer who require post-operative radiation or chemoradiation; Zubrod performance status of 0–2.

**Required Sample Size:** 281 patients
1. Is there a pathologically proven diagnosis of endometrial or cervical cancer?  

2. Has the patient undergone a hysterectomy (total abdominal hysterectomy, vaginal hysterectomy, total laparoscopic hysterectomy or radical hysterectomy) for carcinoma of the cervix or endometrium within 49 days prior to registration?  

3. Has appropriate staging for protocol entry been performed, based upon the following minimum diagnostic workup?
   - History/physical examination within 45 days prior to registration
   - CT/MRI/PET-CT of abdomen/pelvis demonstrating the absence of distant metastasis, performed pre- or post-surgery within 90 days prior to registration
   - Chest x-ray or chest CT (or a PET-CT) performed within 90 days prior to registration

4. Zubrod Performance Status 0-2

5. Is the patient ≥ 18 years of age?

6. Has a CBC/differential been obtained within 14 days prior to registration on study, with adequate bone marrow function defined as follows?
   - Absolute neutrophil count (ANC) ≥ 1,500 cells/mm³;
   - Platelets ≥ 100,000 cells/mm³;
   - Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.)

   For patients receiving chemotherapy:

7. Has the following laboratory been done within 14 days prior to registration?
   - Serum Creatinine ≤ 1.5 mg/dl and calculated creatinine clearance ≥ 50 cc/min. Both tests must be within these limits. The creatinine clearance should be calculated using the Cockroft-Gault formula: (See Section 7.3.1)
   - AST ≤ 2 x ULN
   - Bilirubin ≤ 2 x ULN
   - Alkaline phosphatase, Mg, BUN and electrolytes must be obtained and recorded

8. Does the patient meet criteria for one of the following four questions? Please check one of the following below.

   For patients with endometrial cancer to be treated without weekly cisplatin:
   - Does the patient have the following pathology findings?
     - <50% myometrial invasion, grade 3 adenocarcinoma without uterine serous carcinoma (USC) or clear cell histology
     - ≥50% myometrial invasion grade 1-2 adenocarcinoma without USC or clear cell histology
For patients with endometrial cancer to be treated with or without weekly cisplatin at the treating physician’s discretion:

☐ Does the patient have one of the following pathology findings?
   - ≥ 50% myometrial invasion, grade 3 including USC and clear cell carcinoma.
   - FIGO 2009 stage II endometrial cancer of any grade including USC and clear cell carcinoma.
   - FIGO 2009 IIIC1 (pelvic lymph node positive only, para-aortic nodes negative if removed) including USC and clear cell carcinoma. **Note:** if para-aortic nodes are not removed, CT abdomen or PET-CT must demonstrate no evidence of lymphadenopathy.

For patients with cervical cancer to be treated with or without weekly cisplatin at the treating physician’s discretion:

☐ Does the patient have two of the following risk factors after radical hysterectomy?
   - 1/3 or more stromal invasion
   - Lymph-vascular space invasion
   - Large clinical tumor diameter (> 4 cm)
   - or
   - Has the patient with cervical cancer been treated with a simple hysterectomy with negative margins and negative nodes by CT/MRI/PET-CT?

For patients with cervical cancer to be treated with weekly cisplatin:

☐ Does the patient have any of the following criteria following radical hysterectomy?
   - Positive resected pelvic nodes and para-aortic nodes negative if removed. **Note:** if para-aortic nodes are not removed, CT abdomen or PET-CT must demonstrate no evidence of lymphadenopathy.
   - Microscopic parametrial invasion with negative margins

  9. Has the patient signed the study specific informed consent prior to study entry?
  10. Is the patient willing and able to complete the bowel and urinary domains of the EPIC prior to registration (see Section 3.1.1)?
  11. Does the patient have para-aortic nodal disease or require extended field radiotherapy beyond the pelvis?
  12. Does the patient have a histology consisting of endometrial stromal sarcoma, leiomyosarcoma or malignant mullerian mixed tumor?
  13. Does the patient’s weight/size limits exceed the treatment table or CT scanner?
  14. Does the patient have mental status changes or bladder control problems that make the patient unable to comply with bladder-filling instructions?
  15. Does the patient have positive or close (< 3 mm) resected margins?
  16. Does the patient have a prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years?
  17. Has the patient previously received prior radiation therapy to the pelvis?
  18. Has the patient previously received treatment with platinum-based chemotherapy?
19. Does the patient have active inflammatory bowel disease?

20. Has the patient had unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months?

21. Has the patient had transmural myocardial infarction within the last 6 months?

22. Does the patient have acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration?

23. Does the patient have any other major medical illness which requires hospitalization or precludes study therapy at the time of registration?

24. Does the patient have hepatic insufficiency resulting in clinical jaundice and/or coagulation defects? **NOTE:** coagulation testing is not required prior to protocol entry.

25. Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immunocompromised patients.

26. Is the patient breast feeding?
The following questions will be asked at Study Registration:
IMRT CREDENTIALING AND BRACHYTHERAPY CREDENTIALING IS REQUIRED BEFORE REGISTRATION IF THESE MODALITIES WILL BE USED

1. Institutional person randomizing case.
2. Has the Eligibility Checklist been completed?
3. In the opinion of the investigator, is the patient eligible?
4. Date informed consent signed
5. Patient’s Initials (First Middle Last)
6. Verifying Physician
7. Patient ID
8. Date of Birth
9. Race
10. Ethnicity
11. Gender
12. Country of Residence
13. Zip Code (U.S. Residents)
14. Method of Payment
15. Any care at a VA or Military Hospital?
16. Calendar Base Date
17. Randomization date
18. Medical oncologist’s name
19. Have you obtained the patient's consent for her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?
20. Have you obtained the patient's consent for her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?
21. Have you obtained the patient's consent for her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?
22. Have you obtained the patient's consent for her blood to be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
________(Y/N) 23. Have you obtained the patient’s consent for her blood to be kept for use in research about the correlation between genes and substances found in the blood and radiation side effects?

________(Y/N) 24. Have you obtained the patient’s consent to allow someone from this institution to contact her in the future to take part in more research?

________(Y/N) 25. Did the patient agree to participate in the quality of life component?

__________________________ If no, provide reason:
1. Patient refused due to illness
2. Patient refused for other reason: specify __________________________
3. Not approved by institutional IRB
4. Tool not available in patient’s language
5. Other reason: specify __________________________

__________26. Radiation Dose:
1. 45Gy
2. 50.4Gy

__________27. Use of Chemotherapy?
1. No Chemotherapy
2. 5 cycles of weekly cisplatin at 40mg/m²

__________28. Disease Site:
1. Endometrium
2. Cervix

__________29. Is patient receiving brachytherapy?
1. No
2. Yes

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/NRG Oncology audit.

Completed by ___________________________ Date ___________________________
1.0 INTRODUCTION (8/4/14)

Intensity-modulated radiation therapy (IMRT) is a method of radiotherapy delivery that allows for conforming of the dose distribution to the shape of the target so that dose to adjacent normal tissues is reduced. Despite a wealth of data on the significant dosimetric advantages of IMRT, there have been very few attempts to evaluate the impact of IMRT on clinically meaningful radiation toxicity. In this phase III study, women requiring post-operative pelvic radiation will be randomized to receive pelvic radiation with either standard four-field radiation treatment or IMRT. The goal of the study is to evaluate the clinically significant benefits of IMRT using a patient reported measure of toxicity. In addition, we will compare rates of other toxicities, such as urinary and hematologic toxicity as well as disease control to provide a rigorous assessment of the impact of pelvic IMRT.

IMRT holds particular potential in the delivery of post-operative pelvic radiation due to the complex shape of the target and the significant toxicity as a consequence of radiation of the bowel and bone marrow. Post-operative radiation of the pelvis targets the pelvic lymphatics and vagina which form a “U” shape structure. Treating this volume with three-dimensional treatment requires treating small bowel which is found in the center of the pelvis, and the bone marrow which surround the nodal CTV while these tissues can be spared with IMRT (Figure 1-1).

![Figure 1-1. Standard three-dimensional conformal irradiation (left panel) requires treatment of small bowel (contoured in brown) which can be spared with IMRT (right panel).](image)

The primary endpoint of this study will be to evaluate acute gastrointestinal toxicity with a patient reported measure of toxicity, the Expanded Prostate Cancer Index Composite (EPIC) instrument. The bowel module of EPIC comprehensively evaluates the extent of gastrointestinal (GI) toxicity by evaluating multiple components of radiation enteritis including cramping, looseness, pain, and frequency of bowel movements. Furthermore, this instrument evaluates the extent to which each of these individual symptoms is bothersome to the individual. We anticipate that a patient with significant acute GI toxicity from radiation will experience each of these symptoms which are expected to have major disruptive effects on their ability to function in their daily lives. We anticipate that patients without significant toxicity will rarely report any of these symptoms, and if they do occur, they will have minimal impact on their daily functioning. As a result, this instrument is ideal for accurately determining the clinically meaningful impact of reduced bowel irradiation on acute GI toxicity.

An abundance of retrospective and single institution studies demonstrate less acute GI toxicity with IMRT compared with conventional WPRT, yet there has been no direct comparison of these two treatment approaches to evaluate the benefit of pelvic IMRT. This question has broad relevance to the management of gynecologic cancer and to the field of radiation oncology. The purpose of this randomized phase III study is to investigate the effect of normal tissue sparing with IMRT on acute and chronic toxicity. Patients who require concurrent weekly cisplatin as well as those requiring treatment with radiation therapy alone will be included. In addition to the patient reported assessment of GI toxicity, we will determine if IMRT impacts acute bladder toxicity, hematologic toxicity, and quality of life as well as long term bowel and bladder toxicity.

An assessment of pelvic radiation on quality of life has been investigated in PORTEC-2, in which vaginal cuff irradiation was demonstrated to translate to a clinically significant reduction in toxicity using a patient reported outcome. PORTEC-2 compared standard pelvic radiation to treatment of just the vaginal cuff. Patients in the vaginal cuff group reported better social functioning (P < .002) and lower symptom scores for diarrhea and fecal leakage which resulted in the need to stay close to the toilet, and limited daily
activities (P < .001). The goal of this study will be to determine if sparing bowel with IMRT similarly reduces toxicity for women who require pelvic RT (Nout 2009).

1.1 Conventional Post-Operative Pelvic Radiation

The benefit of pelvic radiation has been demonstrated in multiple phase 3 trials showing that post-operative whole pelvic radiation therapy (WPRT) after hysterectomy for early stage cervical cancer or endometrial cancer reduces the risk of pelvic recurrence in patients with high risk pathologic features (Sedlis 1999, Scholten 2005, Aalders 1980, Keys 2004, Nout 2010). As a result, post-operative WPRT has become the standard of care for patients meeting specific criteria. For women with high risk cervical cancer and some women with high risk endometrial cancer, concurrent chemotherapy is recommended. (Peters 2000).

The toxicity of conventional WPRT in this setting is a result of the large volume of normal tissues which is irradiated, especially small bowel, rectum, bladder and bone marrow. Conventional techniques using two or four photon fields result in the majority of the true pelvis receiving the prescription dose (usually 45-50 Gy in 25-28 fractions). After a hysterectomy, small bowel falls into the pelvis where the uterus previously resided, further increasing the amount of small bowel irradiated to prescription dose. The result is a clinically significant risk of acute and late small bowel toxicity. Rates of grade 2 and higher acute GI toxicity of 50-90% with conventional WPRT have been reported in the literature (Greven 2004, Mundt 2002, Chen 2007). Acute GI symptoms typically involve varying degrees of diarrhea, cramping and abdominal pain, which can negatively impact quality of life during treatment. Grade 2 and higher late GI toxicity occurs in about 15 - 25% of patients (Chen 2007, Mundt 2003) who receive WPRT.

Figure 1-2. Self-reported rates of diarrhea during pelvic radiation. Women treated at MD Anderson Cancer Center with conventional pelvic radiation for 5 weeks with weekly cisplatin completed weekly questionnaires. Diarrhea was scored 1-10 (unpublished data).

Radiation toxicity is cumulative, with the most significant toxicity in the last week of radiation treatment and immediately after completion of treatment. This is supported by reports demonstrating that when radiation is used to treat prostate cancer, GI toxicity peaks in the last week of radiation for both conventional RT and IMRT, using CTCAE measures of toxicity (Arcangeli 2007, Sanguineti 2008). At MD Anderson Cancer Center, women with intact cervical cancer were evaluated with a patient reported measure of gastrointestinal toxicity during radiation (Figure 1-2, unpublished data). Rates of patient reported diarrhea peaked at 5 weeks of radiation, consistent with physician reports of GI toxicity, demonstrating that toxicity is also perceived by patients to be most severe at the end of treatment. As a result, we anticipate that the maximum difference in toxicity between conventional and IMRT treatment will be in the final week (week 5 after 23-25 fractions) of radiation and this will be used as the primary endpoint of the study.

1.2 IMRT For Post-Operative Pelvic Radiation (8/7/2013)

Dosimetric studies have shown a significant reduction in the dose to small bowel with IMRT when compared to conventional WPRT. Heron et al (2003) compared a 7-field IMRT plan with 4-field
box technique on 10 consecutive patients referred for post-operative radiotherapy and showed a 52% reduction in the volume of small bowel receiving more than 30 Gy with the IMRT. A similar study by Roeske et al (2000) reported a 50% reduction in the volume of small bowel irradiated to more than 45 Gy with a 9-field IMRT plan when compared with a conventional 4-field box technique in 10 patients with either endometrial or cervix cancer. Portelance et al (2001) demonstrated a 58-67% reduction in the volume of small bowel receiving more than 45 Gy with IMRT that increased when the number of fields used was increased from 4 up to 9.

Multiple clinical studies have shown that the reduction in dose to the small bowel with IMRT seen in dosimetric comparisons is associated with lower rates of both acute and chronic GI toxicity. Mundt et al (2003) were one of the first groups to report their experience with IMRT in patients with cervical and endometrial carcinoma. They reported a lower rate of acute grade 2 GI toxicity in 40 patients treated with IMRT (60% vs. 91%, p = 0.002) compared with patients treated at the same institution with conventional WPRT (Mundt 2002). In a separate publication, the same group reported on the rate of chronic GI toxicity, showing a rate of only 11% in the patients treated with IMRT, compared with 54% in the patients treated with conventional WPRT (Mundt 2003). Recently, this series was updated to include 111 patients treated with IMRT, with a 45% rate of acute grade 2 GI toxicity (Hasselle 2010). In a study reported from Washington University, patients with locally advanced cervical cancer were treated with either IMRT (135 patients) or conventional 3D-techniques (317 patients) (Kidd 2010). The grade 3 and higher GI and GU toxicity was reduced in the patients treated with IMRT (6% vs. 17%, p = 0.0017).

To evaluate the feasibility of delivering IMRT in a multi-institutional setting, the RTOG recently completed a study, RTOG 0418, in which women with endometrial and cervical cancer were treated with pelvic IMRT. Contouring and treatment planning on this study was performed according to guidelines defined by RTOG. Only 25.3% developed grade 2+ acute GI toxicity, and 7.2% developed late grade 2+ GI toxicity, defined by CTCAE version 3 criteria (unpublished data) which compares favorably with historic controls treated with conventional WPRT (Mundt 2002). Preliminary analysis of hematologic toxicity on this study suggested that patients with reduced volumes of bone-marrow irradiated had lower rates of grade 3 hematologic toxicity (Presented at ASTRO 2010).

Evidence also suggests that IMRT results in similar cancer outcomes as conventional WPRT. A study published from Washington University comparing IMRT to conventional WPRT in patients with locally advanced cervix cancer showed no statistically significant difference in recurrence-free survival between the two groups, and actually better cause-specific and overall survival in the IMRT group (Kidd 2010). RTOG 0418 showed excellent cancer outcomes with IMRT: two year overall survival was 95% for both cervical and endometrial cancer patients, and two year loco-regional failure rates for cervical and endometrial cancer patients were 11% and 7%, respectively (unpublished data). These results are comparable to historical data for conventional WPRT which have shown overall survival rates of 81% and 85-92%, and loco-regional failure rates of 12-20% and 2-5%, for cervical and endometrial cancer, respectively (Sedlis 1999, Scholten 2005, Keys 2004, Nout 2010, Peters 2000). These findings suggest that pelvic IMRT is safe and provides at least equivalent rates of pelvic disease control. To evaluate this issue carefully on this study, we will compare clinical outcomes including local recurrence, progression-free survival or overall survival with IMRT to standard pelvic RT.

1.3 Toxicity Evaluation

Toxicity will be assessed at 6 time points during this study. In addition to the primary endpoint of patient reported GI toxicity, a broad range of other toxicities will be comprehensively evaluated. This will include GI, urinary, and hematologic toxicity which will allow us to determine the effect of IMRT on each of these aspects of toxicity from pelvic radiation. Additionally, we recognize that it is possible that IMRT will increase the risk of toxicity due to the larger volume of tissue which is treated to low doses in some cases. If IMRT does lead to higher rates of some forms of toxicity, this will be detected by the proposed study design which will provide valuable information to advance our understanding of the clinical risks and benefits of IMRT.

Each of the time points for toxicity evaluation and the rational for their inclusion in the study are listed in the left panel of Figure 1-3. The primary endpoint will be acute GI toxicity using the EPIC instrument in the final or 5th week of pelvic radiation. Due to the cumulative nature of acute
radiation toxicity (as shown in Figure 1-2), we anticipate the greatest difference in toxicity between the two arms at this time point.

In total, evaluating toxicity at six time points will allow us to determine if IMRT reduces acute toxicity, impacts resolution of acute toxicity and results in reduced long-term toxicity. Chronic GI toxicity from radiation continues to increase rapidly over 3 years, and then the rate of developing new toxicities slows (Figure 1-3 right panel). As a result, we will capture the majority of chronic radiation induced GI toxicity by evaluating toxicity 3 years after completion of radiotherapy.

### 1.4 Patient Reported Outcome (PRO) Instruments

To evaluate clinically important GI toxicity with a patient reported measure we will utilize the expanded prostate cancer index composite (EPIC) and common toxicity criteria adverse events – patient reported outcome (PRO-CTCAE) instruments.

The development and validation of The Expanded Prostate Cancer Index Composite (EPIC) is well reviewed on the RTOG website, as of March 1, 2012. EPIC includes four domains (urinary, bowel, sexual and hormonal domains); the domains have been validated separately so it is possible to use only the domains of interest (Litwin 1998, Wei 2000). Although the EPIC instrument was originally designed for prostate cancer patients, the items within the urinary and bowel domains do not mention the prostate or cancer, rather they address issues which may arise during radiation therapy, regardless of the reason. For purposes of this study, the EPIC instrument will query patients about toxicity in the past 7 days rather than the past 4 weeks in order to measure acute GI toxicity. GI toxicity increases weekly during the five week course of pelvic radiation. Because of the anticipated change in toxicity over the five weeks of treatment, averaging toxicity over the past four weeks could decrease the power of the instrument to detect differences in the two groups.

