PROTOCOL GOG-0258

A RANDOMIZED PHASE III TRIAL OF CISPLATIN AND TUMOR VOLUME DIRECTED IRRADIATION FOLLOWED BY CARBOPLATIN AND PACLITAXEL VS. CARBOPLATIN AND PACLITAXEL FOR OPTIMALLY DEBULKED, ADVANCED ENDOMETRIAL CARCINOMA (NCT #00942357) **(04/28/2014)**

NCI Version Date: 04/04/2014

Includes Revisions #1-11

POINTS:
PER CAPITA - 20
MEMBERSHIP – 6

TRANSLATIONAL RESEARCH – Award based on specimen submission with 1.0 point for the submission of archival formalin-fixed, paraffin-embedded primary or metastatic tumor tissue and 0.5 points for whole blood.

Lead Organization: NRG / NRG Oncology (04/28/2014)

Participating Organizations (04/28/2014)

ALLIANCE / Alliance for Clinical Trials in Oncology
ECOG-ACRIN / ECOG-ACRIN Cancer Research Group
SWOG / SWOG

STUDY CHAIR
DANIELA MATEI, M.D.
[redacted]

STUDY CO-CHAIRS
MARCUS E. RANDALL, M.D.
See GOG Website Directory

DAVID MUTCH, M.D.
See GOG Website Directory

QUALITY OF LIFE CO-CHAIR
URSULA A. MATULONIS, M.D.
See GOG Website Directory

RTOG CO-CHAIR **(12-14-10)**
I-CHOW HSU, M.D.
See GOG Website Directory

TR CO-CHAIR
MICHAEL J. BIRRER, M.D., PH.D.
See GOG Website Directory

NURSE CONTACT
NANCY MENNING, MSN, ANP-C
[redacted]

STUDY PATHOLOGIST
MARGARET STEINHOFF, M.D.
See GOG Website Directory

STATISTICIAN
GINNY FILIACI, PH.D.
See GOG Website Directory

QUALITY OF LIFE STATISTICIAN
HELEN Q. HUANG, M.S.
See GOG Website Directory

TRANSLATIONAL RESEARCH SCIENTIST
HEATHER A. LANKES, PH.D., M.P.H.
See GOG Website Directory

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CONTACT INFORMATION (04/28/2014)		
To submit site registration documents:	**For patient enrollments:**	**Submit study data**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only)	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Use the SDC Electronic Data Entry System (SEDES) online application found at the GOG Web Menu page, to view and print a copy of each form along with instructions, and to submit forms electronically. All amendments to forms submitted through SEDES must also be submitted through SEDES. The original form and required copies for forms NOT submitted online must be mailed to the GOG SDC. [redacted] Do <u>not</u> submit study data or forms to CTSU Data Operations. Do <u>not</u> copy the CTSU on data submissions.
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. Access to the CTSU members' website 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. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
<u>For clinical questions (i.e. patient eligibility or treatment-related)</u> Contact the Study PI of the Lead Protocol Organization		
<u>For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)</u> contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
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SCHEMA

Enroll patients with either FIGO 2009 surgical Stage III or IVA endometrial carcinoma or patients with FIGO 2009 Stage I or II serous (UPSC) or clear cell endometrial carcinoma and positive cytology. **(01/03/2011)**

TREATMENT RANDOMIZATION

REGIMEN I:
Cisplatin 50 mg/m^2 IV Days 1 and 29 **(06/07/2010)**
plus Volume-directed radiation therapy
followed by Carboplatin AUC 5* plus Paclitaxel 175 mg/m^2 q 21 days for 4 cycles
with G-CSF support
(08/12/09)

or

REGIMEN II: Carboplatin AUC 6 plus Paclitaxel 175 mg/m^2 q 21 days for 6 cycles

* first dose of Carboplatin will be at AUC of 5, in subsequent cycles the dose will be escalated to AUC 6, as described in Section 6.2. **(06/07/2010)**

Translational Research (See Section 7.3)
- Archival formalin-fixed, paraffin-embedded primary or metastatic tumor tissue
- Whole blood

Quality of Life Assessment (See Section 7.4)
- At baseline (within 14 days prior to starting protocol therapy)
- 6 weeks from start of protocol treatment (1 week post-completion of RT for Regimen I or three weeks post completion of 2 cycles of chemotherapy for Regimen II)
- 18 weeks from start of protocol treatment (three weeks after completion of protocol therapy)
- 70 weeks from start of protocol treatment (1 year from completion of protocol therapy)

TABLE OF CONTENTS

PAGE

1.0 OBJECTIVES - 6 -

1.1 Primary Objective: - 6 -
1.2 Secondary Objectives: - 6 -
1.3 Translational Research Objective - 6 -

2.0 BACKGROUND AND RATIONALE - 7 -

2.1 Introduction, hypothesis and significance: - 7 -
2.2 Prior Experience with Chemotherapy and Radiotherapy in Endometrial Cancer - 8 -
2.3 Inclusion of Women and Minorities - 12 -

3.0 PATIENT ELIGIBILITY AND EXCLUSIONS - 13 -

3.1 Eligible Patients - 13 -
3.2 Ineligible Patients - 14 -

4.0 STUDY MODALITIES - 15 -

4.1 Cisplatin (Platinol®-AQ) (NSC #119875) - 15 -
4.2 Carboplatin (Paraplatin®) (NSC # 241240) - 15 -
4.3 Paclitaxel (Taxol®) NSC#673089 - 16 -
4.4 Filgrastim (G-CSF) or Pegfilgrastim - 18 -
4.5 Radiation Therapy - 19 -
4.6 Radiation Therapy Volumes and Technique - 21 -
4.7 Pathology Requirements - 34 -
4.8 Quality of Life Surveys - 34 -

5.0 TREATMENT PLAN AND ENTRY/RANDOMIZATION PROCEDURE **(04/28/2014)** - 36 -

5.1 IROC Houston (formerly the Radiological Physics Center [RPC]) Credentialing Requirements **(04/28/2014)** - 36 -
5.2 Registration Procedures **(04/28/2014)** - 37 -
5.3 Patient Entry and Registration **(04/28/2014)** - 40 -
5.4 Treatment Plan - 41 -

6.0 TREATMENT MODIFICATIONS - 46 -

6.1 Radiation Therapy - 46 -
6.2 Chemotherapy-Hematological Toxicity - 46 -
6.3 Systemic Chemotherapy: Non-Hematologic Toxicity - 48 -
6.4 Discontinuation from protocol - 50 -

7.0 STUDY PARAMETERS - 51 -

7.1 Observations and Tests **(06/07/2010) (01/03/2011) (01/13/14)** - 51 -
7.2 Stained Pathology Slides for Central Pathology Review to Confirm Eligibility - 52 -
7.3 Translational Research **(01/13/14)** - 52 -
7.4 Quality of Life - 53 -

8.0 EVALUATION CRITERIA - 56 -

8.1 Parameters of Response – GOG RECIST Criteria - 56 -

9.0 DURATION OF STUDY - 57 -

9.1 Patients will continue on protocol for a maximum of six cycles of chemotherapy or until disease progression or adverse effects necessitate removal from protocol therapy. - 57 -
9.2 Patients will be followed every three months for two years, then every six months for the next three years. After five years follow-up information will be obtained annually. All subsequent anti-cancer therapies will be reported. **(08/31/2009)** - 57 -
9.3 A patient is considered off study therapy when the patient has either completed the prescribed number of cycles or fractions of study therapy, has progressed or died prior to completion of study therapy, a non-protocol drug or therapy (directed at the disease) is initiated, or ***all*** study therapy is totally discontinued. Report all chemotherapy treatment received on Form D2R, radiation therapy received on Form G, HDRV or LDRV and adverse events on Form T until the patient qualifies as being off study therapy**. (08/12/09)** - 57 -