The EPIC instrument was chosen as the primary GI PRO measure in this study over other PRO instruments because the questions correlate directly to the most common GI toxicities reported in this patient population, namely diarrhea and pelvic pain. In addition, diarrhea is evaluated with regards to urgency, leakage, looseness and discomfort to most sensitively evaluate the degree of toxicity in this domain. Furthermore, in addition to evaluating the severity of the symptoms, the degree to which these symptoms bother the individual is evaluated. This will ensure that clinically important differences are detected. Other GI PRO instruments (i.e. FACE, FACIT-D, EORTC PR25) were considered but found to be inferior to EPIC in terms of the level of detail of questions specific to diarrhea. For example, EPIC is the only instrument that specifically asks about the frequency of loose stools and the total number of bowel movements in a day.

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before RT</td>
<td>Baseline</td>
</tr>
<tr>
<td>3 weeks after RT start</td>
<td>Compare early acute toxicity</td>
</tr>
<tr>
<td>End of RT (5 weeks after RT start)</td>
<td>Maximum difference in acute toxicity</td>
</tr>
<tr>
<td>4-6 weeks after RT</td>
<td>Compare resolution of acute toxicity</td>
</tr>
<tr>
<td>1 year from the start of RT</td>
<td>Early chronic toxicity</td>
</tr>
<tr>
<td>3 years from the start of RT</td>
<td>Long term toxicity</td>
</tr>
</tbody>
</table>

**Figure 1-3. Toxicity assessments in proposed study.** Toxicity will be assessed at six time points in the proposed study (left panel). The majority of long-term toxicity will be appreciated within three years after radiation (right panel) (Eifel 1995) *Primary endpoint.*
Although EPIC has been validated only in men with prostate cancer (Wei 2000) two of the authors of the validation paper, Drs. Litwin and Sanda (the instrument’s principal architect), state there is no problem with using EPIC for this study (personal communication). In fact, the EPIC bowel domain was used as a secondary endpoint in RTOG 0315, a randomized trial comparing octreotide to placebo for the prevention of acute diarrhea in patients undergoing chemoradiotherapy for anorectal cancer (Zachariah 2010). This trial included both men and women, and was able to show a statistically significant correlation between the CTCAE diarrhea grade and the EPIC score. Even though EPIC has been used in women in at least one prior study, a secondary endpoint of the current study is to validate EPIC in this patient population.

In addition, the PRO-CTCAE instrument will be utilized as an additional assessment of GI toxicity. The questions that will be utilized are listed in the Appendix B. Patients will be asked 5 questions to assess 3 symptoms, namely diarrhea, abdominal pain and bowel control. PRO-CTCAE is a group of items currently being developed by the NCI for direct patient-reporting of adverse symptoms in cancer trials and is designed to complement information provided by the CTCAE (Trotti 2007, Bruner 2007). A recent study of lung cancer patients receiving chemotherapy compared patient and clinician reports of six CTCAE symptoms (Basch 2009). Patients tended to report symptoms earlier and more frequently than clinicians and their reports were more strongly associated with measures of daily health status (Basch 2009). A large validation of the PRO-CTCAE is underway across various cancer types. In addition, patients will be asked about the frequency with which they have required anti-diarrhea medications.

To address the secondary endpoints of this study, we will utilize the EPIC instrument to evaluate urinary toxicity and the FACT instrument to address the impact of treatment on quality of life. The Functional Assessment of Cancer Therapy – (FACT-G, Version 4) is a brief, validated, sensitive 27-item measure for evaluating QOL in patients receiving treatment for cancer (Cella 1993). In addition to a total QOL score, subscale scores for physical, functional, social and emotional well-being are produced. Utilization of this questionnaire will allow for a determination of the extent to which the addition of treatment affects overall QOL as well as domain specific QOL (for example, functional well-being).

The Cervix Subscale of the FACT consists of 15 questions developed from interviews with patients and clinicians involved with cervical cancer that are used in addition to the 27 items from the FACT-G. The FACT-G with Cervix Subscale (FACT-Cx) has been used in GOG trials to assess the effect of treatment on overall QOL (McQuellon 2006, Moore 2004, Monk 2005, Long 2006, Monk 2009, Cella 2010). The primary endpoint of the study will be rates of GI toxicity as determined using the EPIC bowel domain between women in the two treatment arms after 5 weeks of treatment. Additional assessments will be made of scores at the other time points.

### 1.5 Health Utilities And Cost Analysis

A health utilities and cost analysis will be performed to evaluate the cost-effectiveness of IMRT. Health utilities are a patient reported outcome resulting in a patient’s preference for certain health states. Health utilities are measured on a scale of 0-1 with 0 being death and 1 being perfect health. There are some states listed with a negative value which would result in a health state worse than death. Health utilities can be measured through an interaction between an interviewer and patient by techniques such as Standard Gamble or Time Trade Off. Health utilities can also be measured by use of instruments including the EQ-5D or Health Utilities Index III. RTOG has utilized the EQ-5D in a number of trials to measure patient utilities in an attempt to calculate quality-adjusted survival (QALY) (Konski 2009). The EQ-5D is a short validated instrument with only 5 questions of 3 responses each in addition to a visual analog scale with a scale from 0-100. The EQ-5D is also translated into many languages. Measuring QALY is appropriate in this trial since the primary endpoint is an evaluation of the use of a specific technology, IMRT, in an attempt to reduce gastrointestinal morbidity. This is particularly important given the significant difference in cost between the two treatments. A cost-utility analysis will be able to be performed by combining cost of care and QALY. We hypothesize that IMRT may reduce complication rates which will translate to a reduction in the overall cost of care despite the higher initial cost of IMRT treatment. We will investigate whether IMRT may be cost effective within the range of acceptability of $50,000/QALY.
1.6 Correlative Study Design (8/4/14)
One of the secondary endpoints of the study will be to identify molecular predictors of radiation toxicity utilizing peripheral blood samples. Peripheral blood samples will be collected and sent to the NRG Oncology Biospecimen Bank for central processing and analysis. In addition, possible tumor samples can be sent to the NRG Oncology Biospecimen Bank for use in future studies.

Serum from peripheral blood samples will be used to characterize circulating cytokines and miRNA. miRNA are small RNA molecules, which are global regulators of gene expression. miRNA have been reported to be misexpressed in the circulating blood of patients with cancer. These circulating miRNAs thus have the potential to serve as novel biomarkers for cancer outcome or radiation toxicity. Samples will be obtained at the time of diagnosis and during the third and final week of radiation, when toxicity is greatest.

Peripheral blood monocytes (PBM) may be used to identify genetic changes which may be used to identify patients with an underlying genetic susceptibility to develop radiation toxicity. To accomplish this, DNA from PBM can subjected to single nucleotide polymorphisms (SNPs) analysis. SNPs are genomic changes which are within a gene or linked to a gene of interest which can be makers of an individual’s underlying susceptibility to developing toxicity. Completion of a genome-wide association study (GWAS) may be performed with samples to identify novel SNPs, or the role of candidate SNPs can be tested with a PCR-based assay.

We hypothesize that clinically significant radiation toxicity can be predicted with circulating biomarkers as miRNA or with genetic polymorphisms.

2.0 OBJECTIVES

2.1 Primary Objectives
To determine if IMRT reduces acute gastrointestinal toxicity in the 5th week (after 23-25 fractions) of pelvic radiation as measured with EPIC.

2.2 Secondary Objectives
2.2.1 To determine if grade 2+ gastrointestinal toxicity (CTCAE v. 4.0) is reduced with IMRT compared to conventional WPRT
2.2.2 To determine if grade 2+ hematologic toxicity (CTCAE v. 4.0) is reduced with IMRT compared to conventional WPRT
2.2.3 To determine if urinary toxicity is reduced with IMRT using the EPIC urinary domain
2.2.4 To validate EPIC bowel and urinary domains in women undergoing either IMRT pelvic radiation treatment or four field pelvic radiation treatment for endometrial or cervical cancer
2.2.5 To assess the impact of pelvic IMRT on quality of life using the FACT-G with cervix subscale
2.2.6 To determine if there is any difference in local-regional control, disease-free survival, and overall survival with IMRT as compared to conventional pelvic RT
2.2.7 To perform a health utilities analysis to measure the financial impact of pelvic IMRT
2.2.8 To identify molecular predictors of radiation toxicity and novel circulating cancer biomarkers
2.2.9 To determine if there is any difference in rate of secondary cancers with IMRT as compared to conventional pelvic RT

3.0 PATIENT SELECTION (8/4/14)
NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED
For questions concerning eligibility, please contact the study data manager.

3.1 Conditions for Patient Eligibility (8/4/14)
3.1.1 Pathologically proven diagnosis of endometrial or cervical cancer.
3.1.2 Patients must have undergone a hysterectomy (total abdominal hysterectomy, vaginal hysterectomy or radical hysterectomy or total laparoscopic hysterectomy) for carcinoma of the cervix or endometrium within 49 days prior to registration. Performance of a bilateral salpingo-oophorectomy will be at the treating surgeon’s discretion.
3.1.3 Appropriate stage for protocol entry, including no distant metastases, based upon the following minimum diagnostic workup:
3.1.3.1 History/physical examination within 45 days prior to registration;
3.1.3.2 CT, MRI or PET-CT including the abdomen and pelvis should be performed for initial radiological staging. This may be performed pre- or post-surgery within 90 days prior to
registration. Imaging performed post-operatively should show no evidence of residual disease. Any evidence of malignancy identified on pre-operative imaging should have been completely resected surgically prior to protocol treatment.

3.1.3.3 Chest CT or chest x-ray must be performed within 90 days prior to registration (unless a PET-CT has been performed)

3.1.4 Zubrod Performance Status 0-2

3.1.5 Age ≥ 18;

3.1.6 CBC/differential obtained within 14 days prior to registration on study, with adequate bone marrow function defined as follows:

3.1.6.1 Absolute neutrophil count (ANC) ≥ 1,500 cells/mm³;

3.1.6.2 Platelets ≥ 100,000 cells/mm³;

3.1.6.3 Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.)

3.1.7 For patients receiving chemotherapy:

3.1.7.1 Within 14 days prior to registration, serum creatinine ≤ 1.5 mg/dL and calculated creatinine clearance ≥ 50 cc/min. Both tests must be within these limits. The creatinine clearance should be calculated using the Cockcroft-Gault formula: (See Section 7.3.1)

3.1.7.2 AST ≤ 2 x ULN

3.1.7.3 Bilirubin ≤ 2 x ULN

3.1.7.4 Alkaline phosphatase, Mg, BUN and electrolytes must be obtained and recorded

3.1.8 Endometrial Cancer:

3.1.8.1 Patients with the following histologic features are eligible for pelvic radiation therapy without weekly cisplatin:

- <50% myometrial invasion, grade 3 adenocarcinoma without uterine serous carcinoma (USC) or clear cell histology
- ≥50% myometrial invasion grade 1-2 adenocarcinoma without USC or clear cell histology

3.1.8.2 Patients with the following histologic features may be treated with pelvic radiation with or without weekly cisplatin. The decision to add weekly cisplatin for these patients is at the treating physician’s discretion:

- ≥50% myometrial invasion, grade 3 including USC and clear cell carcinoma.
- FIGO 2009 stage II endometrial cancer of any grade including USC and clear cell carcinoma.
- FIGO 2009 IIIC1 (pelvic lymph node positive only, para-aortic nodes negative if removed) including USC and clear cell carcinoma. **Note:** If para-aortic nodes are not removed, CT abdomen or PET CT must demonstrate no evidence of lymphadenopathy.

3.1.9 Cervical Cancer:

3.1.9.1 Patients with the following pathology findings may be treated with pelvic radiation with or without weekly cisplatin at the treating physician’s discretion. The decision to add weekly cisplatin for these patients is at the treating physician’s discretion.

3.1.9.1.1 Patients with intermediate risk features including two of the following histologic findings after radical hysterectomy:

- 1/3 or more stromal invasion
- Lymph-vascular space invasion
- Large clinical tumor diameter (> 4 cm)

3.1.9.1.2 Patients with cervical cancer treated with a simple hysterectomy with negative margins

3.1.9.2 Patients with any of the following criteria following radical hysterectomy are eligible for this study and must receive weekly cisplatin:

- Positive resected pelvic nodes and para-aortic nodes negative if removed. **Note:** If para-aortic nodes are not removed, CT abdomen or PET CT must demonstrate no evidence of lymphadenopathy.
- Microscopic parametrial invasion with negative margins

3.1.10 Patient must provide study specific informed consent prior to study entry.

3.1.11 Willingness and ability to complete the bowel and urinary domains of the EPIC prior to registration
3.2 Conditions for Patient Ineligibility

3.2.1 Patients with para-aortic nodal disease or who require extended field radiotherapy beyond the pelvis.

3.2.2 Patients with histology consisting of endometrial stromal sarcoma, leiomyosarcoma or malignant mixed mullerian mixed tumor (MMMT or carcinosarcoma).

3.2.3 Patients who exceed the weight/size limits of the treatment table or CT scanner.

3.2.4 Mental status changes or bladder control problems that make the patient unable to comply with bladder-filling instructions.

3.2.5 Patients with evidence of metastatic disease outside of the pelvis.

3.2.6 Patients with positive or close (< 3 mm) resection margins.

3.2.7 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years.

3.2.8 Prior radiation therapy to the pelvis.

3.2.9 Patients with active inflammatory bowel disease.

3.2.10 Severe, active co-morbidity, defined as follows:

3.2.10.1 Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months.

3.2.10.2 Transmural myocardial infarction within the last 6 months.

3.2.10.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration.

3.2.10.4 Other major medical illness which requires hospitalization or precludes study therapy at the time of registration.

3.2.10.5 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory test coagulation parameters are not required for entry into this protocol.

3.2.10.6 Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immunocompromised patients.

3.2.11 Patients with prior treatment with platinum-based chemotherapy.

3.2.12 Women who are breastfeeding.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

NOTE: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility. See Appendix II for a summary of study assessments and time frames.

4.1 Required Evaluations/Management

4.1.1 Completion of the bowel and urinary domains of EPIC is mandatory for all patients (see Section 3.1.11).

4.1.2 Assessment of weight.

4.2 Highly Recommended Evaluations/Management (8/7/2013)

4.2.1 Formal consultation by nutritionist.

4.2.2 Audiogram at baseline and following treatment at the discretion of the treating physician for patients who are planned to receive concurrent chemotherapy.

4.2.3 Completion of the FACT-Cx, PRO-CTCAE item for GI toxicity and EQ-5D (for patients who consent to the optional quality of life (QOL) component of the study). Note: If the patient consents to participate in the optional QOL component of the study, sites are required to administer the baseline FACT Cx, PRO-CTCAE item for GI toxicity, and EQ-5D prior to the start of protocol treatment.

5.0 REGISTRATION PROCEDURES (8/7/2013)

Access requirements for OPEN AND TRIAD:

Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site. To obtain an active CTEP IAM account, go to https://eapps-ctep.nci.nih.gov/iam.

NOTE: This trial is not utilizing the services of the ITC for dosimetry digital treatment data submission. See below for information on installing TRIAD for submission of digital RT data prior to enrolling patients.
5.1 Pre-Registration Requirements for IMRT/Standard Treatment Approach (8/4/14)

Prior to enrolling patients on this study, each institution must have met specific technology requirements and have provided baseline physics information in order to deliver both IMRT and standard treatment.

5.1.1 Instructions for completing these requirements or determining if they already have been met are available on the Imaging and Radiation Oncology Core (IROC) Houston web site. Visit http://irochouston.mdanderson.org and select “Credentialing” and “Credentialing Status Inquiry”.

An IMRT phantom study with the IROC Houston must be successfully completed (if the institution has not previously met this IMRT credentialing requirement). Instructions for requesting and irradiating the phantom are available on the IROC Houston web site at http://irochouston.mdanderson.org; select “Credentialing” and “RTOG”. Upon review and successful completion of the phantom irradiation, the IROC Houston will notify both the registering institution and NRG Oncology that the institution has completed this requirement. Subsequently, NRG Oncology will notify the institution IMRT credentialing requirement has been met.

5.1.2 The institution or investigator must update or complete a new IMRT Facility Questionnaire (available on the RPC web site at http://irochouston.mdanderson.org) and send it to NRG Oncology for review prior to entering any cases, and set up of a TRIAD account for digital data submission. NRG Oncology will notify the institution when all requirements have been met and the institution is RT credentialed to enter patients onto this study.

5.2 Pre-Registration Requirements for Brachytherapy Treatment Approach (8/4/14)

Brachytherapy can be delivered at the treating physician’s discretion. It is recommended that the High Dose Rate (HDR) be delivered daily after completion of external beam. Two HDR fractions of 6 Gy prescribed to the vaginal surface are recommended.

The Knowledge Assessment Questionnaire available from the IROC Houston website (http://irochouston.mdanderson.org) must be completed prior to enrollment for physicians elective to deliver brachytherapy.

Upon review and successful completion, the IROC Houston will notify both the registering institution and NRG Oncology that the institution has successfully completed this requirement. NRG Oncology will notify the institution when all requirements have been met and the institution is eligible to enter subsequent patients onto this study.

5.3 Digital RT Data Submission to NRG Oncology Using TRIAD (8/7/2013)

TRIAD is the American College of Radiology’s (ACR) image exchange application and it is used by NRG Oncology. TRIAD provides sites participating in NRG Oncology clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements

- Site physics staff who will submit images through TRIAD will need to be registered with The Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to Section 5.0 of the protocol for instructions on how to request a CTEP-IAM account.
- To submit images, the site physics user must have been assigned the ‘TRIAD site user’ role on the relevant Group or CTSU roster. NRG Oncology users should contact your site Lead RA to be added to your site roster. Users from other cooperative groups should follow their procedures for assignment of roster roles.
- RAs are able to submit standard of care imaging through the same method.

TRIAD Installations

When a user applies for a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found on the RTOG website Core lab tab.
This process can be done in parallel to obtaining your CTEP IAM account username and password.

If you have any questions regarding this information, please send an email to the TRIAD Support mailbox at TRIAD-Support@acr.org.

5.4 Regulatory Pre-Registration Requirements (8/4/14)

5.4.1 This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Prior to the recruitment of a patient for this study, investigators must be registered members of a Lead Protocol Organization (LPO). Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch (PMB), CTEP, DCTD, NCI. These forms are available on the CTSU member web: http://ctep.cancer.gov/investigatorResources/investigator_registration.htm. For questions, please contact the CTEP Investigator Registration Help Desk by e-mail at pmbregpend@ctep.nci.nih.gov.

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials). Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account. Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures below for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.) An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members’ website. Additional information can be found on the CTEP website at http://ctep.cancer.gov/branches/pmb/associate_registration.htm. For questions, please contact the CTEP Associate Registration Help Desk by email at ctepreghelp@ctep.nci.nih.gov.

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

**Download Site Registration Documents:**
Site registration forms may be downloaded from the RTOG 1203 protocol page located on the CTSU members’ web site. Go to https://www.ctsu.org and log into the members’ area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the (state organization type e.g. P2C, CITN, NCTN Groupname) link to expand, then select trial protocol, RTOG-1203
- Click on the Site Registration Documents link

Requirements for RTOG 1203 site registration:
- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- IRB/REB approval letter;
- IRB/REB approved consent (English and native language versions*)

**Note:** Institutions must provide certification/verification of IRB/REB consent translation to NRG Oncology (described below in section 5.4.2)
- IRB/REB assurance number
- CTSU RT Facilities Inventory Form
NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the IROC Houston monitoring program. For non-lead group institutions an RT Facilities Inventory Form must be on file with CTSU. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility.

**Submitting Regulatory Documents:**
Submit completed forms along with a copy of your IRB Approval and Informed Consent to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office  
1818 Market Street, Suite 1100  
Philadelphia, PA 19103  
Phone: 1-866-651-2878  
Fax: 215-569-0206  
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

**5.4.2 Non-English Speaking Canadian and Non-North American Participating Sites**
Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved NRG Oncology will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

**5.4.3 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS**

**5.4.3.1** Prior to clinical trial commencement, Canadian institutions must also complete and fax (215-569-0206) or e-mail (CTSURegulatory@ctsu.coccg.org) to the CTSU Regulatory Office Health Canada’s Therapeutic Products Directorates’ Clinical Trial Site Information Form, Qualified Investigator Undertaking Form, and Research Ethics Board Attestation Form.

**5.4.4 Pre-Registration Requirements FOR INTERNATIONAL INSTITUTIONS**

**5.4.4.1** For institutions that do not have an approved LOI for this protocol:
International sites must submit an LOI to NRG Oncology to receive approval to participate in this trial. For more details see link below:
http://www.rtog.org/Researchers/InternationalMembers/LetterofIntent.aspx

**5.4.4.2** For institutions that have an approved LOI for this protocol:
All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

**5.5 OPEN Registration Instructions (8/4/14)**

**5.5.1** Patient registration can only occur after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as ‘approved’ in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at https://eapps-ctep.nci.nih.gov/iam/index.jsp) and a ‘Registrar’ role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members’ web site https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPPA authorization form (if applicable).
6.0 RADIATION THERAPY (8/7/2013)

NOTE: This trial is NOT utilizing the services of ITC for dosimetry digital treatment data submission. See Section 5.3 for information on installing TRIAD for submission of digital RT data PRIOR to enrolling patients.

Protocol treatment (Radiation Therapy) must begin within 63 days (9 weeks) after hysterectomy

NOTE: Rapid reviews are required on the 1st case on each arm for a site. Please allow 3 business days for this to be completed. If a resubmission is required the 3 business day timeline will restart. Treatment cannot begin until approval from NRG Oncology has been received at the site

6.1 Standard (3D) Radiation Therapy (8/4/14)

6.1.1 Standard RT dose specifications

Whole pelvis will be treated with a four-field technique (AP/PA/R lateral/L lateral) to 45 or 50.4 Gy at 1.8 Gy/fraction. The decision to deliver 45 or 50.4 Gy is at the physician’s discretion and must be reported at the time of enrollment. The dose will be prescribed to the isocenter which is defined as the intersection of the four beams. The dose can be normalized to an isodose line between 97-100%.

Patients will be treated once a day, 5 days a week with a daily fraction size of 1.8 Gy. Examples of standard fields are shown below.

6.1.2 Standard Radiation Therapy - Technical Factors

A megavoltage beam of 6 MV or greater with a minimum source-axis distance of 100 cm will be used. Isocentric technique will be used. MLC or custom Cerrobend blocks are acceptable for field shaping. Field in field may be used to increase dose homogeneity by eliminating hot spots. The intended use of field in field is not to increase dose conformality to reduce the bowel dose.

6.1.3 Standard arm Localization, Simulation, and Immobilization

6.1.3.1 All patients will be simulated after randomization. CT simulation must be performed. Patients who are randomized to receive treatment with standard treatment (not IMRT) can be simulated supine or prone. Patients should be simulated and treated with a full bladder (empty bladder acceptable if not tolerated). All fields treated require portal verification on the treatment unit.

6.1.3.2 I.V. contrast may be used during simulation to help better define the vessels; however, it is not required. Oral or rectal contrast is not recommended as it may interfere with the planning process and may possibly cause anatomical distortion. A CT scan without oral or rectal contrast must be used for treatment planning.

6.1.3.3 CT scan thickness should be ≤ 3 through the region that contains the primary target volumes and the critical structures. CT scan should extend at least 4 cm above and below the target volumes. The superior limit of the scan will be at least at the L1/2 interspace and inferior limit will be below the perineum.

6.1.4 Standard arm contouring and treatment planning

Contouring will be performed for patients treated with standard therapy as well as for patients with IMRT treatment. The target structures which will be contoured include a nodal CTV and a vaginal CTV. The bladder, rectum, small bowel and bone marrow will be contoured as avoidance structures. Please see Section 6.2 for contouring details. The only difference between standard and IMRT contours will be that patients treated with standard treatment will only have a vaginal CTV and not ITV since no empty bladder scan will be obtained.
6.1.5 Pelvic Field (See Figure 6-1)

6.1.5.1 AP-PA Portals
Superior Border: A transverse line between L4 and L5
Inferior Border: Transverse line below the lowest extent of the obturator foramen
Lateral Border: 2 cm lateral to widest true bony pelvic diameter.
Custom Blocking: To shield small bowel and femoral heads while maintaining a margin of at least 1 cm from common iliac nodes and should not shield the obturator foramina.

6.1.5.2 Lateral Portals
Superior/Inferior Borders: Identical to AP-PA fields.
Anterior Border: A straight line drawn 5 mm anterior to the symphysis pubis and at least 1 cm anterior to common iliac nodes at L4-L5.
Posterior Border: The posterior border should include S2.

![Figure 6-1](image-url) Examples of standard AP and lateral fields for pelvic radiation. The green volume includes contoured pelvic lymph nodes and the red volume is the vaginal CTV.

Please refer to the RTOG Gynecological Atlas for volume specifications. The Atlas may be accessed on the RTOG website at: [http://www.rtog.org/CoreLab/ContouringAtlases/GYN.aspx](http://www.rtog.org/CoreLab/ContouringAtlases/GYN.aspx)

6.2 Contouring of target structures for standard and IMRT arm (9/16/2013)

6.2.1 Contouring of target structures
6.2.1.1 Target structures will be delineated for both the standard and the IMRT arm of the study. The nodal and vaginal CTV will be the target structures. The avoidance structures to be contouring include the bladder, rectum, small bowel and bone marrow. Description of these contours is described below in Section 6.3.

6.2.2 Target volumes:
6.2.2.1 Nodal CTV contouring
The Nodal Clinical Target Volume (CTV) is defined as nodal regions considered to contain potential microscopic disease, as delineated by the treating physician. An example of the RTOG guidelines for contouring can be reviewed at: [http://www.rtog.org/CoreLab/ContouringAtlases/GYN.aspx](http://www.rtog.org/CoreLab/ContouringAtlases/GYN.aspx)

The nodal CTV should include lymph nodes that drain the involved site and adjacent perinodal soft tissue. This should include the internal (hypogastric and obturator), external, and common iliac lymph nodes. Presacral lymph nodes and 1-2 cm of tissue anterior to the S1, S2 and S3 sacral segments soft tissues should be included for patients with cervical cancer. The nodal CTV will include the vessels, perinodal tissue and pertinent clips. Bone, muscle and intraperitoneal small bowel should be excluded from the CTV. Approximately 1-2 cm of tissue anterior to the S1, S2 and S3 sacral segments should be added to the CTV for patients with cervical carcinoma in order to include the presacral lymph nodes and uterosacral ligaments. The most anterolateral external iliac lymph nodes that lie just proximal to the inguinal canal should be excluded from the CTV (i.e., nodal CTV should stop right at
the level of the femoral head). The CTV of the nodes should end 7 mm from L4/L5 interspace to account for the PTV expansion. The nodal CTV will be named CTVn. Please refer to the RTOG GYN atlas for examples of this volume.

6.2.2.2 Vaginal CTV contouring

The vaginal CTV will include the vagina and the paravaginal soft tissue. Examples are also found on the RTOG GYN atlas. The inferior limit of the vaginal CTV is approximately the level of the upper third of the symphysis pubis but can be individualized based on inferior spread of the patient’s tumor on prior pre-operative physical examination and post-operative pathology reports. The vaginal CTV should extend into the rectum if there is significant rectal distention. This will allow coverage of the vagina if the rectum is decompressed during treatment. The vaginal CTV should be named CTVp (p stands for primary per standardized naming convention) (Santanam 2012).

6.2.2.3 Vaginal ITV for patients treated with IMRT

A vaginal internal target volume to account for organ motion of the vagina will be used only for IMRT planning. Standard fields borders provide a significant margin on the vagina so an ITV is not needed in this setting. The vagina moves significantly with bladder filling and studies have shown that patients are not able to maintain constant levels of bladder filling, despite careful counseling. The ITV will be contoured using a fused image of the full and empty bladder scans and will encompass the vagina and paravaginal soft tissues from both scans. The vaginal ITV is defined as the volume of the vagina that is in both the empty and full bladder CT scans that are done at the time of simulation and fused together. Vaginal ITV will be named ITV.

6.2.3 The Nodal Planning Target Volume (PTV) will provide a 7 mm margin around the nodal CTV. The nodal PTV will be named PTVn. The vaginal CTV (standard patients) and the vaginal ITV (IMRT patients) will be expanded in all dimensions (anterioyly, posteriorly, laterally as well as in the superior and inferior directions) to create the vaginal PTV, which will be called PTVp.

6.2.4 The definition of volumes will be in accordance with the 1993 ICRU Report #50: Prescribing Recording and Reporting Photon Beam Therapy and 1999 ICRU Report #62: Prescribing, Recording and Reporting Photon Beam Therapy (Supplement to ICRU Report 50).

6.3 Normal tissue contours (9/16/2013)

6.3.1 Normal tissue structures will be contoured on the CT scan obtained with a full bladder since treatment will be delivered with a full bladder with the goal of reducing the volume of irradiated bowel. A description for the technique on how to contour these structures can be found at http://www.rtog.org/CoreLab/ContouringAtlases/FemaleRTOGNormalPelvisAtlas.aspx.

6.3.2 Bladder will be outlined on every slice, including the portion inferior to the planning target volume.

6.3.3 Rectum will be outlined on every slice, including the portion inferior to the planning target volume and superior to the level that it leaves the posterior pelvis around the region of the rectosigmoid.

6.3.4 Bowel will be contoured as one structure named, “bowel space”. Bowel space will be outlined on every slice which has visible bowel, extending 2 cm above the planning target volume. Bowel space will include the volume surrounding loops of bowel out to the edge of the peritoneum because the bowel may lie within this space at any time throughout the course of treatment. Bowel Space will include the ENTIRE bowel, including small bowel, colon and sigmoid, in one bowel bag contour. This contour will be named BowelSpace.

6.3.5 The pelvic bone will be contoured as a surrogate for the bone marrow. The pelvic bone from the superior to the inferior aspect of the PTV can be auto-contoured. This can be accomplished with use of a CT-density–based auto-contouring algorithm. The femoral heads but not femoral necks should be included in the bone marrow contour. Please see below for an example of contoured pelvic bone. This contour will be named BoneMarrow.
6.4 Intensity Modulated Radiation Therapy (IMRT) (8/4/14)

6.4.1 IMRT Dose Specifications

6.4.1.1 Prescription dose shall be according to the following specifications:

The vaginal planning target volume (PTV) (ITV with 7.0 mm margin) and nodal PTV will receive 45 Gy in 25 fractions or 50.4 Gy in 28 fractions. The decision to deliver 45 or 50.4 Gy is at the physician’s discretion and must be reported at the time of enrollment. Patients will be treated once a day, 5 days a week with a daily fraction size of 1.8 Gy. All targets will be treated simultaneously.

The dose is prescribed to cover 97% of the vaginal PTV and nodal PTV. A volume of at least 0.03 cc within any PTV should not receive > 110% of the prescribed dose. No volume within the PTV that is 0.03 cc or larger can receive a dose that is < 93% of its prescribed dose. Any contiguous volume of 0.03 cc or larger of the tissue outside the PTVs must not receive > 110% of the dose prescribed to the composite PTV.

6.4.2 IMRT Technical Factors

6.4.2.1 Megavoltage equipment capable of delivering static intensity modulation with a multileaf collimator or dynamic intensity modulation (using a multileaf collimator or tomotherapy) is required. VMAT is allowed. Six or more fields should be utilized with a minimum source-axis distance of 100 cm. The exception is the use of the Tomotherapy unit that uses 80 cm.

6.4.2.2 6-10 MV energy photon beam should be used.

6.4.3 IMRT Localization, Simulation, and Immobilization

Prior to simulation, it is recommended that small radiopaque marker seeds are inserted into the vaginal apex to help identify the vaginal apex on the CT scan. Radiopaque markers that distend or otherwise alter the vaginal anatomy should not be used.

6.4.3.1 Patients must be immobilized supine for IMRT. Patients should at least, be immobilized in a cradle that fixes the position of the lower body, trunk and proximal legs. Patients will be treated in the immobilization device.

6.4.3.2 Treatment planning CT scans will be required to define clinical and planning target volumes. The treatment planning CT scan should be acquired with the patient in the same position and immobilization device as for treatment.

6.4.3.3 Two separate treatment planning CT scans (full bladder and empty bladder CT scans) are required. The patient will be instructed to drink 32 ounces of fluid 30-60 minutes before simulation to obtain the full bladder scan. The second CT scan will be obtained after the patients has voided for the empty bladder scan.

6.4.3.4 I.V. contrast may be used during simulation to help better define the vessels; however, it is not required. Oral or rectal contrast is not recommended as it may interfere with the planning process and may possibly cause anatomical distortion. A CT scan without oral or rectal contrast must be used for treatment planning.

6.4.3.5 CT scan thickness should be ≤ 3 through the region that contains the primary target volumes and the critical structures requiring Dose-Volume Histogram analysis. CT scan should
extend at least 4 cm above and below the target volumes. The superior limit of the scan will be at least at the L1/2 interspace and inferior limit will be below the perineum.

6.4.4 IMRT treatment planning

6.4.4.1 Full and empty bladder scans should be fused together prior to outlining target volumes.

6.4.4.2 A CT scan simulation will be performed with the full bladder, and a second CT after the patient has voided for the empty bladder scan.

6.4.4.3 A nodal CTV and vaginal ITV will be delineated on the full bladder scan for treatment planning purposes. Please see Sections 6.2 and 6.3 for instructions on how to contour the target and normal tissue volumes, respectively.

6.4.4.4 IMRT plan will be prescribed to the PTV on the full bladder scan. The treatment aim will be the delivery of homogeneous prescribed dose radiation to the PTVs while minimizing dose to non-involved tissues.

6.4.4.5 The treatment plan used for each patient will be evaluated based on an analysis of the volumetric dose, including dose volume histogram (DVH) analyses of the PTV and critical normal structures. Full heterogeneity corrections should be utilized and the method used for tissue heterogeneity calculations shall be reported.

6.4.4.6 Planning Priorities

Dose to nodal PTV and vaginal ITV are the most important planning priorities, followed by the dose to critical structures. The critical structure constraints are listed in Section 6.7.

6.5 Compliance Criteria

6.5.1 Treatment delays for both arms of the study as follows:

- Per Protocol: Interruption of 0 days
- Variation Acceptable: Interruption of 1-7 consecutive days
- Deviation Unacceptable: Interruption of ≥ 8 consecutive days

6.6 Target Volume Coverage Homogeneity

6.6.1 Standard arm

The minimum dose to the dose specification point (isocenter or calculation point) is greater than or equal to 43.2 Gy for those patients for whom the intended dose was 45 Gy and greater than or equal to 48.6 Gy for those patients for whom the intended dose was 50.4 Gy. Maximum dose to a volume of ≥0.03 cc of tissue within the convergence of the treatment fields should not exceed 107% of the prescription dose.

Variation Acceptable: Field borders lie more than a cm but less than 2 cm from field edge as shown in Figure 6-1.

Deviation Unacceptable: Field borders lie more than 2 cm from the field edge and shown in Figure 6-1.

6.6.2 IMRT arm

PTV

Per protocol: The prescription criteria in Section 6.2.1 are fulfilled.

Variation Acceptable: The 0.03cc volume of overdose for the PTV exceeds 110% of the prescribed dose but remains below 115%. No volume within this PTV that is 0.03 cc or larger receives a dose that is < 91% of its prescribed dose.

Deviation Unacceptable: A total of 0.03 cc of the PTV receives a dose that is over 115% of the prescribed dose. A volume within this PTV that is 0.03 cc or larger does receive a dose that is < 91% of its prescribed dose.

6.7 Critical structures (9/16/2013)

6.7.1 Standard arm

No criteria for avoidance structures doses are applied for the standard arm. The volume of normal tissues covered will be dictated by the field borders and individual patient’s anatomy.