10.0 STUDY MONITORING AND REPORTING PROCEDURES - 58 -

10.1 ADVERSE EVENT REPORTING FOR ALL REGIMENS (COMMERCIAL AGENTS AND RADIATION THERAPY ADMINISTRATION) **(04/28/2014)** - 58 -
10.2 GOG DATA MANAGEMENT FORMS **(09/21/2009) (01/03/2011) (01/13/14)** - 61 -

11.0 STATISTICAL CONSIDERATIONS - 65 -

11.1 Overview, Study Registration and Randomization***:*** - 65 -
11.2 Relevant data: - 65 -
11.3 Accrual rate, sample size and study duration: - 66 -
11.4 Hypotheses, planning parameters, method of analysis and sample size justification: - 66 -
11.5 Interim analysis***:*** - 70 -
11.6 Planned gender, minority and ethnic inclusion: - 71 -

12.0 BIBLIOGRAPHY - 72 -

APPENDIX I - 77 -

APPENDIX II **(04/28/2014)** - 78 -

APPENDIX III **(04/28/2014)** - 83 -

APPENDIX IV **(04/28/2014)** - 85 -

1.0 OBJECTIVES

1.1 Primary Objective:

1.11 To determine if treatment with cisplatin and volume-directed radiation followed by carboplatin and paclitaxel for 4 cycles (experimental arm) reduces the rate of recurrence or death (i.e., increases recurrence-free survival) when compared to chemotherapy consisting of carboplatin and paclitaxel for 6 cycles (control arm) in patients with Stages III-IVA endometrial carcinoma (<2 cm residual disease) or patients with FIGO 2009 Stage I or II serous (UPSC) or clear cell endometrial carcinoma and positive cytology. **(01/03/2011)**

1.2 Secondary Objectives:

1.21 To determine if treatment with cisplatin and volume-directed radiation followed by carboplatin and paclitaxel for 4 cycles (experimental arm) reduces the rate of death (i.e., increases survival) when compared to chemotherapy consisting of carboplatin and paclitaxel for 6 cycles (control arm) in patients with Stages III-IVA endometrial carcinoma (< 2 cm residual disease) or patients with FIGO 2009 Stage I or II serous (UPSC) or clear cell endometrial carcinoma and positive cytology. **(01/03/2011)**

1.22 To compare the regimens with respect to acute and late adverse effects of therapy.

1.23 To determine the impact on patient-reported Quality of Life during and following treatment for up to 1 year with the two treatment regimens.

1.3 Translational Research Objective

1.31 To bank formalin-fixed, paraffin-embedded (FFPE) tumor tissue and whole blood specimens for future research.

2.0 BACKGROUND AND RATIONALE

2.1 Introduction, hypothesis and significance:

Advanced endometrial cancer (Stages III and IVA) comprises a heterogeneous group of patients, whose survival remains generally poor. Improved surgical therapy and staging (including lymph node assessment and/or dissection) has given clinicians a better understanding of prognostic groups, risk factors, and patterns of recurrence. The survival of patients with Stage III endometrial carcinoma is influenced by several prognostic factors: extent of abdominal/pelvic disease, histological subtype, nodal involvement, presence of extra-nodal disease, and completeness of surgical resection.[1-5] Because of these parameters, which cause wide variability in the pool of patients selected for enrollment in clinical trials, there is a wide range of reported five-year survival for this group of patients (between 40% and 80%).[6-8]

The optimal adjuvant treatment strategy for these patients is still not well defined. In the past surgical resection has been followed by pelvic or whole abdomen radiotherapy. Unfortunately, systemic failures outside the treatment field have limited the impact of radiation on long-term survival. In recent years, chemotherapy has demonstrated significant activity in patients with advanced endometrial cancer and has become the standard treatment. Its benefits rely in the sterilization of systemic foci of metastatic disease. However, if chemotherapy is given alone, the crude proportion of patients with pelvic recurrences is high (18%) and can lead to systemic recurrence and death.[9]
Therefore, it is reasonable to hypothesize that a combined approach (chemotherapy and radiotherapy) may provide better disease control, by preventing both local/pelvic recurrences (radiation), as well as failure at distant sites, as opposed to chemotherapy alone. Such approach has been tested in promising Phase II protocols, but has not been validated in a randomized fashion. The purpose of this trial is to test this hypothesis by utilizing modern tumor volume-directed radiotherapy administered with cisplatin and followed by systemic chemotherapy.

This trial is significant as it could set a new standard of care for women with optimally cyto-reduced Stage III and IVA endometrial cancer. The study builds on the previous experience of the Gynecologic Oncology Group (GOG) and of the Radiation Therapy Oncology Group (RTOG). It is now clear that systemic chemotherapy should be part of the treatment for this patient population (GOG-0122). It is also predicted that radiotherapy would decrease the rate of local failure. However, it is not known whether addition of volume-directed chemo-radiation to chemotherapy alters recurrence-free survival (RFS) and overall survival (OS) in a significant manner. This trial is the logical follow-up to the previous research questions addressed by GOG protocols (0122, 0177, 0184, and 0209). The trial will answer critical questions regarding 1) the impact of chemo-

radiation in this setting, 2) the tolerability of this approach compared to the standard of care, and 3) the short- and long-term impact on the quality of life.

A positive trial would lead to a new standard treatment that could easily be adopted in the community practice. Furthermore, if this regimen proves to be active and is feasible, future research could adopt it as a backbone for treatments incorporating molecularly driven therapies. Based on the known pattern of disease recurrence in endometrial cancer and the role of radiotherapy in preventing local recurrence, it is highly predictable that this will be a positive trial. However, in the event that the results of this trial are negative, a long-term, lingering question will be answered definitively. A negative trial would provide the basis for limiting the role of radiotherapy in this setting and the rationale for focusing future research efforts on exploration of biological pathways important to progression of endometrial carcinoma.

2.2 Prior Experience with Chemotherapy and Radiotherapy in Endometrial Cancer

2.21 *Review of the role of chemotherapy in advanced endometrial carcinoma*
The benefits of chemotherapy in patients with endometrial carcinoma have been recognized during the past decade. Cisplatin, doxorubicin, and paclitaxel are all active agents in the treatment of metastatic or recurrent endometrial cancer.[10-20] More recently, multi-agent chemotherapy emerged as an active therapeutic modality in patients with advanced endometrial cancer, with response rates as high as 70%.[21] The GOG studied the combination of doxorubicin and cisplatin in protocols GOG-0107 and GOG-0163. In both protocols, the overall response rate to cisplatin/doxorubicin was at least 40%, with a complete response observed in approximately 20% of patients. [21] The toxicity profile of the combination arm was acceptable.

A recent randomized Phase III clinical trial conducted by the GOG demonstrated a survival advantage for combination chemotherapy over whole abdominal irradiation (WAI) in patients with advanced endometrial cancer.[9] GOG-0122, a randomized comparison between WAI and combination chemotherapy (AP), showed that combination doxorubicin/cisplatin (AP) improved overall and disease-free survival over whole abdominal radiotherapy in patients with optimally resected advanced endometrial cancer. With a median 74 months of follow-up, the hazard ratio for PFS (HR=0.71) and OS (HR=0.68) favored the chemotherapy arm. This trial set a new standard for patients with advanced endometrial cancer. Importantly, the proportion of patients with an initial pelvic failure in this protocol was 18%, which suggests that despite good systemic control, local control is also needed in this patient population[9]. Other retrospective analyses have also indicated that in the absence of radiotherapy, patients treated with systemic chemotherapy alone experience a high rate (20-30%) of pelvic recurrences.[22-23]

To further improve treatment outcome, three subsequent trials followed: GOG-0177, 0184 and 0209. All these trials addressed changes in the systemic regimen and did not focus on improving local control. GOG-0177 and GOG-0184 looked at further improving the efficacy of combination chemotherapy by adding a third active agent (paclitaxel).