NOTE: All required structures below must be submitted for both arms and labeled per DICOM Standard Name as listed in the table in section 6.7.2.6. Resubmission of data may be required if labeling of structures does not conform to the standard dicom list provided.
6.7.2 IMRT arm

6.7.2.1 Bowel
- **Per Protocol**: Up to 30% receives 40 Gy
- **Variation Acceptable**: More than 30% receives 40 Gy but not more than 70% receives 40 Gy
- **Deviation Unacceptable**: 70% or more receives 40 Gy

6.7.2.2 Rectum
- **Per Protocol**: Up to 80% receives 40 Gy
- **Variation Acceptable**: More than 80% receives 40 Gy but less than 100% receives 40 Gy
- **Deviation Unacceptable**: 100% receives 40 Gy

6.7.2.3 Bladder
- **Per Protocol**: Up to 35% receives 45 Gy
- **Variation Acceptable**: More than 35% receives 45 Gy but not more than 70% receives 45 Gy
- **Deviation Unacceptable**: 70% or more receives 45 Gy

6.7.2.4 Bone marrow
- **Per Protocol**: Up to 90% receives 10 Gy
- **Variation Acceptable**: More than 90% receives 10 Gy but 90% does not receive greater than 25 Gy
- **Deviation Unacceptable**: 90% receives greater than 25 Gy

6.7.2.5 Bone marrow
- **Per Protocol**: Up to 37% receives 40 Gy
- **Variation Acceptable**: More than 37% receives 40 Gy but not more than 60% receives 40 Gy
- **Deviation Unacceptable**: 60% or more receives 40 Gy

6.7.2.6 Standard Structure Names for TRIAD Submission

<table>
<thead>
<tr>
<th>Structure</th>
<th>Arm 1- IMRT</th>
<th>Arm 2 -3D CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vagina</td>
<td>ITV</td>
<td>CTVp</td>
</tr>
<tr>
<td>Vagina</td>
<td>PTVp</td>
<td>PTVp</td>
</tr>
<tr>
<td>Nodes</td>
<td>CTVn</td>
<td>CTVn</td>
</tr>
<tr>
<td>Nodes</td>
<td>PTVn</td>
<td>PTVn</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>BoneMarrow</td>
<td>BoneMarrow</td>
</tr>
<tr>
<td>Bowel</td>
<td>BowelSpace</td>
<td>BowelSpace</td>
</tr>
<tr>
<td>Bladder</td>
<td>Bladder</td>
<td>Bladder</td>
</tr>
<tr>
<td>Rectum</td>
<td>Rectum</td>
<td>Rectum</td>
</tr>
<tr>
<td>External</td>
<td>External</td>
<td>External</td>
</tr>
</tbody>
</table>

6.8 Documentation Requirements
Standard RT arm: JPEGs of the Digitally Reconstructed Radiographs (DRR) with the field shaping included must be submitted for review along with the CT plan. For the IMRT arm just the digital CT plan has to be submitted. A copy of the daily chart is required for all cases. See Section 12.2 for specific details.

6.9 Verification Requirements
6.9.1 Image should be performed at least weekly for patients treated on the IMRT and standard therapy arms, respectively. For patients treated with IMRT dose delivery, orthogonal films to localize the isocenter placement shall be obtained. For patients treated with standard therapy, weekly port films should be obtained. The length of the treatment field shall be indicated on these films. These films will not be collected but should be held by the institution and available for review if requested.
6.10 **Brachytherapy (8/4/14)**

Patients in either arm of the study may be treated with HDR vaginal brachytherapy at the discretion of the treating radiation oncologist. Iridium sources are to be used for intracavitary application with vaginal dome and cylinders with an afterloaded applicator system. Two fractions of 6 Gy should be prescribed to the vaginal dome surface. The largest possible vaginal dome cylinder diameter should be selected that fits into the vaginal apex. Only the top 1/3-1/2 of the vagina should be treated. Brachytherapy must follow the external beam irradiation and be started within 7 days of completion of the pelvic irradiation. Brachytherapy should be completed within 14 days. In general, brachytherapy should be delivered daily on sequential days following completion of external beam radiation. A report on the source specifications, strengths, spacing relative to the applicators, size of applicator, dwell times and dwell positions is required.

Vaginal surface dose may be calculated at the vaginal surface lateral to the midpoint of the surface of the ovoid or cylinder. (See Appendix VI)

The dose at the apex of the cylinder should be calculated to be as close as possible (within +/- 25%) to the lateral vaginal surface dose (See Appendix VI). Dose points 0.5 cm posterior and anterior to the cylinder or colpostat should be calculated. (See Appendix VI)

6.11 **Compliance Criteria for Brachytherapy (8/7/2013)**

*Per Protocol:* See Section 6.10

*Variation Acceptable:* Brachytherapy starting greater than 7 days from the completion of external beam RT.

*Deviation Unacceptable:* Brachytherapy starting after 14 days from the completion of external beam RT.

6.12 **R.T. Quality Assurance Reviews**

The Radiation Oncology Co-Chairs, Ann Klopp, M.D., and Anamaria Yeung, M.D., will perform a rapid review remotely for the first cases performed by each Institution on the standard and IMRT arm. The contours will be reviewed for IMRT cases and JPEG DRR’s with the field shaping will be reviewed for patients receiving standard treatment. The remaining cases will be reviewed on an ongoing basis. Study chairs will not review cases from their own institutions; they will be reviewed by the other RT study chair.

6.13 **Radiation Therapy Adverse Events**

All toxicities will be recorded on data collection forms.

6.13.1 Side effects expected from radiation therapy include:

- Fatigue, diarrhea, rectal irritation, urinary frequency and dysuria, loss of pubic hair, darkening of skin in the treatment portal, and low blood counts.

6.13.2 Long-term

6.13.2.1 *Common long-term effects include:*

- Vaginal narrowing and shortening and dyspareunia.

6.13.2.2 *Uncommon long-term side effects include:*

- Rectal bleeding, loose stool, rectal ulcer, dysuria, urinary frequency, hematuria, and vaginal vault necrosis.

6.13.2.3 *Rare long-term side effects include:*

- Bowel obstruction, urethral obstruction, and vesicovaginal or rectovaginal fistula.

6.14 **Radiation Treatment Interruptions**

6.14.1 Interruptions in radiotherapy may be necessitated by uncontrolled diarrhea, or other acute complications. The reason for and the length of any such interruption must be documented. If the sum total of such interruptions exceeds five normally scheduled treatment days, the treatment may be considered in major violation of protocol. Radiation therapy will be continued without interruption if at all possible.

6.14.2 If radiation therapy is held, then chemotherapy will also be held. (If chemotherapy is held for toxicity, the missed treatments are not completed after RT ends. Chemotherapy stops at the completion of RT.)

6.14.2.1 If chemotherapy is held, radiation therapy will continue. (If chemotherapy is held for toxicity the missed treatments are not completed after RT ends. Chemotherapy stops at the completion of RT.)
6.15 Radiation Therapy Adverse Event Reporting
See AE Reporting Requirements in Section 7.7

7.0 DRUG THERAPY (3/16/15)
Protocol treatment (chemotherapy) must begin within 63 days (9 weeks) after surgery.

Weekly cisplatin may be delivered for patients at physician discretion based on criteria delineated in Section 3.0.

7.1 Cisplatin (Platinol®) Agent Information (8/7/2013)
Consult the package insert for detailed pharmacologic and safety information.

7.1.1 Formulation: Cisplatin is available as a dry powder supplied in 10 mg and 50 mg vials and in aqueous solution in 50 mg and 100 mg vials with 100 mg mannitol and 90 mg sodium chloride.

7.1.2 Preparation: The 10 mg and 50 mg vials should be reconstituted with 10 ml or 50 ml sterile water for injection USP, respectively. Each ml of the resulting solution will contain 1 mg of cisplatin. Reconstitution (as recommended) results in a clear, colorless solution.
NOTE: Aluminum reacts with cisplatin, causing precipitation formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of cisplatin.

7.1.3 Storage: Unopened vials of dry powder are stable for the lot life indicated on the package when stored at room temperature. The aqueous solution should be stored at room temperature and protected from light. The reconstituted solution is stable for 20 hours at room temperature. Unopened containers should not be refrigerated; and should be stored at 15-20°C; and should be protected from light.
NOTE: Once reconstituted, the solution should be kept at room temperature. If the reconstituted solution is refrigerated, a precipitate will form.

7.1.4 Adverse Effects: The following events are expected with the administration of cisplatin:
7.1.4.1 Nephrotoxicity: Dose-related and cumulative renal insufficiency is one of the major dose-limiting toxicity of cisplatin. Renal toxicity has been noted in 28-36% of patients treated with a single dose of 50 mg/m². It is first noted in the second week after a dose and is manifested as elevated BUN, serum creatinine, and serum uric acid, or as a decrease in creatinine clearance. Because renal toxicity becomes more prolonged and severe with repeated courses of cisplatin, renal function must return to normal before another dose can be given. Severe renal toxicity might be minimized by induction of diuresis before, during and after treatment.

7.1.4.2 Ototoxicity: Observed in up to 31% of patients treated with a single dose of cisplatin 50 mg/m2. It is manifested by tinnitus and/or hearing loss in the high frequency range. Deafness has been rarely reported.

7.1.4.3 Hematologic Toxicity: Myelosuppression occurs in 25-30% of patients treated with cisplatin. Nadirs in circulating platelets and leukocytes occur between Days 18 and 23 with most patients recovering by Day 39. Thrombocytopenia, anemia, neutropenia, and fever are also possible adverse events.

7.1.4.4 Gastrointestinal Toxicity: Marked nausea and vomiting occur in almost all patients treated with cisplatin. Diarrhea and anorexia have also been reported.

7.1.4.5 Neurotoxicity: Usually characterized by peripheral neuropathies, has been reported. Neuropathy usually occurs after prolonged therapy (4 to 7 months); however, symptoms have been reported after a single dose. Muscle cramps, loss of taste, seizures, autonomic neuropathy, dorsal column myelopathy, and Lhermitte’s sign have also been reported.

7.1.5 Supply: Commercially available.
7.1.6 Treatment

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Route</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>40 mg/m² (max total weekly dose = 70 mg)</td>
<td>IV</td>
<td>Infuse over 1 hour once weekly (on Monday or Tuesday) X 5 weeks</td>
</tr>
</tbody>
</table>

7.2 Treatment with Cisplatin (3/16/15)

7.2.1 Dose definition- Cisplatin should be delivered at 40 mg/m² for patients whom the physician elects to deliver Cisplatin 40 mg/m² IV over 1 hour once weekly starting on a Monday or a Tuesday for 5 weeks concurrently with IMRT. Dose rounding is permitted as long as the final dose is within 5% of the calculated dose. Patients will receive antiemetic premedication as per institutional standards but should include: 5HT3 antagonist plus steroid at time of administration. Patient should be given antiemetics for prevention (scheduled) and management (breakthrough) nausea and vomiting as per institutional standards.

7.2.2 Technique of administration — Prehydration with ½ NS or NS 500 mL with magnesium sulfate 16 mEq IV over 1 hour followed by Cisplatin is given over 60 minutes in 500 mL of NS followed by NS 500 mL with magnesium sulfate 16 mEq and potassium chloride 10 mEq IV over 2 hours. Modification of the fluid regimen for specific reasons and the anti-emetic regimen for this combination is to be determined by the treating physician, and documented in patients' treatment record. The maximum total dose of cisplatin is 70 mg. Close attention should be paid to potassium and magnesium levels and additional supplementation given when necessary. Cisplatin will be delivered weekly on Monday or Tuesday for 5 weeks.

7.2.3 Duration of treatment — Cisplatin will be delivered weekly on Monday or Tuesday for 5 weeks. If RT is held, chemotherapy should be held for that week. If chemotherapy is held due to hematologic toxicity or other chemotherapy related toxicity, radiation therapy should be continued. When toxicity resolves, chemotherapy can be restarted on the following week. Missed cycles do not need to be made up.

7.3 Dose Modifications

7.3.1 Based on blood work performed prior to each cycle

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Parameters</th>
<th>Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine clearance</td>
<td>* ≤ 50 mL/min but &gt; 20 mL/min, ** &lt; 20 mL/min</td>
<td>* Reduce cisplatin dose by 50% (20 mg/m²)</td>
</tr>
<tr>
<td>ANC</td>
<td>&lt; 1500 mm³</td>
<td>Hold for that week and use neupogen x3 days, repeat CBC diff. next week, if above parameter treat with 40 mg/m², otherwise hold, use neupogen x3 and repeat CBC diff. next week, if still not within parameters discontinue chemotherapy.</td>
</tr>
</tbody>
</table>
Toxicity Parameters Modification

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Parameters</th>
<th>Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets</td>
<td>&lt; 100,000 mm$^3$</td>
<td>Hold for that week, repeat CBC diff. next week; if above parameter treat 40 mg/m$^2$, otherwise hold and repeat CBC diff. and platelets next week, if still not within parameters discontinue chemotherapy.</td>
</tr>
<tr>
<td>Platinum-related neuropathy</td>
<td>≥ grade 2</td>
<td>Discontinue chemotherapy</td>
</tr>
<tr>
<td>Ototoxicity</td>
<td>≥ grade 2</td>
<td>Discontinue chemotherapy</td>
</tr>
</tbody>
</table>

**A creatinine clearance must be obtained as per the Cockroft-Gault formula: (140-age) (kg actual wt) / 72 x (serum creatinine) x 0.85 or nomogram calculation (valid only if serum creatinine is not changing rapidly), and the dose modified as indicated. Note: if patient has BMI > 30, an adjusted body weight should be used here. SrCr lower limit of 0.8 mg/dL. Chemotherapy can be held up to 2 weeks, if longer, then chemotherapy should be stopped.**

7.3.2 If chemotherapy is held, radiation therapy will continue. (If chemotherapy is held for toxicity the missed treatments are not completed after RT ends. Chemotherapy stops at the completion of RT.)

7.3.3 If radiation therapy is held, then chemotherapy will also be held.

7.4 Adjuvant Chemotherapy After Completion of Radiation Therapy

Adjuvant chemotherapy: Patients may receive additional chemotherapy after pelvic radiation based on physician preference. This is not a component of the protocol treatment but should be reported when delivered. Three to four cycles of carboplatin/paclitaxel is recommended.

7.5 Criteria for Removal From Protocol Treatment (8/4/14)

- Progression of disease;
- Unacceptable toxicity to the patient (at the discretion of the treating physician) — Reasons for removal must be clearly documented on the appropriate case report form/flowsheet, and NRG Oncology data management must be notified;
- A delay in chemotherapy > 2 weeks; discontinue chemotherapy;
- The patient may withdraw from the study at any time for any reason. The institution must notify Data Management about this in writing, and follow the applicable guidelines.

7.6 Modality Review (8/4/14)

The Medical Oncology Co-Chair, Shannon N. Westin, M.D., M.P.H. will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: Per Protocol/Acceptable Variation, Not Per Protocol, and Not Evaluable. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

The Medical Oncology Co-Chair, Shannon N. Westin, M.D., M.P.H. will perform a Quality Assurance Review after complete data for the first 25 cases enrolled has been received at IROC Philadelphia RT. Dr. Westin will perform the next review after complete data for the next 25 cases enrolled has been received at IROC Philadelphia RT. The remaining cases will be reviewed in groups of 50 with the final cases reviewed within 3 months after this study has reached the target...
accrual or as soon as complete data for all cases enrolled has been received at IROC Philadelphia RT, whichever occurs first.

7.7 **Adverse Events (8/4/14)**

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for adverse event (AE) reporting. The CTCAE version 4.0 is located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

Adverse events (AEs) that meet expedited reporting criteria defined in the table(s) below will be reported via the CTEP-AERS (CTEP Adverse Event Reporting System) application accessed via the CTEP web site (https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613).

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to 1-800-227-5463, ext. 4189, for instances when Internet fails. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

7.7.1 **Adverse Events (AEs)**

**Definition of an AE**: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. February 29, 2012 http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm].

7.7.2 **Serious Adverse Events (SAEs)** — Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table in Section 7.8 will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table in Section 7.8. **Contact the CTEP-AERS Help Desk if assistance is required.**

**Definition of an SAE**: Any adverse drug event (experience) occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.7.3 **Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)**

AML or MDS that is diagnosed as a secondary malignancy during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the CTEP-AERS system within 30 days of AML/MDS diagnosis.

**Secondary Malignancy**

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

**Second Malignancy**
A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

### 7.8 CTEP-AERS Expedited Reporting Requirements (8/4/14)

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the Adverse Event Expedited Reporting System, accessed via the CTEP web site, [https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613](https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613). Submitting a report via CTEP-AERS serves as notification to NRG Oncology and satisfies requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to 1-800-227-5463, ext. 4189, for instances when Internet fails. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

- **CTEP-AERS-24 Hour Notification** requires that a CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a CTEP-AERS 5 Calendar Day Report. Serious adverse events that require 24 hour CTEP-AERS notification are defined in the expedited reporting table below.

- Supporting source document is not mandatory. However, if the CTEP-AERS report indicates in the Additional Information section that source documentation will be provided, then it is expected. If supporting source documentation accompanies an CTEP-AERS report, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation to the NRG Oncology dedicated SAE FAX, 215-717-0990.

- A serious adverse event that meets expedited reporting criteria outlined in the following table but is assessed by the CTEP-AERS System as “expedited reporting NOT required” must still be reported to fulfill NRG Oncology safety reporting obligations. Sites must bypass the “NOT Required” assessment; the CTEP-AERS System allows submission of all reports regardless of the results of the assessment.
Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur within 30 Days of the Last Administration of the Protocol Treatment

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

**ALL SERIOUS** adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<thead>
<tr>
<th>Hospitalization</th>
<th>Grade 1 Timeframes</th>
<th>Grade 2 Timeframes</th>
<th>Grade 3 Timeframes</th>
<th>Grade 4 &amp; 5 Timeframes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resulting in Hospitalization ≥ 24 hrs</td>
<td>Not required</td>
<td>10 Calendar Days</td>
<td>24-Hour 5 Calendar Days</td>
<td></td>
</tr>
<tr>
<td>Not resulting in Hospitalization ≥ 24 hrs</td>
<td>Not required</td>
<td>10 Calendar Days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NOTE**: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

**Expedited AE reporting timelines are defined as:**

- “24-Hour; 5 Calendar Days” - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- “10 Calendar Days” - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

1Serious adverse events that occur more than 30 days after the last administration of the commercially available agent and have an attribution of possible, probable, or definite require reporting as follows:

**Expedited 24-hour notification followed by complete report within 5 calendar days for:**
- All Grade 4, and Grade 5 AEs

**Expedited 10 calendar day reports for:**
- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

2 For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote “1” above applies after this reporting period.

Effective Date: May 5, 2011

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials: None
8.0 **SURGERY**

All patients will undergo surgery for their cancer prior to enrolling in this protocol.

9.0 **OTHER THERAPY (8/7/2013)**

9.1 **Permitted Supportive Therapy**

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site’s source documents as concomitant medication.

9.1.1 Patients may receive antidiarrheals as needed. Imodium is recommended as needed. If diarrhea persists, lomotil is recommended.

9.1.2 Patients may receive antiemetics as needed

9.1.3 Patients may receive analgesics as needed

9.1.4 Patients may receive erythropoietin (Aranesp® [darbepoetin alfa], Procrit® [epoetin alfa]) for management of anemia AFTER documentation of hemoglobin less than 10 g/dl

9.1.5 Caution should be exercised when using anticonvulsants during cisplatin therapy as the plasma levels of anticonvulsants may become subtherapeutic

9.2 **Non-permitted Supportive Therapy**

9.2.1 Patients will NOT receive growth factors (filgrastim [G-CSF], sargramostim [GM-CSF], pegfilgrastim [Neulasta]) UNLESS they experience neutropenic complications

9.2.2 Patients will NOT receive prophylactic thrombopoietic agents. If they experience thrombocytopenia, treatment should be initiated following the judgment of the treating physician

9.2.3 Patients may NOT receive amifostine or other protective reagents

10.0 **TISSUE/SPECIMEN SUBMISSION**

**NOTE:** Patients must be offered the opportunity to participate in the tissue/specimen submission component of the protocol. If the patient consents to participate in this component of the study, the site is required to submit the patient’s specimens as specified below.

Sites are not permitted to delete the tissue/specimen submission component from the protocol or from the sample consent (Appendix I).

10.1 **Tissue/Specimen Submission**

The NRG Oncology Biospecimen Bank at the University of California San Francisco acquires and maintains high quality specimens from NRG Oncology trials. Tissue from each block is preserved through careful block storage and processing. NRG Oncology encourages participants in protocol studies to consent to the banking of their tissue. NRG Oncology Biospecimen Bank–San Francisco provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions.

In this study, tissue will be submitted to the NRG Oncology Biospecimen Bank for the purpose of tissue banking, (recommended) and blood will be submitted for translational research (recommended). The translational research component will require that blood samples are submitted prior to treatment and at weeks three and five.

For patients who have consented to participate in the tissue/blood component of the study (See Appendix I).

10.2 **Specimen Collection for Tissue Banking (Strongly Recommended) (4/29/14)**

For patients who have consented to participate in the tissue/blood component of the study (See Appendix I and specimen collection summary table in Section 10.5).

The following must be provided in order for the case to be evaluable for the Biospecimen Bank:

10.2.1 One H&E stained slide (slide can be a duplicate cut stained H&E; it does not have to be the diagnostic slide)
10.2.2 A corresponding paraffin-embedded tissue block of the tumor (the block must match the H&E being submitted) or one 5 mm diameter core of tumor tissue punched from the tissue block containing the tumor with a punch tool and submitted in a plastic tube labeled with the surgical pathology number. For sites unable to submit a block or punch, 10-15 unstained slides from the same block as H&E is an acceptable alternative. **Note:** A kit with the punch, tube, and instructions can be obtained free of charge from the Biospecimen Bank. Block or core must be clearly labeled with the pathology identification number that corresponds to the Pathology Report. **Note:** If site cannot send a 5mm core, then two 2mm cores is an acceptable alternative.

- The submitted material must be from malignant tumor, not necrotic or fibrotic tissue. If the submitted material is reviewed and is not tumor, the site may be assessed a protocol violation.

10.2.3 A Pathology Report documenting that the submitted block or core contains tumor. The report must include the protocol number and patient’s case number. The patient’s name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

10.2.4 A Specimen Transmittal (ST) Form clearly stating that tissue is being submitted for the NRG Oncology Biospecimen Bank; if for translational research, this should be stated on the form. The form must include the NRG Oncology protocol number and patient’s case number.

10.3 **Translational Research** (Highly Recommended) (8/7/2013)

10.3.1 **Rationale**

10.3.1.1 **Approach to develop molecular predictors of radiation toxicity**

A secondary aim of the study will be to identify molecular predictors of radiation toxicity. Molecular predictors of toxicity have the potential to guide treatment decisions in the future, such as identifying patients who may benefit from IMRT or other approaches to reduce the volume of normal tissue irradiated.

Response factors, such as circulating cytokines and miRNAs which may change in response to treatment, as well as genomic predictors, such as single nucleotide polymorphisms, will be investigated. To accomplish this, serum from patients under treatment and DNA samples will be collected from all patients enrolled in this study.

This study will provide the high quality data needed for investigating the predictive value of these biomarkers. In addition to the careful documentation of toxicity, we will have dose volume data for each of the organs at risk. Dose volume effects can confound the association of biomarkers with toxicity, since patients treated to larger volumes of normal tissue may have greater changes in circulating response factors. The incorporation of dose volume effects has been shown to improve the statistical power to develop biomarkers of toxicity (Bentzen 2010).

A number of candidate molecular predictors of radiation toxicity have been identified, including inflammatory cytokines, such as IL-6 and single nucleotide genetic polymorphisms, in genes such as TGF-β (Alsner 2008). However, a recent study failed to validate the predictive value of genetic factors in predicting toxicity following radiation (Barnett 2012). This analysis highlights the complexities of this type of analysis and the need for high quality data such as this study will provide.

Peripheral blood monocytes (PBM) may be used to isolate DNA which can be used to identify genetic changes which underlying inherited susceptibility to develop radiation toxicity. To accomplish this, DNA will be isolated from peripheral blood samples. DNA from PBM can subjected to single nucleotide polymorphisms (SNPs) analysis. SNPs are genomic changes which are within a gene or linked to a gene of interest which can be markers of an individual’s underlying susceptibility to developing toxicity. Candidate SNPs can be evaluated in genes with known roles in mediating radiation toxicity, such as TGF-β, or a genome-wide association study (GWAS) can be performed with samples to identify novel SNPs.

To profile response markers, serum will also be collected at baseline as well as week 3 and 5 to evaluate circulating proteins and RNA of interest which may be upregulated following
radiation. Cytokine expression will be tested utilizing a Luminex assay which can evaluate a set of cytokines of interest, such as those with known roles in mediating an inflammatory response. In addition, serum will be used to measure expression of circulating miRNAs. miRNAs are small non-coding RNAs which are global regulators of gene expression. Recently, these small RNA molecules have found to be misexpressed in the circulating blood of patients with cancer. These circulating miRNAs thus have the potential to serve as novel biomarkers for cancer outcome or radiation toxicity. For example, miRNA-34, is associated with radiation toxicity in mouse models. (Liu 2011)

10.3.1.2 Specific Hypothesis
Molecular predictors of radiation toxicity in combination with dose-volume parameters can identify patients at high risk for toxicity. These patients may derive particular benefit from IMRT.

In addition to collecting samples for toxicity predictors, tumor specimens can also be sent to the NRG Oncology tumor bank for use in future correlative studies

10.3.2 Specimen Submission
See Section 10.6 for the address information for sending specimens.

10.3.3 Specimen Collection for Translational Research
For patients who have consented to participate in the tissue/blood component of the study (See Appendix I and specimen collection summary table in Section 10.4).

To evaluate genetic and response markers, blood will be collected from patients at three different time points. Prior to treatment blood will be collected for DNA, serum and plasma. Samples will be collected, stored and shipped as described below. At weeks three and five, additional samples will be collected for serum and plasma as described below.

The following materials must be provided to the NRG Oncology Biospecimen Bank: A Specimen Transmittal (ST) Form documenting the date of collection of the biospecimen, the NRG Oncology protocol number, the patient’s case number, time point of study, and method of storage, (for example, stored at -80°C), must be included.

10.4 Specimen Collection Summary for Tissue Banking and Translational Research (Highly Recommended) (9/16/2013)

<table>
<thead>
<tr>
<th>Specimens for Tissue Banking (Highly Recommended)</th>
<th>Collected when:</th>
<th>Submitted as:</th>
<th>Shipped:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specimens taken from patient:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Representative H&amp;E stained slides of the primary tumor</td>
<td>Pre-treatment</td>
<td>H&amp;E stained slide</td>
<td>Slide shipped ambient</td>
</tr>
<tr>
<td>A corresponding paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or one 5 mm diameter core of tissue, punched from the tissue block with a punch tool. <strong>NOTE:</strong> If site cannot send a 5mm core, then two 2mm cores is an acceptable alternative. Unstained slides are ONLY permitted if sites are unable to provide the block or punches</td>
<td>Pre-treatment</td>
<td>Paraffin-embedded tissue block or punch biopsy from same block as H&amp;E. For sites unable to submit a block or punch, 10-15 unstained slides from same block as H&amp;E is an acceptable alternative.</td>
<td>Block or punch(es) shipped ambient. Use of cold packs are encouraged during warm weather months.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specimens for Translational Research (Highly Recommended)</th>
<th>Collected when:</th>
<th>Submitted as:</th>
<th>Shipped:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specimens taken from patient:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SERUM: 5-10 mL of whole blood in 1 red-top tube and centrifuge</td>
<td>(1) Pre-treatment (2) Week 3 of radiation</td>
<td>Frozen serum samples containing 0.5 mL per aliquot in 1 mL</td>
<td>Serum sent frozen on dry ice via overnight carrier</td>
</tr>
</tbody>
</table>
### 10.5 Storage Conditions

Store frozen specimens at -80°C (-70°C to -90°C) until ready to ship. If a -80°C freezer is not available:

- Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday).

**OR:**

- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

**OR:**

- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

### 10.6 Submit materials for Tissue Banking and Translational Research as follows:

**U. S. Postal Service Mailing Address:** For Non-frozen /Non-Urgent Specimens Only

NRG Oncology Biospecimen Bank-San Francisco

University of California San Francisco

Campus Box 1800

2340 Sutter Street, Room S341

San Francisco, CA 94143-1800

**Courier Address (FedEx, UPS, etc.):** For Frozen/Trackable Specimens

NRG Oncology Biospecimen Bank-San Francisco

University of California San Francisco

2340 Sutter Street, Room S341

San Francisco, CA 94115

Questions: 415-476-7864/FAX 415-476-5271; RTOG@ucsf.edu

### 10.7 Reimbursement (3/16/15)

NCI funds for reimbursement for protocol-specified biospecimen materials will be distributed per the requirements/methods specified by the National Clinical Trials Network (NCTN). This information will be made available with the other registration materials in the Oncology Patient Enrollment Network (OPEN) portal system.

### 10.8 Confidentiality/Storage


#### 10.8.1 Upon receipt, the specimen is labeled with the NRG Oncology protocol number and the patient’s case number only. The NRG Oncology Biospecimen Bank database only includes the

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cryovials (five to ten)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(3) Week 5 of radiation treatment</td>
<td></td>
</tr>
<tr>
<td><strong>PLASMA:</strong> 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/ lavender top) and centrifuge</td>
<td>(1) Pre-treatment</td>
</tr>
<tr>
<td></td>
<td>(2) Week 3 of radiation treatment</td>
</tr>
<tr>
<td></td>
<td>(3) Week 5 of radiation treatment</td>
</tr>
<tr>
<td></td>
<td>Frozen plasma samples containing <strong>0.5 mL</strong> per aliquot in 1 mL cryovials (five to ten)</td>
</tr>
<tr>
<td></td>
<td>Plasma sent frozen on dry ice via overnight carrier</td>
</tr>
<tr>
<td><strong>Whole blood for DNA:</strong> 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/ lavender top) and mix</td>
<td>Pre-treatment <strong>Note:</strong> If site missed this whole blood collection for DNA, they may collect at any follow up visit but must note this on the ST form</td>
</tr>
<tr>
<td></td>
<td>Frozen whole blood samples containing <strong>1 mL</strong> per aliquot in 1 mL cryovials (three to five)</td>
</tr>
<tr>
<td></td>
<td>Whole blood sent frozen on dry ice via overnight carrier</td>
</tr>
</tbody>
</table>
following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.8.2 Specimens for tissue banking will be stored for an indefinite period of time. Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters: See Appendix II for a summary of patient assessments and timeframes.

11.2 Evaluation During Treatment (3/16/15)

11.2.1 For patients receiving chemotherapy, CBC w/ diff & ANC will be drawn prior to each chemo cycle.

11.2.2 For patients receiving chemotherapy, BUN, creatinine, creatinine clearance, magnesium, electrolytes, AST, ALT, alkaline phosphatase, total bilirubin will be obtained prior to each chemo cycle.

11.2.3 For patients not receiving chemotherapy, a CBC with diff will be obtained with 7 days (+/-7 days) of completing radiation.

11.3 Evaluation Following Treatment (3/16/15)

11.3.1 Chest x-ray will be performed every 6 months (+/- 30 days) for the first two years and then annually (+/- 30 days) for eight years (for a total of ten years) during follow-up unless there is a reason to perform it sooner. Audiogram is highly recommended at 4-6 weeks after radiation for patients receiving chemotherapy.

11.3.2 Chest CT, abdomen/pelvic CT, MRI or PET-CT will be performed at years 1 and 3 from the start of treatment (+/- 30 days) during follow-up unless there is a reason to perform it sooner.

11.3.3 A pap smear will be performed for patients with cervical cancer annually for years 3-10 from the start of RT. A pap smear is not required at progression/relapse.

11.4 Health Related Quality of Life (HRQOL) (10/4/12)

The bowel and urinary domains of the EPIC will be collected at 6 time points: baseline (pretreatment), after 3 weeks (13-15 treatments), and 5 weeks (23-25 treatments) of radiation, and 4-6 weeks after completion of radiation treatment. To evaluate long term toxicity, toxicity will be assessed at 1 year and 3 years from the start of radiation treatment. The FACT-Cx, PRO-CTCAE, and EQ-5D will be collected at 5 times points: baseline (pretreatment), 5 weeks (23-25 fractions) of radiation, 4-6 weeks after completion of radiation treatment and 1 and 3 years from the start of radiation treatment. Please see Appendix II for the times of collection for all toxicity assessments.

Women who experience treatment delays: The time points are expressed relative to the beginning and ending of RT (after 13-15 fractions of RT, after 23-25 fractions of RT, 4-6 weeks after last fraction of RT, 1 year from the start of RT and 3 years from the start of RT. Women who experience treatment termination should be given the QOL assessments at the specified times.

11.4.1 The Expanded Prostate Cancer Index Composite (EPIC): The EPIC is a comprehensive instrument designed to evaluate bowel and urinary function and bother during and following radiation treatment of the pelvis. There are a total of 26 questions that cover both domains. The items within the bowel and urinary domains do not mention the word “prostate.”

NOTE: As stated on the NRG Oncology/RTOG website, EPIC is in the public domain and available for use free of charge for NRG Oncology protocols. It is available and validated in Spanish.

11.4.2 The Functional Assessment of Cancer Therapy (FACT-G, Version 4): FACT-G is a brief, validated, sensitive 27-item measure for evaluating QOL in patients receiving treatment for cancer. In addition to a total QOL score, subscale scores for physical, functional, social and emotional well-being are produced. Utilization of this questionnaire will allow for a determination of the extent to which the addition of treatment affects overall QOL as well as domain specific QOL (for example, functional well-being).
11.4.2.1 The Cervix Subscale of the FACT consists of 15 questions developed from interviews with patients and clinicians involved with cervical cancer that are used in addition to the 27 items from the FACT-G. The FACT-G with Cervix Subscale (FACT-Cx) has been widely used in GOG trials to assess effect of treatment on overall QOL.

**NOTE:** The FACT-G and subscales are owned and copyrighted by Dave Cella, Ph.D. but are available for use free of charge following registration for permission at facit.org. The FACT-Cx has been validated in Spanish.

11.4.3 **PRO-CTCAE:** The PRO-CTCAE instrument will be utilized as an additional assessment of GI toxicity. Patients will be asked 5 questions to assess 3 symptoms, namely diarrhea, abdominal pain and bowel control. In addition, patients will be asked about the frequency with which they have required anti-diarrhea medications.

11.4.4 **EQ-5D:** Health utilities will be evaluated to measure quality adjusted life years (QALY) with the EQ-5D. The EQ-5D is a short validated instrument with only 5 questions of 3 responses each in addition to a visual analog scale with a scale from 0-100. RTOG has utilized the EQ-5D in a number of trials to measure patient utilities in an attempt to calculate quality-adjusted survival (QALY). A cost-utility analysis will be able to be performed by combining cost of care and QALY.

**NOTE:** The instruments should be administered by the site research nurse or CRA. Patients should be told they will be asked to complete the same questionnaires at specific times. The site research nurse or CRA is encouraged to be sensitive to each patient's demeanor. If patients appear particularly uncomfortable answering a question, they will be informed that they can skip that question. Otherwise, patients will be encouraged to complete every item and to circle the response that is most applicable. The site research nurse or CRA may provide clarification but should not rephrase questions or suggest answers. The site research nurse or CRA may give patients a short break if the patient appears fatigued or otherwise in need of a few minutes break.

**NOTE:** Respondent burden for completion of the FACT is typically minimal given that the questionnaire is written at the 4th grade-reading level, and is specifically formatted for ease of self-administration (Webster 2003). Average time to complete the 27-item FACT-G is 5–10 minutes, and even less for the stand-alone scales and symptom indices. As a rule of thumb, it takes 2–3 minutes to complete 10 questions, so administration length can be estimated after one selects the subscales to be combined in one's assessment plan.

There are a total of 74 QOL items (EPIC, FACT-Cx, PRO-CTCAE, anti-diarrhea medication use); using a conservative estimate of 3 minutes/10 questions suggests a total time to complete these items of approximately 20 minutes.

11.5 **Measurement/Definition of Progression/Recurrence**

Local recurrence is defined as a disease in the radiation treatment field. This can include a local vaginal recurrence or nodal disease within the field. Para-aortic recurrence is defined as new lymphadenopathy in the para-aortic distribution. Distant metastasis is defined as involvement of another organ or peritoneal disease. Evidence of distant metastases or new lymphadenopathy on surveillance imaging should be biopsied if possible to document disease recurrence.

11.6 **Criteria for Discontinuation of Protocol Treatment**

11.6.1 Progression of disease

11.6.2 Adverse events that require discontinuation of protocol treatment. The decision to proceed with treatment or discontinue treatment will be left to the discretion of the treating physician. If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.
Data should be submitted to:

NRG Oncology*
1818 Market Street, Suite 1720
Philadelphia, PA 19103

*If a data form is available for web entry, it must be submitted electronically.