In GOG-0177, the combination doxorubicin/cisplatin (AP) was compared to the triplet doxorubicin/cisplatin/paclitaxel (TAP) in women with measurable metastatic or recurrent endometrial cancer.[24] The triplet was more active. Response rates were 57% for TAP (22% CR, 35% PR) versus 34% for AP (7% CR, 26% PR); $p<0.001$ and the hazard ratio for progression or death for TAP relative to AP was 0.60 (95% CI 0.46-0.78, $p<0.001$). This translated into a median progression-free survival (PFS) of 8.3 for TAP versus 5.3 months for AP, and a median overall survival of 15.3 for TAP versus 12.3 months for AP ($p=0.037$).[24] However, the toxicity of the regimen was high and growth factor support was mandatory. The proportion of patients with a maximum of Grade 2, 3, and 4 neuropathy was 27%, 12%, and 0%, respectively. Interestingly, when the TAP regimen was taken to the adjuvant setting, following volume-directed RT in stage III-IVA endometrial cancer (GOG-0184), preliminary results of mature data suggest that there was no disease-free survival benefit noted compared to AP (unpublished results). Furthermore, the crude proportion of patients with acute Grade 3-4 GI toxicity was 13% in the AP arm and 18.3% in the TAP arm, and 80% of all patients completed the planned six cycles of systemic treatment. In the TAP arm, protocol therapy was discontinued in 14% of patients due to toxicity and an additional 4.6% due to patient refusal. The crude proportion of patients with late Grade 3-4 GI toxicity, including bowel obstruction and fistula, in both doxorubicin containing regimens was 6-8% (this estimate does not account for competing risks). These results suggest that although highly active in the metastatic setting, the triplet TAP regimen is not superior and is too toxic to be administered after RT in the adjuvant setting. The long-term adverse effects of chemotherapy on quality of life in these studies have not yet been analyzed, but an adverse impact due to neurotoxicity is expected to emerge. These considerations led to a well justified interest in developing a less toxic regimen for this patient population. This objective is addressed by protocol GOG-0209, designed to compare the commonly used and popular regimen carboplatin/paclitaxel (CT) vs. TAP. The CT regimen had been tested in several Phase II studies, with encouraging preliminary results.[25, 26] Hoskins and co-workers reported a 78% response rate in patients with advanced non-serous endometrial cancer, and a response rate of 51% in patients with serous papillary uterine cancer.[25] The three-year survival for patients with advanced non-serous papillary endometrial cancer was 62%, whereas patients with advanced papillary serous endometrial carcinoma had a 39% three-year overall survival

probability. Nakamura reported a complete response rate to CT of 45.5%.[26] Similarly, Price reported a 63% response rate in their series of 20 patients.[27] Lastly, a randomized Phase II trial suggested that the combination carboplatin/paclitaxel is at least as active as doxorubicin/cisplatin, with response rates of 44% (CT) versus 26% (AP).[28] The results of GOG-0209 are not yet available. However, because of its ease of administration and reduced toxicity, in face of significant short- and long-term toxicity with the doxorubicin containing regimens, carboplatin/paclitaxel has been selected as the regimen for the control arm in the current protocol.

2.22 *The role of radiation therapy in Stage III endometrial carcinoma*

Traditionally, radiation therapy has been employed in patients with endometrial carcinoma to improve local control after surgery.[29] Its role has been established in patients with early-stage intermediate and high risk endometrial cancer.[30] Although pelvic radiotherapy is commonly used in patients with advanced uterine carcinoma,[31] to date a survival advantage with adjuvant radiotherapy has not been proven by a randomized study. Several retrospective case series have reported the impact of adjuvant radiotherapy in this setting, but most cohorts of patients are small and non-homogenous. In general, these studies suggest a modest benefit from adjuvant radiotherapy after complete surgery in this setting, with the majority of patients relapsing systemically.[32-34] These studies also reflect the fact that Stage III endometrial cancer is often a systemic disease, where disease control requires effective systemic therapy.

2.23 *Role of combined chemotherapy and radiation therapy in advanced endometrial cancer*

Based on these considerations, it is compelling to hypothesize that a strategy combining chemotherapy and radiotherapy would yield better results in this patient population by controlling both systemic and local recurrences. It is important to note that 30% of patients included in GOG-0122 treated with systemic chemotherapy recurred in the pelvis and in the abdomen. This observation suggests that patients treated with systemic chemotherapy experience a significant rate of local failure, which leads to compromise in overall survival. Inclusion of tumor volume-directed radiotherapy could prevent local recurrences and potentially would lead to an improvement in overall survival. This is a crucial question that to date has not been addressed relative to this patient population in a randomized trial. Several small studies have suggested that combination therapy can indeed yield survival benefit. Onda reported that among 30 patients with Stage IIIC endometrial cancer treated with combination WAI and chemotherapy, the five-year OS was 84%.[35] A recent study reported by Bruzzone notes DFS of 30% and OS of 53% among 45 poor-prognosis

patients with Stages III and IV uterine cancer treated with pelvic radiotherapy and chemotherapy (cisplatin, epidoxorubicin and cyclophosphamide).[36]

The Phase II trial run by the RTOG (Protocol 9708) demonstrated feasibility and high efficacy of a combined chemo-radiation approach in endometrial cancer patients at high risk of recurrence.[37] The regimen studied here involved cisplatin given together with pelvic radiation (45Gy) followed by four cycles of cisplatin and paclitaxel. At four years the cumulative proportions of patients with pelvic, regional and distant recurrence are 2%, 2%, and 19%, respectively. The percent of patients alive or alive and disease free at 4 years are 85% and 81%, respectively. For Stage III patients, four-year OS and DFS was 77% and 72%, respectively. These compelling results provide a preliminary basis suggesting the feasibility of this approach and also support studying this regimen in a randomized fashion. Successful combination of a chemo-radiation approach in high risk endometrial cancer has been suggested in another Italian pilot study using paclitaxel with EBRT.[38] The combined modality approach has demonstrated efficacy and feasibility in many other tumor types,[39-42] including cervical cancer.[43-46]

Finally, the recently reported results of GOG-0184 suggest that a combined radiotherapy and chemotherapy approach in this setting yields three-year DFS of 62-64%. In this protocol, women with optimally debulked Stage III and IVA endometrial cancer were randomized to pelvic radiotherapy followed by systemic chemotherapy. The two arms of the trial compared outcomes with TAP vs. AP chemotherapy, the primary endpoint being DFS. There was no statistically significant difference in DFS with the addition of paclitaxel to the AP regimen. The overall survival data is not yet reported. The results of the trial further support feasibility of the approach.[47]

The advantages of administering up-front chemotherapy with radiation are several: 1) synergistic, anti-tumor activity and modulation of the effects of radiation by cisplatin;[40, 41] 2) administration of the systemic agent up-front, which circumvents concern related to possible systemic relapses during the delay imposed by delivery of radiotherapy; 3) good track record and experience with this approach from the cervical cancer studies.[43-46]

2.23 *Measurement of Quality of Life (QOL) in Endometrial cancer*
Little information exists on the impact of initial treatment on patients' QOL as well as the long term QOL implications, and these QOL assessments may be crucial in help deciding treatment plans when treatments may offer comparable results. QOL domains that are particularly important during platinum-based chemotherapy and

radiotherapy include neuropathy, overall general well being, fatigue, and gastrointestinal toxicity, and these will be the focus of this current study.