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

### 12.1 Summary of Data Submission

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of registration</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>EPIC bowel and urinary domain (FA)</td>
<td>At week 3 of radiation therapy</td>
</tr>
<tr>
<td>FACT-Cx (QL)</td>
<td>If there are no AEs to report submit a communication memo requesting the form to be deleted</td>
</tr>
<tr>
<td>EQ-5D (QF)</td>
<td></td>
</tr>
<tr>
<td>PRO-CTCAE items for GI toxicity (PQ)</td>
<td></td>
</tr>
<tr>
<td>Adverse Events (AE)</td>
<td></td>
</tr>
<tr>
<td>EPIC bowel and urinary domain (FA)</td>
<td></td>
</tr>
<tr>
<td>Treatment Form (TF)</td>
<td>5 weeks (21-25 fractions) after the start of radiation therapy. If the patient has a treatment break, the forms are to be submitted at the end of radiation therapy.</td>
</tr>
<tr>
<td>EPIC bowel and urinary domain (FA)</td>
<td>If the patient comes off protocol treatment, the forms are to be submitted 5 weeks after the start of radiation therapy.</td>
</tr>
<tr>
<td>FACT-Cx (QL)</td>
<td></td>
</tr>
<tr>
<td>EQ-5D (QF)</td>
<td></td>
</tr>
<tr>
<td>PRO-CTCAE items for GI toxicity (PQ)</td>
<td></td>
</tr>
<tr>
<td>Follow-up Form (F1)</td>
<td>4-6 weeks post RT, then every 6 months from the start of RT for the first 2 years, then annually for the next 8 years for a total of 10 years. Also at progression/relapse and at death</td>
</tr>
</tbody>
</table>
EPIC bowel and urinary domain (FA) 4-6 weeks post RT and at 1 and 3 years from the start of RT

FACT-Cx (QL)
EQ-5D (QF)
PRO-CTCAE items for GI toxicity (PQ)

## 12.2 Summary of Dosimetry Digital Data Submission (Submit to TRIAD; see Section 5.3) (3/16/15)

NOTE: ALL DIGITAL RT DATA REQUIRED IN DICOM FORMAT VIA TRIAD (SEE SECTION 5.3)
ALL REQUIRED STRUCTURES MUST BE LABELED PER DICOM STANDARD NAME AS LISTED IN SECTION 6.7.2.6

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preliminary Dosimetry Information</td>
<td></td>
</tr>
<tr>
<td><strong>Digital data submission for IMRT includes the following:</strong></td>
<td></td>
</tr>
<tr>
<td>• CT dataset with contours for all critical normal structures, GTV, CTV, and PTVs</td>
<td>Within 1 week of start of RT</td>
</tr>
<tr>
<td>• Digital beam geometry for initial beam sets</td>
<td></td>
</tr>
<tr>
<td>• Doses for all concurrently treated beams</td>
<td></td>
</tr>
<tr>
<td>• Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan</td>
<td></td>
</tr>
<tr>
<td><strong>Digital data submission for standard treatment includes the following:</strong></td>
<td></td>
</tr>
<tr>
<td>• CT dataset with dose</td>
<td></td>
</tr>
<tr>
<td>• Digitally Reconstructed Radiographs (DRRs) for all treatment fields as a “screen capture” with field outlines sent as jpg files.</td>
<td></td>
</tr>
<tr>
<td>• Completed Data sheet (DV) available on the NRG Oncology/RTOG Website submitted via TRIAD. The “RTOG 1203 Datasheet” is available in the Forms section of the of the NRG Oncology/RTOG web site: <a href="http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1203&amp;mode=html&amp;ptid=383">http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1203&amp;mode=html&amp;ptid=383</a> Submit via TRIAD with the digital data listed above.</td>
<td></td>
</tr>
<tr>
<td><strong>Note:</strong> All simulation and portal films and/or digital film images will be kept by the institution and only submitted if requested.</td>
<td></td>
</tr>
<tr>
<td>Final Dosimetry Information</td>
<td>Within 1 week of RT end</td>
</tr>
<tr>
<td>Radiotherapy Form (T1) [copy to HQ]</td>
<td></td>
</tr>
<tr>
<td>Daily Treatment Record (T5) [copy to HQ]</td>
<td></td>
</tr>
<tr>
<td>Modified digital patient data as required through consultation with Image-Guided Therapy QA Center</td>
<td></td>
</tr>
</tbody>
</table>
12.2.1 TRIAD
See Section 5.3 for account access and installation instructions.

12.3 Summary of Brachytherapy Data Submission (Submit to IROC Houston) (8/4/14)

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final Dosimetry Information</td>
<td>Within 1 week of RT end</td>
</tr>
<tr>
<td>Daily Treatment Record [T5] [copy to HQ and IROC Houston]</td>
<td></td>
</tr>
<tr>
<td>Treatment Plan (source specifications, spacing relative to the applicator, size of applicator and dosimetry calculation for all points, isodose distributions)</td>
<td></td>
</tr>
<tr>
<td>Treatment Plan Report (include source activity, dwell positions, dwell times)</td>
<td></td>
</tr>
<tr>
<td>Verification Films (include magnification factors and points of dose calculation should be marked, as well as for bladder and rectum if calculated)</td>
<td></td>
</tr>
</tbody>
</table>

Hardcopies should be sent to:

IROC Houston  
ATTN: Dosimetry  
8060 El Rio Street  
Houston, TX 77054  
713-745-8989  
FAX 713-794-1364  
Email: irochouston@mdanderson.org

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint  
Acute gastrointestinal toxicity, as measured by bowel domain of EPIC, at 5 weeks from the start of pelvic radiation

13.1.2 Secondary Endpoints
- Validation of EPIC Bowel and Urinary domains
- Toxicity, as measured by CTCAE v. 4.0
- Urinary toxicity, as measured by EPIC urinary domain
- Quality of life, as measured by the FACT-G with cervix or endometrial subscale
- Health utilities, as measured by EQ-5D
- Local-regional control
- Disease-free survival
- Overall survival
- Identification of molecular predictors of radiation toxicity and novel circulating cancer biomarkers
- Rate of secondary cancers

13.2 Sample Size Calculation (3/16/15)

13.2.1 Stratification  
There are 3 stratification factors in this study. Patients will be stratified by type of cancer (endometrial or cervical), chemotherapy (none or 5 cycles of weekly cisplatin at 40 mg/m²), and radiation dose (45 Gy or 50.4 Gy) then randomized to receive IMRT or 4-field pelvic radiation treatment.

13.2.2 Sample Size Derivation  
The primary endpoint is change in acute GI toxicity, as measured by the EPIC bowel domain, from baseline to 5 weeks after the first fraction of radiation is delivered. If a patient experiences a treatment delay, then the EPIC bowel domain will be given during the last week of treatment. It is hypothesized that patients treated with IMRT will have reduced acute GI toxicity compared to those treated with conventional WPRT. Since there is no prior data using this tool in this
patient population, an effect size of 0.4 will be used to calculate sample size. The hypothesis to be tested is:

\[
H_0 : \Delta_{IMRT} = \Delta_{2D-RT} \quad \text{vs.} \quad H_1 : \Delta_{IMRT} \neq \Delta_{2D-RT}
\]

Based on a two-sample t-test with one interim look and a two-sided alpha=0.05, a sample size of 225 is needed to achieve 85% statistical power. Assuming an attrition rate of 10%, 250 patients will be required to ensure there are at least 225 evaluable patients. Since a patient-reported outcome is the primary endpoint for this study and thus compliance is an added concern, the sample size will be increased by an additional 10%, requiring a maximum of 281 patients in order to ensure 225 evaluable patients for the primary endpoint analysis. Compliance for the bowel domain of the EPIC at baseline and 5 weeks from the start of treatment will be monitored on a monthly basis. If the compliance rate is high, accrual may be halted at 250 patients.

13.2.3 Statistical Power Information for Toxicity Secondary Endpoint

GI, urinary and hematologic toxicity will be measured by the CTCAE v.4 at 3 weeks and 5 weeks of radiation and 4-6 weeks, 1 year and 3 years after completion of radiation treatment. Specifically of interest is acute grade 2+ GI toxicity as measured by the CTCAE v.4 at 5 weeks from the start of treatment. Based on the data from Mundt et al (2003), >90% of patients receiving conventional WPRT experienced acute grade 2 toxicity. Therefore, assuming 90% of patients in the control arm experience acute grade 2+ toxicity, there will be 91% statistical power to detect a 20% relative reduction of toxicity in the IMRT arm using a 2-sample test of difference in proportions.

13.3 Patient Accrual

The proposed eligibility criteria for this study are quite broad, and are designed to include all women with endometrial and cervical cancer who require post-operative pelvic radiation. As a result, the study has the potential to accrue patients rapidly. RTOG 0418, the phase II study designed to evaluate the feasibility of IMRT treatment in a multi-institutional setting had the same eligibility criteria as this proposed study. This study enrolled 106 eligible patients (58 with endometrial cancer and 48 with cervical cancer) between March 20, 2006 and October 6, 2008. The first cohort of 58 patients with endometrial cancer was enrolled over 15 months which translates to an average of 3.8 patients per month. In addition, this study will be available on the CTSU Menu, which will further speed enrollment. It is assumed that there will be no accrual for the first 6 months while sites obtain IRB approval. After this period, accrual is estimated to be 4 patients/month for 71 months to accrue 281 patients (77 months to accrue patients). Therefore, the maximum study duration will be 77 months (approximately 6.5 years). If only 250 patients are required, the study duration will be under 6 years (69 months).

13.4 Analysis Plan (3/16/15)

13.4.1 Analysis for Primary Endpoint

The primary endpoint is change in acute gastrointestinal (GI) toxicity from baseline to 5 weeks from the start of treatment (after approximately 23-25 fractions) as measured by the bowel domain of EPIC. If a patient experiences a treatment delay, then the EPIC bowel domain will be given during the last week of treatment. The EPIC has four domains (bowel, urinary, sexual, and hormonal) that have been validated separately, which allows use of only the domains of interest. The EPIC bowel domain consists of 14 items and has a function subscale (7 items) and bother subscale (7 items). For each domain, responses form a Likert scale and multi-item scale scores are transformed linearly to a 0-100 scale, where higher scores correspond to better quality of life. At least 80% of the items in a domain or subscale of the domain must be completed in order to compute the score.

The bowel domain of EPIC is collected at baseline (pretreatment), after 3 weeks (13-15 treatments) and 5 weeks (23-25 treatments) of radiation, 4-6 weeks after completion of radiation treatment and 1 year and 3 years from the start of radiation treatment. The primary endpoint will be evaluated using the bowel domain summary change score at 5 weeks from the start of treatment and compared between both treatment arms using a t-test with a two-sided sided alpha=0.05.
Following descriptive statistics and the test of the primary endpoint, the bowel domain score at each time point will be tested using t-tests to compare the early acute GI toxicity (3 weeks from start of treatment), resolution of acute GI toxicity (4-6 weeks from end of treatment), early chronic GI toxicity (1 year), and long-term chronic GI toxicity (3 years). Patient compliance at each time point will also be assessed. A longitudinal analysis will be conducted that will focus on patterns of scores over all time points where the bowel domain of EPIC is collected. Specifically, a general linear model will be performed, allowing for adjustments due to covariates of interest such as treatment arm, disease site, radiation dose, chemotherapy and body mass index.

The distributions of bowel domain of EPIC data collection patterns over all collection points in each treatment arm will be described. To inspect the missing data mechanism for each tool, at least a graphical method will be used. A missing completely at random (MCAR) mechanism exists when missing values are randomly distributed across all observations. A missing at random (MAR) mechanism exists when values are not randomly distributed across all observations, rather than one or more sub-samples.

If the cause of missing data is MCAR, listwise deletion (complete case analysis) will be done. If the MAR assumption is supported by the data, then an imputation method such as multiple imputation will be applied to impute missing data. If the MAR assumption is not supported by the data, then adjusting for covariates (such as the baseline bowel domain of EPIC score) might reduce the conditional association between outcomes and missing values. If missing data patterns look similar when stratified by such covariate(s), then an analysis that adjusts for such covariate(s) will be conducted and an imputation method, such as multiple imputation, will be applied. If approximate conditional independence cannot be obtained with any set of covariates, then MNAR (missing not at random) must be addressed by an explicit model for the missing data mechanism and then an imputation method, such as multiple imputation, will be applied. All results from the imputed analysis using multiple imputation will be compared to the complete case analysis results to assess any potential biases.

Multiple imputation procedure provides a valid strategy for dealing with missing data sets, properly reflecting the uncertainty due to missing values and will be used for estimating the missing data. Other imputation methods will be used to assess the sensitivity of imputation. In the propensity score method, a logistic regression model will be used to generate a propensity score for each live patient indicating the probability of that observation being missing given patient baseline bowel domain of EPIC score and treatment group. The observations are then grouped based on these propensity scores, and an approximate Bayesian bootstrap imputation is applied to each group (Yuan 2002). If the missing data are determined to be MNAR, then methods such as pattern mixture models or selection models will be utilized.

If a large number (>30%) of women did not experience treatment per protocol or with an acceptable variation, a sensitivity analysis will be conducted to determine if bowel toxicity at the end of RT differs between these two subsets.

13.4.2 Interim Analysis to Monitor the Study Progress (8/4/14)
Interim reports with statistical analyses will be prepared twice a year until the initial treatment results have been presented/published. In general, the interim reports will contain the following information:

- Patient accrual rate with a projected completion date (while the study is still accruing)
- Total patients accrued
- Distributions of important pretreatment and prognostic baseline variables
- Frequencies and severity of adverse events by treatment arm.
- Compliance rates of treatment delivery

The interim reports will not contain the results from the treatment comparisons with respect to the primary endpoint, DFS, or any secondary endpoints.
This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

Phase III trials are required by NCI Cooperative Group Program Guidelines to be reviewed by a Data and Safety Monitoring Committee (DSMC). This study will be reviewed by the NRG Oncology Data Monitoring Committee (DMC) on a semi-annual basis in January and June.

Since this trial compares two different treatment methods, local-regional (LR) control is also of interest. A confidence interval will be used to determine if the LR failure rate in the IMRT arm is greater than conventional WPRT at 1 year. Specifically, the local-regional failure rate in the control arm is expected to be 5% at 1 year, using data obtained from GOG 92 and GOG 99. Table 13.1 depicts the 95% confidence intervals around the 5% rate for increasing sample sizes. These confidence limits are in agreement with preliminary data from RTOG 0418, a phase II study comparing IMRT with and without chemotherapy in a similar patient population. Each time 50 patients have at least 1 year of follow-up on the IMRT arm, the LR failure rate for these patients will be compared to the appropriate upper bound from Table 13.1. Therefore, if the IMRT arm has a LR failure rate outside of the confidence interval, then the rate of LR failures and corresponding 95% confidence interval in the conventional RT arm will be calculated and compared to that of the IMRT arm. If the rate in the IMRT arm falls outside of the 95% confidence interval in the conventional RT arm, then IMRT would be deemed unacceptable. The results from each of these looks will be presented to the NRG Oncology DMC to determine if the study can proceed as planned.

<table>
<thead>
<tr>
<th>n</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
<th>Projected Time of Analysis from Activation</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>0.0%</td>
<td>11.0%</td>
<td>43 months</td>
</tr>
<tr>
<td>100</td>
<td>0.7%</td>
<td>9.3%</td>
<td>53 months*</td>
</tr>
<tr>
<td>140</td>
<td>1.4%</td>
<td>8.6%</td>
<td>89 months</td>
</tr>
</tbody>
</table>

*Sample size based off of IMRT arm only.
*Based on the projected accrual (Section 13.3), this will be the last look prior to completing accrual.

The interim efficacy analysis will be reported to the NRG Oncology DMC when 50% of evaluable patients (113 patients) have reached the primary endpoints assessment time (5 weeks from the start of RT). The analysis guidelines are detailed in Section 13.4.1 for the primary endpoint. The significance level for the interim analysis is 0.003 using an O'Brien and Fleming boundary. The significance level for the final analysis is 0.049, preserving an overall significance level of 0.05.

13.4.3 Analysis for Secondary Endpoints

13.4.3.1 Validation of EPIC

Since the EPIC has not been validated in this patient population, a secondary endpoint is to validate the bowel and urinary domains of EPIC in women undergoing either IMRT pelvic radiation treatment or four field pelvic radiation treatments for endometrial or cervical cancer. The bowel and urinary domains of the EPIC can be administered individually since they are separate and distinct modules of the robust and comprehensive EPIC tool (Wei 2000, 2002).

To measure internal consistency reliability, Cronbach’s alpha will be calculated for the urinary and bowel subscales at each timepoint. Acceptable reliability will be considered an alpha of 0.6-0.7 while good reliability will be indicated with alpha of 0.8. The correlation between function and bother within the urinary and bowel domains will be calculated along with pairwise Spearman correlation coefficients for all of the items in the bowel and urinary domains to assess conceptual independence. The urinary and bowel domains of the EPIC will be correlated with the FACT-Cx, CTCAE (v4.0) and PRO-CTCAE to determine criterion validity at baseline, 5 weeks from the start of RT and 4-6 weeks from the end of RT, and 1 and 3 years from the start of RT. Correlations with the CTCAE v4.0 will also be done at 3 weeks from the start of treatment. Higher correlations (0.70-0.85) are expected between the bowel and urinary domains of EPIC with the relevant CTCAE v4.0 items (diarrhea for the
bowel domain and urinary frequency and urgency for the urinary domain) and GI PRO-CTCAE items. Moderate correlations (0.5-0.7) are expected when correlated with the FACT-Cx. The subscales within each domain will specifically be evaluated for internal consistency reliability using Cronbach's alpha, criterion, concurrent validity by correlating with other EPIC subscales, FACT-Cx and relevant GI PRO-CTCAE and CTCAE v4.0 items, and sensitivity to treatment differences (baseline to week five). The sensitivity of the subscales to treatment will be examined with paired t tests between baseline and week 5.

13.4.3.2 Patient-Reported Outcomes

There are 4 patient-reported outcomes (PROs) on this study. The EPIC will be collected at baseline (pretreatment), after 3 weeks (13-15 treatments) and 5 weeks (23-25 treatments) of radiation, 4-6 weeks after completion of RT, 1 year and 3 years from the start of RT. The FACT-Cx PRO-CTCAE, and EQ-5D will not be collected after 3 weeks (13-15 treatments) of radiation but will be collected at baseline (pretreatment), after 5 weeks (23-25 treatments) of radiation and 4-6 weeks after completion of RT, and 1 year and 3 years from the start of radiation treatment.

Quality of life (QOL) will be measured by the FACT-Cx which is the FACT-G with cervix subscale. The FACT-G is a validated, 27-item measure where a higher score represents higher QOL (Cella 1993). In addition to a total QOL score, subscale scores for physical, functional, social and emotional well-being are produced and of interest. The cervix subscale is a 15-item assessment developed for patients with cervix cancer but is also relevant to endometrial cancer patients. For the FACT-Cx, a higher score indicated better QOL. All items in a subscale are added together to obtain subscale totals. Certain items, identified on the FACT-G scoring guides, must be reversed before it is added by subtracting the response from 4. All subscale totals are added together to form the FACT-G total score. The cervix subscale is scored in a similar way but will be analyzed separately from the FACT-G. Each subscale requires at least 50% of the items to be completed while the overall response rate must be greater than 80%. If items are missing, the subscale scores can be prorated.

Since both disease sites will be treated the same and no differences in sexual functioning due to treatment are expected, it is felt that the FACT-Cx will provide valuable information for both disease sites that can be compared among treatment groups for all patients.

The change from baseline to each of the time points (5 weeks from the start of RT, 4-6 weeks post RT, and 1 year and 3 years from the start of RT) will be assessed using a t-test to determine the effect of IMRT on QOL as compared to conventional WPRT for overall QOL (FACT-G), for QOL specific to cervix cancer patients (cervical subscale). In addition to the overall FACT-G score, the 4 subscales of the FACT-G will also be compared between treatment arms. The type I error will be controlled by using a Bonferroni adjusted alpha of 0.0125 for each subscale analysis. Descriptive statistics will be provided and patient compliance assessed at each time point QOL across all time points will be examined using a general linear model, allowing for adjustments due to covariates of interest such as treatment arm, disease site, radiation dose, chemotherapy and body mass index. Missing data will be performed as described in Section 13.4.1 for the primary endpoint analysis.