QOL was measured during GOG study 0122, and newly diagnosed patients with either stage III or IV cancer were randomized to whole abdominal radiation versus doxorubicin and cisplatin (60 mg/m^2 IV and 50 mg/m^2, resp., IV once every 3 weeks for 8 cycles).[9,48] QOL measures used in this study included Functional Assessment of Cancer Therapy (General) (FACT-G), Fatigue Scale, Assessment of Peripheral neuropathy, and Functional Alterations due to Changes in Elimination (FACE). FACT-G scores were not different between the two treatment arms, but peripheral neuropathy was higher amongst patients receiving chemotherapy, and fatigue and FACE scores were worse in those patients receiving whole abdominal radiotherapy.

In this current study, the following QOL measures will be used: FACT-G (physical and functional well being), [49] FACT-Endometrial which remains exploratory, a four-item subscale of FACT-GOG neuropathy, and two questions from FACT-C (FACT-colon cancer). [50] These questions will answer both short-term as well as long-term side effect impact of therapy.

2.3 Inclusion of Women and Minorities

The Gynecologic Oncology Group and GOG participating institutions will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the entire endometrial cancer population treated by participating institutions.

3.0 PATIENT ELIGIBILITY AND EXCLUSIONS

3.1 Eligible Patients

3.11 All patients with Surgical Stage III or IVA endometrial carcinoma per FIGO 2009 staging criteria, including clear cell and serous papillary and undifferentiated carcinomas. **(06/07/2010)(01/03/2011)**

Surgical Stage III disease includes those patients with positive adnexa, parametrial involvement, tumor invading the serosa, positive pelvic and/or para-aortic nodes, or vaginal involvement. **(01/03/2011)**

Surgical Stage IVA includes patients with bladder or bowel mucosal involvement, but no spread outside the pelvis.

3.12 Patients with FIGO 2009 surgical Stage I or II endometrial clear cell or serous carcinoma and with positive peritoneal cytology. **(01/03/2011)**

3.13 Surgery must have included a hysterectomy and bilateral salpingo-oophorectomy. Pelvic lymph node sampling and para-aortic lymph node sampling are optional.

3.14 Patients with a GOG Performance Status of 0, 1, or 2.

3.15 Patients with adequate organ function, reflected by the following parameters:

WBC ≥ 3000/mcl
Absolute neutrophil count (ANC) ≥ 1500/mcl
Platelet count ≥ 100,000/mcl
SGOT, SGPT, and alkaline phosphatase ≤ 2.5 X upper limit of normal (ULN) **(06/07/2010)**
Bilirubin ≤ 1.5 X ULN **(06/07/2010)**
Creatinine ≤ institutional ULN **(06/07/2010)**

3.16 Patients who have met the pre-entry requirements specified in Section 7.0; testing values/results must meet eligibility criteria specified in Section 3.1.

3.17 Patients who have signed an approved informed consent and authorization permitting release of personal health information.

3.18 Patients must be 18 years of age or older.

3.19 Entry into the study is limited to no more than 8 weeks from the date of surgery. **(06/07/2010)**

3.2 Ineligible Patients

3.21 Patients with carcinosarcoma.

3.22 Patients with recurrent endometrial cancer.

3.23 Patients with residual tumor after surgery (any single site) exceeding 2 cm in maximum dimension.

3.24 Patients who have had pelvic or abdominal radiation therapy.

3.25 Patients with positive pelvic washings as the only extra-uterine disease are NOT eligible if the histology is other than **clear cell or papillary serous carcinoma.**

3.26 Patients with a history of other invasive malignancies, with the exception of non-melanoma skin cancer, are excluded if there is any evidence of active malignancy within the last five years. Patients are also excluded if their previous cancer treatment contraindicates this protocol therapy.

3.27 Patients with a history of serious co-morbid illness or uncontrolled illnesses that would preclude protocol therapy.

3.28 Patients with an estimated survival of less than three months.

3.29 Patients with FIGO 2009 Stage IVB endometrial cancer. **(01/03/2011)**

3.210 Patients with parenchymal liver metastases.

3.211 Patients who have received prior chemotherapy for endometrial cancer.

3.212 Patients with a history of myocardial infarction, unstable angina, or uncontrolled arrhythmia within 3 months from enrollment.

4.0 STUDY MODALITIES

4.1 Cisplatin (Platinol®-AQ) (NSC #119875)

4.11 Formulation: Cisplatin is a sterile aqueous solution, each mcl containing 1 mg cisplatin and 9 mg sodium chloride. Cisplatin is supplied in multidose vials with 50 mg and 100 mg of cisplatin.

NOTE: Aluminum reacts with Platinol® 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 Platinol®.

4.12 Storage: Store at 15° to 25°C. Do not refrigerate. Protect unopened container from light. The cisplatin remaining in the amber vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light.

4.13 Adverse effects: leukopenia, thrombocytopenia, anemia, nausea, vomiting, nephrotoxicity, ototoxicity, peripheral neuropathy, electrolyte imbalance, hypocalcemia, hypomagnesemia, aminoglycoside ototoxicity, ocular toxicity, and allergic reactions. Infrequent: Cardiac abnormalities, anorexia, elevated SGOT, rash, alopecia, and acute myeloid leukemia.

NOTE: Aminoglycoside antibiotics given before, with, or after cisplatin may potentiate renal toxicity and should be avoided whenever possible.

Severe renal toxicity can be largely avoided by induction of a diuresis before, during and after treatment.

Mild renal dysfunction is a common complication (10%) of chronic therapy and may require discontinuation of therapy if BUN > 30 mg/dl or creatinine > 2.0 mg/dl develop.

4.14 Supplier: Commercially available from Bristol Laboratories Oncology Products.

*Refer to Package Insert for additional information.

4.2 Carboplatin (Paraplatin®) (NSC # 241240)

4.21 Formulation: Paraplatin is supplied as a sterile lyophilized powder available in single-dose vial containing 50 mg, 150 mg, and 450 mg of carboplatin for administration by intravenous infusion. Each vial contains equal parts by weight of carboplatin and mannitol.

4.22 Preparation: Immediately before use, the content of each vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP, according to the following schedule:

Vial Strength	Diluent Volume
50 mg	5 ml
150 mg	15 ml
450 mg	45 ml

These dilutions all produce a carboplatin concentration of 10 mg/ml. When prepared as directed, Paraplatin solutions are stable for eight hours at room temperature, since no antibacterial preservation is contained in the formulation it is recommended that Paraplatin solutions be discarded eight hours after dilution.

NOTE: Aluminum reacts with Paraplatin causing precipitate 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 Paraplatin.

4.23 Storage: Unopened vials of Paraplatin are stable for the life indicated on the package when stored at controlled room temperature and protected from light.

4.24 Adverse effects: Myelosuppression, nausea, vomiting, peripheral neuropathy, ototoxicity, hepatic toxicity, electrolyte imbalance, hypomagnesemia, hypocalcemia, and allergic reaction.

4.25 Supplier: Commercially available from Bristol-Myers Oncology.

4.26 Administration: See Section 5.3.

4.27 Dose Calculations: See Appendix IV for current instructions. **(01/03/2011)**

*Refer to Package Insert for additional information.

4.3 Paclitaxel (Taxol®) NSC#673089

4.31 Formulation: Paclitaxel is a poorly soluble plant product from the western yew, *Taxus brevifolia*. Improved solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride or 5% dextrose in water.

4.32 Supplier/How Supplied: Commercially available from Bristol-Myers Oncology. A sterile solution concentrate, 6 mg/ml available in 5 ml (30mg/vial), 16.7 ml (100mg/vial) and 50 ml (300mg/vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. The contents of the vial must be diluted just prior to clinical use.

4.33 Solution Preparation: Paclitaxel, at the appropriate dose, will be diluted in 500 – 1000 ml of 0.9% Sodium Chloride injection, USP or 5% Dextrose injection, USP (D_5W) (500 cc's is adequate if paclitaxel is a single agent). Paclitaxel must be prepared in glass or polyolefin containers due to leaching of diethylhexlphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized.

NOTE: Formation of a small number of fibers in solution (within acceptable limits established by the USP Particulate matter test for LVP's) has been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: IVEX-II, IVEX-HP or equivalent) into the IV fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

4.34 Storage: The intact vials should be stored between 20^0-25^0C (68^0-77^0F), in original package. Neither freezing nor refrigerator adversely affects the stability of the product.

4.35 Stability: Commercially available paclitaxel will be labeled with an expiration date. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3 – 1.2 mg/ml) are physically and chemically stable for 27 hours at ambient temperature (~25^0C) .

4.36 Administration of Paclitaxel: Paclitaxel, at the appropriate dose and dilution, will be given as a continuous IV infusion. Paclitaxel will be administered via an infusion control device (pump) using non-PVC tubing and connectors, such as the IV administration sets (polyethylene or polyolefin), which are used to infuse parenteral Nitroglycerin. Nothing else other than 0.9% sodium chloride is to be infused through the line where paclitaxel is being administered.

4.37 Adverse Effects:
Hematological: Myelosuppression
Gastrointestinal: Nausea and vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, ischemic colitis, neutropenic enterocolitis
Heart: Arrhythmia, heart block, ventricular tachycardia, myocardial infarction (MI), bradycardia, atrial arrhythmia
Pulmonary: Pneumonitis
Blood Pressure: Hypotension, hypertension (possibly related to concomitant medication--Dexamethasone)
Neurological: Sensory (taste), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy
Skin: Infiltration: erythema, induration, tenderness, rarely ulceration, radiation-recall reactions, erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)
Allergy: Anaphylactoid and urticarial reactions (acute), flushing, rash, pruritus
Liver: Increased SGOT, SGPT, bilirubin and alkaline phosphatase, hepatic failure, hepatic necrosis
Other: Alopecia, fatigue, arthralgias, myalgias, light-headedness, myopathy
Other, Vision: Sensation of flashing lights, blurred vision, scintillating scotomata

*Refer to Package Insert for additional information

4.4 Filgrastim (G-CSF) or Pegfilgrastim

4.41 Formulation: Filtrate (G-CSF) is available at a concentration of 300 mcg/ml in 1.0 and 1.6 single-use glass vials. It is formulated as a sterile, clear, colorless liquid in a 10 mm sodium acetate buffer at pH 4.0. The quantitative composition (per ml) is:

Filgrastim (G-CSF)	300 mcg
Acetate	0.59 mg
Mannitol*	50.0 mg
Tween 80™	0.004%
Sodium	0.035 mg
Water for injection to 1 ml	

* Beginning in 1997, Mannitol will be replaced by sorbitol. Because Sorbitol improves product stability, it will be permissible to use Sorbitol-containing Filgrastim if it becomes accidentally frozen in transit for < 24 hours.

4.42 Preparation: For this protocol, filgrastim will be given subcutaneously. It can be used directly from the vial.

4.43 Storage: The intact vials of filgrastim should be stored under refrigeration (2^o to 8^o C).

4.44 Adverse Effects: The adverse effects associated with G-CSF are usually mild and include bone pain and, rarely, splenomegaly. Laboratory effects include increases in alkaline phosphatase, LDH, WBC, and uric acid. G-CSF should not be used in patients with known hypersensitivity to E. Coli-derived drug preparations.

4.45 Supplier: Commercially available from Amgen.

4.46 Administration: G-CSF will be given as a subcutaneous injection. (See Section 6.241.) The appropriate volume of G-CSF should be withdrawn and injected subcutaneously daily. Injection sites should be rotated. If the volume to be injected is greater than 1.5 ml, the dose should be divided in half, and both doses should be given at the same time in two sites.

*Refer to Package Insert for additional information.

4.47 Pegfilgrastim (G-CSF) may be used as an alternative to Filgrastim and should be administered as a single subcutaneous dose of 6 mg on Day 2, 24 hours after administration of the chemotherapy. Pegfilgrastim should not be administered within 14 days of subsequent chemotherapy.

4.5 Radiation Therapy

Patients randomized to Regimen I will receive concomitant chemo-radiation therapy followed by systemic chemotherapy. Radiation Therapy will be given to the pelvis or pelvis and para-aortic fields (extended field RT), as described below. Given that nodal staging is optional for this study, it is the intention of the study that some flexibility be given to the treating physicians regarding the extent of the radiation therapy fields (See below.) Adequate hematological parameters as evidenced by WBC≥3000/mcl, ANC≥1500/mcl, platelet count ≥ 100000/mcl are required prior to initiating chemo-radiotherapy.

4.51 Treatment will be randomized after enrollment to either chemo-radiation therapy followed by systemic chemotherapy or to chemotherapy alone.

4.52 Chemotherapy will be administered concomitantly with the radiation therapy. Cisplatin (50 mg/m2) will be given on Days 1 and 29 of the course of external beam radiation therapy. (See Chemotherapy section.) **(06/07/2010)**

4.53 Physical Factors: All treatment will be delivered by megavoltage equipment ranging from 6 MV to a maximum of 25 MV photons. Cobalt-

60 equipment will not be acceptable for treatment on this protocol. Tomotherapy is allowed.

4.54 Localization and Simulation Methods: Localization images taken on the conventional or CT-simulator will be necessary in all cases.

4.55 Treatment Plan and Dose Specification: Patients may be treated with either conventional radiation therapy approaches or with IMRT. (See Sections 4.62, 4.64 and 5.1 for credentialing requirements.) For patients treated with a conventional 4 field approach, it is highly recommended that each patient swallow a dilute solution of an appropriate contrast material at least 30 minutes before simulation so that the small bowel can be identified on the simulator films. The use of individualized custom blocking is required. **(06/07/2010)**

Before ANY patient is enrolled on this study, each treating radiation oncologist must complete on-line a Knowledge Assessment Questionnaire found on the IROC Houston (formerly known as the Radiologic Physics Center [RPC]) website (http://irochouston.mdanderson.org). For patients treated with IMRT, the treatment plan for the first patient to be treated by each radiation oncologist on this protocol must be digitally submitted to TRIAD where it will be processed in preparation for rapid review. A rapid review will be performed PRIOR TO DELIVERING ANY PROTOCOL TREATMENT. The rapid review will be conducted by IROC Houston (RPC), and suggestions regarding protocol compliance will be forwarded to the participating institution's radiation oncologist. Instructions for electronically submitting the patient case can be found on the IROC Houston web site: http://irochouston.mdanderson.org. The treatment plans for the subsequent patients enrolled at a site will not be required to be reviewed prior to treatment, but a review will be performed. Once data has been submitted to TRIAD, complete a DDSI contact information form at [redacted] **(06/07/2010) (04/28/2014)**

4.56 Daily Tumor Dose, Total Dose, and Overall Treatment Time: A daily tumor dose of 180 cGy per day will be given to a total dose of 4500 cGy (180 cGy *x* 25 treatments) in approximately five weeks. Treatment will be given 5 days a week, from Monday through Friday

4.57 Dose Distribution (Site): Dose to the CTV should not vary by more than +/- 5% from the prescribed dosage for 3D conformal plans. The use of tissue wedges and/or compensating filters may be necessary to accomplish this goal. Isodose distributions shall be obtained and submitted for review.