In addition the bowel domain of EPIC, patient-reported toxicity will also be assessed using the urinary domain of EPIC and 6 PRO-CTCAE items for GI toxicity. The PRO-CTCAE questions will assess 3 symptoms, namely diarrhea, abdominal pain and bowel control as well as the frequency with which they have required anti-diarrhea medications. The EPIC urinary domain consists of 12 total items and 4 subscales, functional (5 items), bother (7), incontinence (4) and irritative/obstructive (7). The EPIC urinary domain is scored and will be analyzed in a similar manner as described in Section 13.4.1. Descriptive statistics and patient compliance will be provided and the urinary domain score for EPIC and each PRO-CTCAE item at each time point will be tested using t-tests to compare the early acute GI toxicity (3 weeks from start of treatment), resolution of acute toxicity (4-6 weeks from end of treatment) for EPIC only, early chronic toxicity (1 year), and long-term chronic toxicity (3 years). A longitudinal analysis will be conducted that will focus on patterns of scores over all time points where the EPIC urinary domain is collected. Specifically, a general linear model will be performed for the urinary domain of EPIC, allowing for adjustments due to covariates
of interest such as treatment arm, disease site, radiation dose, chemotherapy and body mass index.

As there are competing pros and cons of both conventional WPRT and IMRT, it is useful to combine these factors into one equation to determine whether the potential benefits of IMRT outweigh the potential risks, in terms of negatively impacting on global HRQOL, compared to conventional WPRT. Such a quality adjusted survival analysis can be invaluable for assisting in the decisions of future patients as well as clinicians faced with these treatment options.

Quality-adjusted survival can be defined by the weighted sum of different time episodes added up to a total quality-adjusted life-year \[ U = \sum_{i=1}^{K} q_i s_i \] (Glasziou 1990):

We will use Glasziou’s multiple health-state (Q-TwiST) models to use the repeated measures of EQ-5D. Because Glasziou’s method incorporates longitudinal QOL data into an analysis of quality-adjusted survival, the health stated model must be constructed on the following assumptions:

A1) QOL is independent from treatment.
A2) A health state is independent from previous states.
A3) Proportionality of quality-adjusted duration and duration of the actual state of health

Assumption A1 can be checked by plotting QOL over time according to treatment, and the t-test can be used to compare the mean QOL scores of each treatment arm. Assumption A2 can be checked by comparing the QOL for patient groups in a given health state where the groups are defined by duration of previous health state experience using a regression model. Suitable checks for assumption A3 at minimum would be a simple plot. If data does not support these assumptions, we will use a method which uses the longitudinal QOL data directly. We will use the 5-item utility score in EQ-5D for the cost-utility analysis. We will use the Z-test to test the hypothesis that the cost-utility in the 2 treatment arms is the same at 1 year after initiation of treatment with a significance level of 0.05 and a 2-sided test. The remaining timepoints in which the EQ-5D is collected will also be assessed using similar longitudinal analysis techniques as described for the primary endpoint.

13.4.3.3 Adverse Events

In addition to the primary endpoint looking at patient-reported toxicity, adverse events (AEs) will also be collected using the CTCAE v.4. Of interest are grade 2+ GI and hematologic toxicity. AEs will be collected at all follow-up times (3 and 5 weeks from the start of treatment, 4-6 weeks post RT, then every 6 months from the start of RT for the first 2 years, then annually for the next 5 years. Also at progression/relapse and at death. The percentage of adverse events in each treatment group at each time point will be compared using a test of proportions to determine if IMRT reduces the incidence of toxicity compared to conventional WPRT. Specifically of interest is acute grade 2+ GI toxicity at 5 weeks from the start of treatment.

13.4.3.4 Estimation of secondary endpoints related to efficacy

The cumulative incidence approach will be used to estimate the failure rates for local-regional failures (Kalbfleish 1980). It is hypothesized that both treatment arms will have similar local-regional failure rates. Progression-free survival (PFS) and overall survival (OS) will be estimated using the Kaplan-Meier method (Kaplan 1982) and compared between the treatment arms using the log-rank test.

13.4.3.5 Rate of secondary cancers

The rate of secondary cancers will be compared between the treatment arms to determine if a difference exists. A test of the difference in proportions of all secondary cancers will be performed. Due to the requirement for long term follow-up to detect secondary cancers, this will not be reported with the primary endpoint.

13.4.4 Analysis for Reporting the Initial Treatment Results

The primary hypothesis of this study is that IMRT reduces acute gastrointestinal toxicity in the 5th week (after 23-25 fractions) of pelvic radiation as measured with the EPIC bowel domain. The analysis reporting the treatment results will be carried out after 225 evaluable patients
have been followed for 5 weeks from the start of treatment. The difference in acute GI toxicity between conventional WPRT and IMRT will be assessed using a t-test with a two-sided alpha=0.05 as described in Section 13.4.1. It will include tabulation of all cases entered and those excluded from the analyses with the reasons for such given; the distribution of the important prognostic baseline variables; safety treatments; compliance with submission of QOL questionnaires; and observed results with respect to the primary and secondary endpoints. All eligible patients randomized will be included in the comparison and will be grouped by assigned treatment in the analysis (intent-to-treat analysis). The general linear model including the stratification variables will be used for exploratory analyses of treatment comparisons. Also, where feasible, treatment comparisons with respect to all endpoints will be compared within gender and ethnic/racial categories.

13.5 Gender and Minorities
In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, participation rates of women and minorities will be examined during the interim reports. Based on accrual statistics from RTOG 0418, the projected accrual by gender, race and ethnicity is shown below:

<table>
<thead>
<tr>
<th>Projected Distribution of Gender and Minorities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ethnic Category</strong></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td><strong>Ethnic Category: Total of all subjects</strong></td>
</tr>
<tr>
<td><strong>Racial Category</strong></td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
</tr>
<tr>
<td>Asian</td>
</tr>
<tr>
<td>Black or African American</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td><strong>Racial Category: Total of all subjects</strong></td>
</tr>
</tbody>
</table>
REFERENCES (9/16/2013)


A RANDOMIZED PHASE III STUDY OF STANDARD VS. IMRT PELVIC RADIATION FOR POST-OPERATIVE TREATMENT OF ENDOMETRIAL AND CERVICAL CANCER (TIME-C)

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have endometrial or cervical cancer that has a high risk of coming back in the pelvis or vagina.

Why is this study being done?

The purpose of this study is to test whether the use of a radiation therapy delivery technique called intensity-modulated radiation therapy (IMRT) can reduce the amount and severity of gastrointestinal side effects (such as diarrhea) that result from radiation, compared with standard radiation techniques. In this study, you will get either the IMRT or the standard radiation.

Many normal tissues, including small bowel and large bowel, are very close to areas at high risk of cancer coming back, such as nodes and vagina. Standard radiation techniques cannot avoid delivering radiation to these normal tissues that do not need to get radiation. IMRT tries to lower the amount of radiation that normal tissues receive, while still delivering the desired amount of radiation to your cancer and to areas that the study doctor thinks may have cancer cells, such as lymph nodes in the pelvis. IMRT does this by using multiple, complicated computer-controlled radiation beams aimed at your cancer.

How many people will take part in the study?

About 281 people will take part in this study

What will happen if I take part in this research study? (3/16/15)

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.
• History and physical examination which will include a record of your weight and an assessment of your ability to carry out activities of daily living
• Surgery (Hysterectomy)
• Blood tests
• Contrast-enhanced CT (a computerized tomography scanner that sends x-rays through the body at many different angles) or MRI of the abdomen and pelvis (an image of your stomach and pelvis produced by magnetic rays) OR a whole-body PET-CT (a type of nuclear medicine imaging used to provide images that pinpoint the location of an abnormal group of cells within the body.)
• Chest x-ray or CT scan of the chest (unless you had a whole-body PET-CT)
• You will be asked to complete a questionnaire about any bowel or urinary symptoms or problems you may have. Completion of this questionnaire will take about 10 minutes and is required for this study.

During the study …
If the exams, tests and procedures show that you can be in the study, and you choose to take part, you will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your study doctor can choose the group you will be in. You will have an equal chance of being placed in either group.

If you are in group 1 (often called "Arm A"), you will receive IMRT radiation therapy. This radiation technique is not the standard technique in this setting. The radiation therapy will be given once daily, 5 days a week, for 5-6 weeks. The treatment takes about 5-15 minutes each day. You may or may not receive weekly IV cisplatin chemotherapy (this will be decided by your doctor).

If you are in group 2 (often called "Arm B"), you will receive standard three-dimensional radiation therapy. This is the standard radiation technique in this setting. The radiation therapy will be given once daily, 5 days a week, for 5-6 weeks. The treatment takes about 5-15 minutes each day. You may or may not receive weekly IV cisplatin chemotherapy (this will be decided by your doctor).

Your study doctor may decide in addition to the external beam treatment you may receive a different type of radiation treatment known as a “vaginal cuff boost”. The vaginal cuff boost is where the physician places radiation inside the vagina to treat the top of the vagina. The physician places an applicator that has a hollow tube into the vagina, and then the radiation goes through the hollow tube and treats the vagina. The applicator is similar to placing a large tampon in the vagina. This internal treatment takes about 2-5 minutes for each treatment. You will get 2-3 treatments, given once or twice weekly.

After randomization, you will need these tests and procedures that are part of regular cancer care:
- Weekly visits with the Radiation Oncologist which will include an assessment of your ability to carry out activities of daily living (during weeks 3 and 5 of radiation therapy)
• If your study doctor decides you will receive chemotherapy, you will have blood tests before the start of each chemotherapy cycle.

You will need these tests and procedures that are either being tested in this study or being done to see how the study is affecting your body.

• Assessment of any side effects you may be experiencing from the treatment (during weeks 3 and 5 of radiation therapy)
• You will be asked to complete a questionnaire called “EPIC” about any bowel or urinary symptoms or problems you may have at 3 and 5 weeks from the start of RT. Completion of this questionnaire will take about 10 minutes and is required for this study. EPIC stands for “The Expanded Prostate Cancer Index Composite”. It was designed to measure quality of life issues in patients with prostate cancer, but also applies to patients getting radiation to the pelvis for cervix and endometrial cancer.

Before you begin study treatment, you may be asked to meet with a trained person who can help with your dietary needs and restrictions and if your study doctor decides that you will receive chemotherapy, you may be asked to have a hearing test.

When you are finished receiving all treatment, you will have the following tests and procedures

4-6 weeks after completing your radiation therapy, then every 6 months for the first 2 years from the start of your radiation therapy, then once every year for the next 8 years for a total of 10 years:

• Physical exam which will include a record of your weight and an assessment of your ability to carry out activities of daily living
• Assessment of any side effects you may be experiencing from the treatment

Every 6 months for the first 2 years from the start of your radiation therapy then once every year for 8 years for a total of 10 years:

• X-ray of the chest. You may have this test done sooner if your doctor thinks it is necessary.

1 and 3 years from the start of your radiation therapy:

• Contrast-enhanced CT (a computerized tomography scanner that sends x-rays through the body at many different angles) of the chest. You may have this test done sooner if your doctor thinks it is necessary.
• Contrast-enhanced CT or MRI (an image of your stomach and pelvis produced by magnetic rays) of the abdomen and pelvis OR a whole-body PET-CT (a type of nuclear medicine imaging used to provide images that pinpoint the location of an abnormal group of cells within the body.) You may have these tests done sooner if your doctor thinks it is necessary.
For patients with cervical cancer: Every 6 months for the first 2 years from the start of your radiation therapy, then once a year for years 3-10:

- Pap Smear

You will also need these tests and procedures:

- You will be asked to complete the EPIC questionnaire about any bowel or urinary symptoms or problems you may have 4 to 6 weeks after completing radiation therapy and at 1 and 3 years from the start of your radiation therapy. Completion of this questionnaire will take about 10 minutes and is required for this study.

**Study Plan**

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.

- **Start Here**
- **Cervix or Endometrial Cancer Surgery**
- **Randomize** (You will be in one Group or the other)

**Group 1**
Radiation Therapy using IMRT technique once daily, 5 days a week for 5-6 weeks

**Group 2**
Radiation Therapy using standard three-dimensional technique once daily, 5 days a week for 5-6 weeks
How long will I be in the study?

The study treatment will take 5-6 weeks to complete. Follow-up visits will be scheduled 4-6 weeks after completion of your radiation therapy, and then every 6 months during years 1 and 2 from the start of your radiation therapy and then once every year for 8 years for a total of 10 years. These are follow-up visits that your doctor would normally schedule even if you were not in the study.

The study doctor may take you off study treatment if:

- It is in your best medical interest, or
- your condition worsens, or
- new information becomes available that suggests that the treatment is not working or is unsafe for you.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the radiation therapy can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study? (3/16/15)

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don’t know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop receiving the radiation therapy and chemotherapy. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.
### Possible Side Effects of Pelvic Radiation Therapy

#### COMMON, SOME MAY BE SERIOUS

In 100 people receiving radiation therapy, more than 20 may have:

- Hair loss in the treatment area, may be permanent
- Diarrhea
- Need to urinate often
- Urgency with urination
- Slower urinary flow
- Tiredness
- Pain, including with urination and/or bowel movements
- Nausea, vomiting
- Painful sexual intercourse

#### OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving radiation therapy, from 4 to 20 may have:

- Chronic bowel/bladder symptoms as described above
- Blood in urine
- Inability to control urine, inability to control bowel movements
- Mucous-like stools
- Bleeding of the rectum
- Swelling, redness, rash, skin changes, or itching in the area of radiation

#### RARE, AND SERIOUS

In 100 people receiving radiation therapy, 3 or fewer may have:

- Weight loss
- Blockage of internal organs that may require surgery
- A tear or hole in internal organs that may require surgery
- Bladder shrinkage, discomfort, or bleeding which may require medication or surgery, including removal of the bladder.
- Internal bleeding which may cause bleeding of the rectum, black tarry stool, blood in vomit, blood in urine, and may require surgery.
- Infection which may cause painful and frequent urination
- A new cancer resulting from treatment of earlier cancer

Radiation to the pelvis will cause sterility (inability to become pregnant). Women of childbearing potential will go through menopause and may require the use of hormones given orally to replace the hormones normally produced by the ovaries.
Possible Side Effects of Cisplatin

<table>
<thead>
<tr>
<th>COMMON, SOME MAY BE SERIOUS</th>
<th>In 100 people receiving Cisplatin, more than 20 and up to 100 may have:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nausea, vomiting</td>
<td></td>
</tr>
<tr>
<td>• Infection, especially when white blood cell count is low</td>
<td></td>
</tr>
<tr>
<td>• Anemia which may cause tiredness, or may require blood transfusions</td>
<td></td>
</tr>
<tr>
<td>• Bruising, bleeding</td>
<td></td>
</tr>
<tr>
<td>• Kidney damage which may cause swelling, may require dialysis</td>
<td></td>
</tr>
<tr>
<td>• Hearing loss including ringing in ears</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OCCASIONAL, SOME MAY BE SERIOUS</th>
<th>In 100 people receiving Cisplatin, from 4 to 20 may have:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat</td>
<td></td>
</tr>
<tr>
<td>• Confusion</td>
<td></td>
</tr>
<tr>
<td>• Difficulty with balance</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RARE, AND SERIOUS</th>
<th>In 100 people receiving Cisplatin, 3 or fewer may have:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cancer of bone marrow caused by chemotherapy later in life</td>
<td></td>
</tr>
<tr>
<td>• Seizure</td>
<td></td>
</tr>
<tr>
<td>• Loss of muscle or nerve function, which may cause weakness or numbness in your hands and feet</td>
<td></td>
</tr>
</tbody>
</table>

Risks Associated with Blood Drawing

• You may experience some discomfort, bruising and/or bleeding at the site of the needle insertion. Occasionally, some people experience dizziness or feel faint. In rare instances, infection may develop at the site of the needle insertion.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. Doctors hope IMRT will have fewer side effects than the usual treatment, but there is no proof of this yet. We do know that the information from this study will help doctors learn more about IMRT as a treatment for cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:
• Getting treatment or care for your cancer without being in a study
• Taking part in another study
• Getting no treatment
• Getting radiation therapy based on your institution’s standard of treatment

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private? (8/4/14)

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

• NRG Oncology
• The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
• The Cancer Trials Support Unit (CTSU), a service sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials, may also view your records if you are participating in this trial through one of their institutions.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

[Note to Informed Consent Authors: the above paragraph complies with the new FDA regulation found at 21 CFR 50.25(c) and must be included verbatim in all informed consent documents. The text in this paragraph cannot be revised.]

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this study? (8/7/2013)

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

You will not be paid for taking part in this study.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, __________________ [investigator’s name(s)], if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at __________________ [telephone number].
You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor __________________ [name(s)] at __________________ [telephone number].

For questions about your rights while taking part in this study, call the __________________ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at __________________ (telephone number).

[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say ‘no’ to taking part in any of these additional studies.

You can say “yes” or “no” to each of the following studies. Please mark your choice for each study.

Quality of Life Study

We want to know your view of how your life has been affected by cancer and its treatment. This study looks at how treatment affects your quality of life, your functioning, and how you are able to carry out your day-to-day activities. This information will help doctors better understand
how participants feel during treatments and what effects the treatments are having. In the future, this information may help participants and doctors as they decide which treatments to choose based on what matters most to the participant.

If you agree to participate in the optional part of the quality of life study, you will be asked to complete 3 additional questionnaires (besides the questionnaire about any bowel or urinary symptoms or problems you may have which is part of the main study). The 3 questionnaires are the EQ-5D, FACT-CX, and the PRO-CTCAE items for gastrointestinal toxicity.

The EQ-5D is a questionnaire used to measure your general health status, has 5 questions and only takes a few minutes of your time to complete.

The FACT-CX is a questionnaire used to measure your physical, functional, social and emotional well-being. It also has questions specific to participants with gynecological cancer and has a total of 42 questions. It should take about 10 minutes to complete this questionnaire.

The PRO-CTCAE items for gastrointestinal toxicity are questions used to measure any bowel symptoms or problems that you have. It should take about 20 minutes to complete all 3 questionnaires.

You will be asked to fill out the additional questionnaires for EQ-5D, FACT-CX, and the PRO-CTCAE at the following time points: immediately before you start radiation therapy; 5 weeks after starting radiation therapy; 4-6 weeks after completing radiation therapy; and then at 1 year and 3 years from the start of your radiation therapy.

If any questions make you feel uncomfortable, you may skip those questions and not give an answer. You may change your mind about completing the questionnaires at any time and you may choose to discontinue answering the questionnaires altogether at any time.

No matter what you decide to do, it will not affect your care.