4.58 As a general rule, only pelvic radiation therapy will be given, unless there is imaging, intra-operative, histologic, or other evidence of para-aortic

node involvement. However, the treating radiation oncologist may reasonably elect to treat with extended-field radiation therapy in the setting of positive pelvic nodes in the absence of adequate surgical staging data indicating the para-aortic lymph nodes are negative. Similarly, the treating radiation oncologist might elect not to treat the para-aortic field (only in the absence of proven metastatic disease in this region) to improve the patient's acute tolerance to RT. In general these treatment decisions will not be deemed protocol violations, given sufficient information regarding the decision-making process.

4.59 If there is tumor extension into the vagina, the external beam fields will be modified to include the disease volume with at least a 2 cm margin. For involvement of the distal 1/3 of the vagina, inguino-femoral nodes should also be covered in the external beam RT ports. If the patient's tumor extends into the cervix, or invades deeply and extends into the lower uterine segment, or if there is lymph-vascular space invasion by tumor, or if the tumor has extended into the vagina, such a patient will receive intravaginal boost brachytherapy (HDR or LDR) at the discretion of the radiation oncologist. Patients with residual gross disease in the vagina following surgery are eligible as long as the maximum dimension is no greater than 2 cm by physical exam and imaging studies, if indicated.

4.6 Radiation Therapy Volumes and Technique

4.61 Pelvic field: 3D Conformal

Portal and Treatment Volume Definition:

The boundaries are as follows:

AP/PA Fields: Cephalad Border:

A transverse line drawn within 2 cm of the L5-S1 interspace, or higher if necessary to include known areas of lymph node involvement by tumor.

AP/PA Fields: Caudal Border:

The mid-portion of the obturator foramen or a minimum of 4 cm margin on the vaginal cuff, preferably defined by marker seed placement or by placement of a vaginal swab at the time of simulation.

Lateral Borders:

≥1 cm beyond the lateral margin of the true pelvis at its widest points. Alternatively, use of a CT scan to outline the target vessels with a border of at least 1 cm is acceptable.

Lateral Pelvic Fields:

The cephalad and caudal borders are same as above.

Anterior Border:

A horizontal line drawn anterior to the symphysis pubis. When extended in the cephalad direction, this line should pass at least 1 cm anterior to known nodal regions or, in the absence or radiographic documentation, the line should pass at least 1.5 cm anterior to the L5 vertebral body. Individualized custom blocks can be used to achieve this goal.

Posterior Border:

A cephalo-caudal line passing through the third sacral vertebra. Every effort should be made to include the upper vaginal stump with a margin of at least 3 cm.

4.62 Pelvic Radiation Therapy: IMRT

In addition to the rapid review requirements for all radiation oncologists treating on this protocol (see Section 4.55), please note that all institutions that are considering the use of IMRT MUST be credentialed by IROC Houston (RPC) at M.D. Anderson Cancer Center before entering any patient on this study. (See Section 5.1). A pre-treatment review will be performed PRIOR TO DELIVERING ANY PROTOCOL TREATMENT. The rapid review will be conducted by IROC Houston , and suggestions regarding protocol compliance will be forwarded to the participating institution – radiation oncologist. Instructions for electronically submitting the patient case can be found on the IROC Houston web site [redacted] Institutions that have been previously credentialed for IMRT by RTOG or GOG via the head and neck phantom or the pelvic phantom can determine what additional requirements must be completed by filling out the "Credentialing Status Inquiry" form on the IROC Houston website. IROC Houston will issue credentials for this protocol to the institution and notify the GOG Statistical and Data Center. **(06/07/2010) (04/28/2014)**

Institutions that have **not** been credentialed by GOG or RTOG must apply for IMRT credentialing. See Section 5.1 for credentialing requirements.

Portal and Treatment Volume Definition:

4.621 Patient Immobilization: Prior to simulation, it is recommended that radiopaque marker seeds be inserted into the vaginal apex to

help to identify the area by CT scan. Patients are to be immobilized in the supine position in an immobilization device such as Vac-lok or alpha-cradle, with fixation of the upper body, trunk, and proximal thighs. Patients are to be treated in the immobilization device. CT scan thickness should be 3 mm or smaller through the region that contains the PTV, extending from at least L3-4 level to below the perineum.

4.622 Simulation: CT simulation is required to define clinical target volume (CTV) and planning target volume (PTV). The CT scan should be acquired in the same position and immobilization device as for treatment. The use of IV contrast and bowel prep-contrast are highly recommended for better delineation of the contrast-enhanced pelvic vessels used as a surrogate for regional nodal delineation, as well as small bowel contouring, respectively.

4.623 Contouring the Target volumes:

4.6231 Please refer to the ***RTOG Gynecological Atlas for volume specification. The atlas may be accessed on the RTOG website at:*** [redacted]

4.6232 The Clinical Target Volume (CTV) is defined as the vaginal apex with margins as given in Section 4.6, in addition to pelvic nodal regions lying within the field borders given in Section 4.61.

If gas/stool distends the rectum, the CTV is to be expanded to include the anterior half of the rectum to account for evacuation of the rectum. **(03/14/2011)**

4.6233 The nodal portion of the CTV should include the internal (hypogastric and obturator), and external iliac lymph node regions. The CTV should be delineated using the contrast-enhanced (preferably IV contrast administered) iliac vessels, in addition to the perinodal soft tissue (minimum of 6 mm axial margin around the vessels). Bone and intraperitoneal small bowel should be excluded from the CTV as much as possible (leaving at least 6 mm margin around the vessels).

Approximately 1-2 cm of tissue anterior to the sacrum (S1-S3) may be added to the CTV for adequate coverage of pre-sacral nodes, although this is optional and at the discretion of the treating radiation oncologist. In addition the most antero-lateral margin of the external iliac nodes that lie just

proximal to the inguinal canal should be excluded from the CTV (nodal CTV should stop at the femoral head). Proximally, the CTV should end 7 mm from the L5-S1 interspace to account for the PTV.

The CTV should include the inguino-femoral nodes if the distal one-third of the vagina is involved with tumor.

4.6234 The PTV should provide a 7 mm-1 cm margin in all directions around the CTV.

4.6235 The definitions of volumes will be in accordance with the 1993 ICRU report #50. Prescribing, recording and reporting photon beam therapy and 1999 ICRU report #62.

4.6236 Critical normal surrounding structures:

4.62361 Bladder will be contoured in each slice in which it appears.

4.62362 Rectum will be contoured in each slice in which it appears. As a general guideline, the radiation oncologist can consider the maximum caudal extent of the rectum to lie 1.5-2.0 cm from the bottom of the ischial tuberosities. Superiorly, judgment will be required to establish where the rectum ends and the sigmoid colon begins. The transition to the sigmoid colon is marked by increased curvature and tortuosity in its path.

4.62363 Small bowel will be contoured in each slice in which it appears, including at least 2 cm above the PTV. The small bowel will be contoured in its entirety within these parameters, including adipose and mesentery.

4.62364 Femoral heads will be contoured in all the slices in which they appear.

4.624 Constraints: Participants are strongly encouraged to respect the following limits, whether 3-D conformal or IMRT approaches are used.