If you decide to take part in this study, the only thing you will be asked to do is fill out the questionnaires noted above.

Just like in the main study, we will do our best to make sure that your personal information will be kept private.

Please circle your answer.

I choose to take part in the optional Quality of Life Study. I agree to fill out the 3 Quality of Life Questionnaires. (EQ-5D, FACT-CX, and the PRO-CTCAE items for gastrointestinal toxicity)

YES  NO
Consent Form for Use of Tissue and Blood for Research (3/16/15)

About Using Tissue and Blood for Research

You have had surgery for your cancer. Your doctor has removed some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. An information sheet is available to all at http://www.cancer.gov/cancertopics/factsheet/clinicaltrials/donating-tissue-research.

The research that may be done with your tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

In addition, you will have blood tests before you start treatment and at weeks 3 and 5 of your radiation treatment. We would like to keep about four teaspoons of blood for future research as well. If you agree, this blood will be kept and may be used in research to learn more about cancer and other diseases as well as looking for any markers in the blood that are associated with a higher rate of side effects from the radiation therapy.

Reports about research done with your specimens will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over tissue and blood for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your tissue and blood can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue and blood. Then any tissue and blood that remains will no longer be used for research.

In the future, people who do research may need to know more about your health. While the study doctor/institution may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes specimens are used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.

Your tissue and blood will be used only for research and will not be sold. The research done with your tissue may help to develop new products in the future.

Benefits
The benefits of research using tissue and blood include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them. However, there will be no direct benefit to the participant.

Risks (8/7/2013)

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included. The samples are given a code to protect your privacy before they are used. Any related information given to researchers will also be coded. Researchers will receive the code instead of any information that might directly identify you.

There can be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a research study. Even though your genes are unique, you share some of the same genes with your blood relatives.

Although we are not able to know all of the risks from taking part in research on inherited traits, we believe that the risks to you and your family are very low, because your samples will be coded. Research results will not be returned to you or your doctor.

Very rarely health or genetic information could be misused by employers, insurance companies, and others. For example, life insurance companies may charge a higher rate based on this information.

Many states have laws to protect against genetic discrimination [list appropriate state information if your state or locality has such laws]. Additionally, a federal law called the Genetic Information Non-Discrimination Act, or GINA is in effect. This law prohibits health insurer or employer discrimination. The law does not include other types of misuse by life insurance, disability, or long term care insurance. To learn more about the GINA Law, please ask (Note to Local investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here).

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB’s phone number.

No matter what you decide to do, it will not affect your care.

1. My tissue may be kept for use in research to learn about, prevent, or treat cancer.
2. My tissue may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

   Yes    No

3. My blood may be kept for use in research to learn about, prevent, or treat cancer.

   Yes    No

4. My blood may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

   Yes    No

5. My blood may be kept for use in research to learn about the association between genes and substances found in the blood and radiation side effects.

   Yes    No

6. Someone may contact me in the future to ask me to take part in more research.

   Yes    No

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

   1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/

   - For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
   - For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.
Signature

I have been given a copy of all _____ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _______________________________________

Date _____________________________________________
## APPENDIX II (3/16/15)
### STUDY PARAMETER TABLE

*Note: *See Sections 3.0 and 4.0 (pre-study entry), and 11.0 (during treatment/follow-up) for details and/or exceptions to this table.

<table>
<thead>
<tr>
<th></th>
<th>Pre-Treatment</th>
<th>During Treatment</th>
<th>Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease Documentation</strong></td>
<td>Prior to Study Registration</td>
<td>Week 3 of RT</td>
<td>Week 5 of RT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-6 wks after RT</td>
<td>Q 6 months for years 1 and 2 from the start of RT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Annually for years 3-10 from the start of RT; also at progression/relapse and at death</td>
</tr>
<tr>
<td><strong>Hysterectomy</strong></td>
<td>≤ 49 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>History/physical</strong></td>
<td>≤ 45 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chest X-ray</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chest CT</strong></td>
<td>≤ 90 days* (Chest CT or Chest x-ray)</td>
<td></td>
<td>1 and 3 years from the start of treatment *</td>
</tr>
<tr>
<td><strong>Abd/Pelvic CT, MRI or PET-CT</strong></td>
<td>Pre – or post- surgery ≤ 90 days</td>
<td></td>
<td>1 and 3 years from the start of treatment *</td>
</tr>
<tr>
<td><strong>Physical exam, performance status/weight</strong></td>
<td>≤ 45 days</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>CBC w/ diff &amp; ANC</strong></td>
<td>≤ 14 days</td>
<td></td>
<td>See Section 11.2</td>
</tr>
<tr>
<td><strong>Audiogram</strong></td>
<td>Highly recommended for patients receiving chemo. See section 4.2.2</td>
<td></td>
<td>Highly recommended for patients receiving chemo. See section 4.2.</td>
</tr>
<tr>
<td><strong>Consultation with a nutritionist</strong></td>
<td>Highly recommended</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BUN, Creatinine, clearance, AST, bilirubin, Alkaline phosphatase, Mg, electrolytes</strong></td>
<td>Only for patients receiving chemo, See Section 3.1.7</td>
<td>See Section 11.2</td>
<td></td>
</tr>
<tr>
<td><strong>Informed consent</strong></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pap Smear</strong></td>
<td></td>
<td></td>
<td>Cervical cancer patients only X*</td>
</tr>
<tr>
<td><strong>CTCAE Toxicity evaluation</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
## Appendix II: STUDY PARAMETER TABLE (continued)

<table>
<thead>
<tr>
<th>QUALITY OF LIFE</th>
<th>Pre-Treatment</th>
<th>During Treatment</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prior to Study Registration</td>
<td>Week 3 of RT</td>
<td>Week 5 of RT</td>
</tr>
<tr>
<td>Bowel &amp; Urinary Domain of EPIC</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>FACT-Cx, PRO-CTCAE items for GI toxicity, EQ-5D (if patient consents)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Tissue for Banking (if patient consents)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood for Translational Research (if patient consents)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
## APPENDIX III

**ZUBROD PERFORMANCE SCALE**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all predisease activities without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair 50% or more of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on self-care. Totally confined to bed</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>
APPENDIX IV (8/4/14)

AJCC STAGING SYSTEM

CERVICAL CANCER

Primary Tumor (T)

<table>
<thead>
<tr>
<th>TNM Categories</th>
<th>FIGO Stages</th>
<th>FIGO Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td></td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td></td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis*</td>
<td></td>
<td>Carcinoma in situ (preinvasive carcinoma)</td>
</tr>
<tr>
<td>T1</td>
<td>I</td>
<td>Cervical carcinoma confined to uterus (extension to corpus should be disregarded)</td>
</tr>
<tr>
<td>T1a**</td>
<td>IA</td>
<td>Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification</td>
</tr>
<tr>
<td>T1a1</td>
<td>IA1</td>
<td>Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread</td>
</tr>
<tr>
<td>T1a2</td>
<td>IA2</td>
<td>Measured stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less</td>
</tr>
<tr>
<td>T1b</td>
<td>IB</td>
<td>Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2</td>
</tr>
<tr>
<td>T1b1</td>
<td>IB1</td>
<td>Clinically visible lesion 4.0 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T1b2</td>
<td>IB2</td>
<td>Clinically visible lesion more than 4.0 cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>II</td>
<td>Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina</td>
</tr>
<tr>
<td>T2a</td>
<td>IIA</td>
<td>Tumor without parametrial invasion</td>
</tr>
<tr>
<td>T2a1</td>
<td>IIA1</td>
<td>Clinically visible lesion 4.0 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T2a2</td>
<td>IIA2</td>
<td>Clinically visible lesion more than 4.0 cm in greatest dimension</td>
</tr>
<tr>
<td>T2b</td>
<td>IIB</td>
<td>Tumor with parametrial invasion</td>
</tr>
<tr>
<td>T3</td>
<td>III</td>
<td>Tumor extends to pelvic wall and/or involves lower third of vagina, and/or causes hydronephrosis or non-functioning kidney</td>
</tr>
<tr>
<td>T3a</td>
<td>IIIA</td>
<td>Tumor involves lower third of vagina, no extension to pelvic wall</td>
</tr>
<tr>
<td>T3b</td>
<td>IIIB</td>
<td>Tumor extends to pelvic wall and/or causes hydronephrosis or non-functioning kidney</td>
</tr>
<tr>
<td>T4</td>
<td>IVA</td>
<td>Tumor invades mucosa of bladder or rectum, and/or extends beyond true pelvis (bulla edema is not sufficient to classify a tumor as T4)</td>
</tr>
</tbody>
</table>

*Note: FIGO staging no longer includes Stage 0 (Tis).
**Note: All macroscopically visible lesions—even with superficial invasion—are T1b/IB.

Regional Lymph Nodes (N)

<table>
<thead>
<tr>
<th>TNM Categories</th>
<th>FIGO Stages</th>
<th>FIGO Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td></td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td></td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>IIIB</td>
<td>Regional lymph node metastasis</td>
</tr>
</tbody>
</table>

Distant Metastasis (M)

<table>
<thead>
<tr>
<th>TNM Categories</th>
<th>FIGO Stages</th>
<th>FIGO Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td></td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>IVB</td>
<td>Distant metastasis (including peritoneal spread, involvement of supraclavicular, mediastinal, or para-aortic lymph nodes, lung, liver, or bone)</td>
</tr>
</tbody>
</table>

(Continued on Next Page)
### ANATOMIC STAGE/PROGNOSTIC GROUPS (FIGO 2008)

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0*</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IA1</td>
<td>T1a1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IA2</td>
<td>T1a2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB1</td>
<td>T1b1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB2</td>
<td>T1b2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA1</td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA2</td>
<td>T2a1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T3a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T3b</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1-3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

*Note: FIGO no longer includes Stage 0 (Tis).*
APPENDIX IV con't (8/4/14)

AJCC STAGING SYSTEM

ENDOMETRIAL CANCER

Primary Tumor (T) (Surgical-Pathologic Findings)

<table>
<thead>
<tr>
<th>TNM Categories</th>
<th>FIGO Categories</th>
<th>Stages</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tis*</td>
<td>Carcinoma in situ (preinvasive carcinoma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Tumor confined to corpus uteri</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor limited to endometrium or invades less than one-half of the myometrium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor invades less than one-half or more of the myometrium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades stromal connective tissue of the cervix but does not extend beyond uterus**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3a</td>
<td>Tumor involves serosa and/or adnexa (direct extension or metastasis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3b</td>
<td>Vaginal involvement (direct extension or metastasis) or parametrial involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades bladder mucosa and/or bowel mucosa (bullous edema is not sufficient to classify a tumor as T4).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: FIGO no longer includes Stage 0 (Tis).  
** Endocervical glandular involvement only should be considered as Stage I and not as Stage II.

Regional Lymph Nodes (N)

<table>
<thead>
<tr>
<th>TNM Categories</th>
<th>FIGO Categories</th>
<th>Stages</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis to pelvic lymph nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>Regional lymph node metastasis to para-aortic lymph nodes, with or without positive pelvic lymph nodes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Distant Metastasis (M)

<table>
<thead>
<tr>
<th>TNM Categories</th>
<th>FIGO Categories</th>
<th>Stages</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>Distinct metastasis (including metastasis to inguinal lymph nodes intraperitoneal disease, or lung, liver, or bone. It excludes metastasis to para-aortic lymph nodes, vagina, pelvic serosa, or adnexa)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Continued on Next Page)
## ANATOMIC STAGE/PROGNOSTIC GROUPS

### Carcinomas*

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0**</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IA</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IB</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T3a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIC1</td>
<td>T1-T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>IIIC2</td>
<td>T1-T3</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>IVA</td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>IVB</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

*Carcinosarcomas should be staged as carcinoma

**Note:** FIGO no longer includes Stage 0 (Tis).
APPENDIX V (3/16/15)

Appendices for NRG Oncology Biospecimen Collection (as specified by the protocol).

FFPE Specimen Plug Kit Collection
Blood Collection Kit Instructions

Shipping Instructions:

U.S. Postal Service Mailing Address: For FFPE or Non-frozen/Non Urgent Specimens Only
NRG Oncology Biospecimen Bank-San Francisco
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen or Trackable Specimens
NRG Oncology Biospecimen Bank-San Francisco
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

- Include all NRG Oncology paperwork in pocket of biohazard bag.
- Check that the Specimen Transmittal Form (ST) has the consent boxes checked off.
- Check that all samples are labeled with the NRG Oncology study and case number, and include date of collection as well as collection time point (e.g., pretreatment, post-treatment).

- **FFPE Specimens:**
  - Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container. If you can hear the slides shaking it is likely that they will break during shipping.
  - FFPE Blocks can be wrapped with paper towel, or placed in a cardboard box with padding. Do not wrap blocks with bubble wrap or gauze. Place padding in top of container so that if you shake the container the blocks are not shaking. Slides, Blocks, or Plugs can be shipped ambient or with a cold pack either by United States Postal Service (USPS) to the USPS address (94143) or by Courier to the Street Address (94115). **Do NOT ship on Dry Ice.**

- **Frozen Specimens:**
  - Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.
  - Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
  - Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  - Send frozen specimens via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80°C until ready to ship.

- For Questions regarding collection/shipping please contact the NRG Oncology Biospecimen Bank by e-mail: RTOG@ucsf.edu or phone: 415-476-7864 or Fax: 415-476-5271.
APPENDIX V (continued)

FFPE SPECIMEN PLUG KIT INSTRUCTIONS

This Kit allows sub-sampling of an FFPE block for submission to the NRG Oncology Biospecimen Bank. The plug kit contains a shipping tube and a punch tool.

**Step 1**
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.

**Step 2**
Label the punch tool with the proper specimen ID. Include the pathology number and block ID. DON'T remove specimen from the punch.

Use a separate punch tool for every specimen. Call or e-mail us if you have any questions or need additional specimen plug kits.

**Step 3**
Once punch tool is labeled, place in shipping tube and mail to address below. Please do not mix specimens in the same tube.

We will remove core specimen from the punch, embed in a paraffin block, and label with specimen ID.

**NOTE:** If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the NRG Oncology Biospecimen Bank and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block.

Ship specimen plug kit, specimen in punch tool, and all paperwork to the address below. For Questions regarding collection/shipping or to order an FFPE Specimen Plug Kit, please contact the NRG Oncology Biospecimen Bank by e-mail: RTOG@ucsf.edu or call 415-476-7864/Fax 415-476-5271.

**U.S. Postal Service Mailing Address:** For Non-frozen/Non Urgent Specimens Only
NRG Oncology Biospecimen Bank-San Francisco
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

**Courier Address (FedEx, UPS, etc.):** For Frozen Specimens or Trackable shipments
NRG Oncology Biospecimen Bank-San Francisco
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
APPENDIX V (continued)

BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of serum, plasma, or whole blood (as specified by the protocol):

Kit contents:
- One Red Top tube for serum (A)
- One Purple Top EDTA tube for plasma (B)
- One Purple Top EDTA tube for Whole Blood (C)
- Twenty-five (25) 1 ml cryovials
- Biohazard bags (3) and Absorbent shipping material (3)
- Styrofoam container (inner) and Cardboard shipping (outer) box
- UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal Form (ST) and Kit Instructions

PREPARATION AND PROCESSING OF SERUM, PLASMA AND WHOLE BLOOD:

(A) Serum (if requested): Red Top Tube
- Label as many 1ml cryovials (5 to 10) as necessary for the serum collected. Label them with the NRG Oncology study and case number, collection date, time, and time point, and clearly mark cryovials “serum”.

Process:
1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST.
3. Aliquot 0.5 ml serum into as many cryovials as are necessary for the serum collected (5 to 10) labeled with NRG Oncology study and case numbers, collection date/time, protocol time-point collected (e.g. pretreatment, post-treatment), and clearly mark specimen as "serum".
4. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C, and store frozen until ready to ship. See below for storage conditions.
5. Store serum at -70 to -90°C until ready to ship on dry ice. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the ST.

(B) Plasma (If requested): Purple Top EDTA tube #1
- Label as many 1ml cryovials (5 to 10) as necessary for the plasma collected. Label them with the NRG Oncology study and case number, collection date/time, time point collected and clearly mark cryovials "plasma".

Process:
1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST.
3. If the interval between specimen collection and processing is anticipated to be more than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot 0.5 ml plasma into as many cryovials as are necessary for the plasma collected (5 to 10) labeled with NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as “plasma”. Avoid pipetting up the buffy coat layer.
5. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C.
6. Store frozen plasma until ready to ship on dry ice.
7. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the ST.

(continued on next page)
(C) Whole Blood for DNA (if requested): Purple Top EDTA tube #2

- Label as many 1ml cryovials (3 to 5) as necessary for the whole blood collected. Label them with the NRG Oncology study and case number, collection date/time, and time point, and clearly mark cryovials “blood”.

**Process:**
1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot **1.0 ml** blood into as many cryovials as are necessary for the blood collected (3 to 5) labeled with NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as “blood”.
3. Place cryovials into biohazard bag and freeze immediately at -70 to -80°C Celsius.
4. Store blood samples frozen until ready to ship on dry ice.
5. See below for storage conditions.

Please make sure that every specimen is labeled and include collection time point on ST.

**Freezing and Storage:**
- No dry ice is required with liquid nitrogen.
- **Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.**
- **Store at –80°C (-70°C to -90°C) until ready to ship.**
  - If a -80°C Freezer is not available, Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
  - **OR:** Samples can be stored in plenty of dry ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only; Canada: Monday-Tuesday only).
  - **OR:** Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
- Please indicate on Specimen Transmittal (ST) Form the storage conditions used and time stored.

**Shipping/Mailing:**
- **Ship specimens on Dry Ice overnight Monday-Wednesday (Monday-Tuesday from Canada) to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.**
- **Include all NRG Oncology paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.**
- **Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag.**
  - Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). **Add padding to avoid the dry ice from breaking the tubes.**
- **Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.**
APPENDIX V (continued)

BLOOD COLLECTION KIT INSTRUCTIONS (continued)

- Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice. Add padding to avoid the dry ice from breaking the tubes.
- For questions regarding collection, shipping or to order a Blood Collection Kit, please e-mail RTOG@ucsf.edu or call (415)476-7864.

Shipping Address:

Courier Address (FedEx, UPS, etc.): For all Frozen Specimens
NRG Oncology Biospecimen Bank-San Francisco
University of California San Francisco
2340 Sutter St, Room S341
San Francisco, CA 94115
For questions, call 415-476-7864 or e-mail: RTOG@ucsf.edu
APPENDIX VI
DEFINITION OF BLADDER AND RECTAL POINTS

Vaginal Cylinder

Active intravaginal sources

Bladder reference point (balloon 7 cm³)

Vaginal surface dose

0.5 cm

Rectal reference point

Points of Calculation

Ovoids

Prescription point

Cylinder

Apex

Prescription point