4.6241 Small bowel: <30% to receive ≥ 40Gy, Dmax ≤46 Gy

4.6242 Rectum: < 80% to receive ≥ 40Gy, Dmax ≤55 Gy **(03/14/2011)**

4.6243 Bladder: < 50% to receive ≥ 45Gy, Dmax ≤60 Gy

4.6244 Femoral heads: < 50% to receive ≥ 40Gy, Dmax ≤50 Gy.

4.6245 Unspecified tissue (tissue contained within the skin or any other normal structure not delineated above and outside the PTV, not included within any other structure): No more than 1% or 1 cc (whichever is smaller) of the tissue outside the PTV will receive > 110% of the dose prescribed to the PTV.

4.63 Extended Field Radiation Therapy: 3D Conformal

Portal and Treatment Volume: The boundaries are as follows:

AP/PA Fields: Cephalad Border:

A transverse line drawn within 2 cm of the T11-T12 interspace.

AP/PA Fields: Caudal Border:

The mid-portion of the obturator foramen or a minimum of 4 cm margin on the vaginal cuff, preferably defined by marker seed placement or by placement of a vaginal swab at the time of simulation.

Lateral Borders:

In the pelvis >1 cm beyond the lateral margin of the true pelvis at its widest points. Alternatively, use of a CT scan to outline the target vessels with a border of at least 1 cm is acceptable. Moving superiorly, the width of the field will taper to the lateral aspects of the spinal transverse processes at L4 and superior to L4. The approximate field width for the para-aortic portion of the field should be 8 cm, although some variation is expected.

Lateral Pelvic Fields:

The cephalad and caudal borders are same as above.

Anterior Border:

A horizontal line drawn anterior to the symphysis pubis. When extended in the cephalad direction, this line should pass at least 1 cm anterior to

known nodal regions or, in the absence or radiographic documentation, the line should pass at least 1.5 cm anterior to the L5 vertebral body. Individualized custom blocks can be used to achieve this goal. Moving superiorly, the anterior border of the para-aortic field should remain a minimum of 1.5-2 cm anterior to the anterior border of the vertebral body. Again, some variation is expected, particularly in patients who have positive PA nodes or in patients who kidneys are located more anteriorly than normal. The overall width of the PA field should be at least 5 cm.

Posterior Border:

A cephalo-caudal line passing through the third sacral vertebra. Every effort should be made to include the upper vaginal stump with a margin of at least 3 cm. Moving superiorly, the posterior border of the PA field should extend back approximately 50% of the width of each vertebral body.

Suggested technique: Different techniques have been used to deliver extended field radiation therapy. The suggested technique for this study is to treat the pelvic and para-aortic fields in continuity, as opposed to splitting fields, or treating the para-aortic portion with AP-PA fields only. Treating in continuity, it is suggested that the AP-PA fields be weighted 70:30 in relation to the lateral fields, in terms of isocenter dose. This technique strikes an appropriate balance, in most cases, between small bowel dose and kidney dose. Other techniques or beam weightings are potentially permissible, if appropriate dose distributions to PTV and organs at risk (OAR's) are obtained. Should there be questions, the treating radiation oncologist is encouraged to contact the Radiation Oncology Co-Chair.

4.64 Extended Field Radiation Therapy: IMRT **(04/28/2014)**

In addition to the rapid review requirements for all radiation oncologists treating on this protocol (see Section 4.55), please note that all institutions that are considering the use of IMRT MUST be credentialed by IROC Houston before entering any patient on this study. (See Section 5.1.) **(06/07/2010)**

Please note that ALL institutions, when IMRT is to be used, must submit and successfully complete a plan for the first patient to be treated by each radiation oncologist treating on this protocol. A rapid review will be performed PRIOR TO DELIVERING ANY PROTOCOL TREATMENT. The rapid review will be conducted by IROC Houston, and suggestions regarding protocol compliance will be forwarded to the participating institution – radiation oncologist. Instructions for electronically submitting the patient case Via TRIAD can be found on the IROC Houston web site:

[redacted] The treatment plans for the subsequent patients enrolled at a site will not be required to be reviewed prior to treatment, but a review will be performed. **(06/07/2010)**

4.641 Rapid Review Data Submission for IMRT via TRIAD: **(04/28/2014)**

For Submission via TRIAD, the structure names must match the following list exactly or resubmission will be required. After submission is completed submit a DDSI contact information form. The DDSI can be found at [redacted]

Structure Name	**Description**
CTV_4500	CTV **Required**
CTVn	Nodal CTV portion **Required**
PTV_4500	PTV **Required**
Bladder	Bladder **Required**
Femurs	Femoral Heads **Required**
Kidneys	Kidneys **Required**
Rectum	Rectum **Required**
BowelSpace	Bowel **Required**
SpinalCord	Spinal Cord **Required**
NonPTV	Unspecified tissue (External minus PTV) **Required**
External	External Skin **Required**

Portal and Treatment Volume Definition:

4.641 Patient Immobilization:

Prior to simulation, it is recommended that radiopaque marker seeds are inserted into the vaginal apex to help to identify the area by CT scan. Patients are to be immobilized in the supine position in an immobilization device such as Vac-lok or alpha-cradle, with fixation of the upper body, trunk, and proximal thighs. Patients are

to be treated in the immobilization device. CT scan thickness should be 3 mm or smaller through the region that contains the PTV, extending from at least L3-4 level to below the perineum.

4.642 Simulation:

CT simulation is required to define clinical target volume (CTV) and planning target volume (PTV). The CT scan should be acquired in the same position and immobilization device as for treatment. The use of IV contrast and bowel prep-contrast are highly recommended for better delineation of the contrast-enhanced pelvic vessels used as a surrogate for regional nodal delineation, as well as small bowel contouring, respectively.

4.643 Contouring the Target volumes: Contouring in the pelvis is identical to that described in Sections 4.61- 4.63. **(06/14/2010)**

4.6431 The Clinical Target Volume (CTV) is defined as the vaginal apex with margins as given in Section 4.6 in addition to pelvic and para-aortic nodal regions lying within the field borders given in Sections 4.61- 4.63.

4.6432 The nodal portion of the CTV should include the internal (hypogastric and obturator), external iliac lymph node, and para-aortic regions. The CTV should be delineated using the contrast-enhanced (preferably IV contrast administered) iliac vessels, in addition to the perinodal soft tissue (minimum of 6 mm axial margin around the vessels). Bone and intraperitoneal small bowel should be excluded from the CTV as much as possible (leaving at least 6 mm margin around the vessels).

Approximately 1-2 cm of tissue anterior to the sacrum (S1-S3) may be added to the CTV for adequate coverage of presacral nodes, although this is optional and at the discretion of the treating radiation oncologist. In addition, the most antero-lateral margin of the external iliac nodes that lie just proximal to the inguinal canal should be excluded from the CTV (nodal CTV should stop at the femoral head. Proximally, the CTV should end 7 mm from the T11-T12 interspace to account for the PTV.

4.6433 The PTV should provide a 7 mm-1 cm margin in all directions around the CTV.

4.6434 The definitions of volumes will be in accordance with the 1993 ICRU report #50. Prescribing, recording and reporting photon beam therapy and 1999 ICRU report #62.

4.6435 Critical normal surrounding structures: **(06/14/2010)**

4.64351 Bladder will be contoured in each slice in which it appears.

4.64352 Rectum will be contoured in each slice in which it appears. As a general guideline, the radiation oncologist can consider the maximum caudal extent of the rectum to lie 1.5-2.0 cm from the bottom of the ischial tuberosities. Superiorly, judgment will be required to establish where the rectum ends and the sigmoid colon begins. The transition to the sigmoid colon is marked by increased curvature and tortuosity in its path.

4.64353 Small bowel will be contoured in each slice in which it appears, including at least 2 cm above the PTV. The small bowel will be contoured in its entirety within these parameters, including adipose and mesentery.

4.64354 Femoral heads will be contoured in all the slices in which they appear.

4.6436 Constraints: Participants are strongly encouraged to respect the following limits, whether 3-D conformal or IMRT approaches are used. **(06/14/2010)**

4.64361 Small bowel: <30% to receive ≥ 40Gy, Dmax ≤46 Gy

4.64362 Rectum: < 60% to receive ≥ 40Gy, Dmax ≤55 Gy

4.64363 Bladder: < 50% to receive ≥ 45Gy, Dmax ≤60 Gy

4.64364 Femoral heads: < 50% to receive ≥ 40Gy, Dmax ≤50Gy.

4.64365 Kidney volume (combined right and left): <40% to receive ≥15 Gy **(06/07/2010)**

4.64366 Spinal cord: <10% to receive ≥40 Gy, Dmax ≤45 Gy **(06/07/2010)**

4.64367 Unspecified tissue (tissue contained within the skin or any other normal structure not delineated above and outside the PTV, not included within any other structure): No more than 1% or 1 ml (whichever is smaller) of the tissue outside the PTV will receive > 110% of the dose prescribed to the PTV.

4.65 Boosts to Gross Disease

4.651 As reflected in the eligibility and ineligibility criteria, otherwise eligible patients with up to 2 cm of residual disease (single site) are eligible. For these patients, it is permissible to deliver a radiotherapy boost to these areas provided that they are clearly definable by standard imaging modalities, allowing the radiation boost to be accurately targeted.

4.652 Dose
A further 10-15 Gy in 5-8 fractions can be delivered at the discretion of the radiation oncologist. The boost dose can be delivered to the initial volume of gross disease as identified on the initial imaging studies. Should the initial chemo-radiation treatment result be a partial or complete response of the identifiable gross disease, the boost dose should be limited to 10 Gy.

4.653 Margin and Definition of Volume

The original gross disease with a 1.0-1.5 cm margin should be targeted.

4.654 Technique

Either 3-D conformal or IMRT techniques can be used. However, as noted in Section 4.62, it is NOT acceptable to treat initially with 3-D conformal treatment and then switch to IMRT for the boost.

The actual treatment technique is expected to vary considerably due to the location of the targeted area, surrounding radiosensitive structures, and dose distribution of the initial treatment.

4.66 Treatment Plan, Dose Specification, and Distribution

4.661 The volume irradiated with the whole pelvic fields will include the CTV and PTV as defined above.

4.662 The whole pelvis will receive a total dose of 4500 cGy in 25 fractions at 180 cGy/fx. For patients treated with IMRT, the prescription dose is the isodose that encompasses at least 97% of the PTV. No more than 20% of any PTV should receive >110% of the prescribed dose. No more than 1% of the PTV should receive <93% of the prescribed dose. No more than 1% or 1 cc (whichever is smaller) of the tissue outside the PTV will receive >110% of the dose prescribed to the PTV. However, with respect to this last constraint, it is recognized that there may be patients in which, due to obesity or other factors, this constraint may not be obtainable if other constraints, e.g. rectum, are met. In these cases it is recommended that the OAR constraints be favored to the extent possible that is consistent with good radiotherapy practice.

4.67 Documentation requirements

See Section 5.14 for instructions to set up TRIAD for digital submissions. **(04/28/2014)**

4.671 For 3-D conformal treatments, digital reconstructed radiographs (DRR) of the treatment fields with the three-dimensional reconstruction of the CTV are to be obtained and submitted for evaluation.

4.672 For 3-D conformal plans, localization or block-check images of virtually simulated fields are to be obtained in the simulator and/or treatment machine for all the treatment fields independently, whether cerrobend blocks or multi-leaf collimators are used.

4.673 For 3-D conformal plans, all plans must be submitted electronically via TRIAD. See IROC Houston (RPC) website for details: [redacted] **(04/28/2014)**

4.674 For IMRT plans, all plans must be submitted electronically via TRIAD for review, in addition to what is required from IROC Houston (RPC) in Section 10.2. **(04/28/2014)**

4.675 For IMRT plans, Dose-Volume Histograms (DVHs) are to be obtained for each one of the target volumes defined above, as well as the critical surrounding structures, and need to be submitted for evaluation. For detailed description of radiation pelvic fields, please see Section 4.62.

4.68 Therapy Interruptions: If interruption of two weeks or less occurs, radiation should be completed to the prescribed total dose. Therapy interruptions of more than two weeks will be considered a major or minor deviation from the protocol, depending on clinical circumstances, and resumption of therapy will be at the discretion of the radiation oncologist. Follow-up must continue regardless of radiation treatment received.

4.69 Expected Toxicity: Toxicity will vary depending upon tolerance of individual patient, daily dose, total dose, overall treatment time, associated illness, etc. The following toxicity criteria may be used:

Gastrointestinal: Nausea and vomiting is unusual, but may be seen after pelvic radiation. Antiemetics may be used during treatment or may be given prophylactically the night prior to treatment. Intractable nausea or vomiting is rarely seen with pelvic radiation alone and is usually the result of another process, i.e., bowel obstruction. Increased bowel activity with diarrhea usually can be controlled with low- fiber, low-fat, bland diets, and anti-diarrhea medications. Should G.I. toxicity become severe, hospitalization may be required, at which time the treatment is interrupted temporarily until the patient's condition improves.

Hematological: Hematological toxicity is seen infrequently, unless pelvic radiation is accompanied by chemotherapy. A CBC should be obtained weekly during radiotherapy. If the ANC falls below 1,000 /mcl or the platelet count below 50,000/mcl, the CBC should be obtained twice weekly. Radiotherapy should be stopped when ANC < 500 and/or platelets < 25,000. Radiotherapy should be temporarily halted if on successive measurements the platelet count declines rapidly below 50,000. Radiotherapy may be resumed when ANC > 500/mcl and platelets > 50,000/mcl. **(06/22/09)**

4.610 Brachytherapy: If a vaginal brachytherapy boost is to be given based on the criteria given in Section 4.59, it should commence within 2 weeks of completion of the external beam RT. It should be delivered with a vaginal cylinder (HDR or LDR) or colpostats (LDR), and in the absence of gross residual disease following surgery the treating physician must choose one of the following:

A) HDR: 600 cGy x 2-3, weekly, prescribed at the vaginal surface. Dose optimization should be used in an effort to create reasonable homogeneity of dose around the surface of the applicator. A minimum of 4 cm of vaginal length should be treated.

B) LDR 2000-3500 cGy prescribed at the vaginal surface in 1 insertion at a dose rate of 40-100 cGy/hr. A minimum of 4 cm of vaginal length should be treated.

In cases where the patient has small volume (≤2 cm) residual disease in the vagina following surgery, the patient may have intra-cavitary treatment as described above only if the residual thickness following external RT is less that 0.5 cm. If the residual lesion is greater than 1 cm in thickness, a low dose-rate interstitial implant is recommended to deliver approximately 3500 cGy to the residual volume.

4.611 Physical Factors **(06/14/2010)**

If an intravaginal boost is to be used, it should be delivered with an intravaginal cylinder (HDR or LDR). Acceptable isotopes include cobalt or iridium for HDR, radium or cesium for LDR.

4.612 Expected Toxicity **(06/14/2010)**

4.6121 Gastrointestinal: Nausea and vomiting may occur after extended field (PAN) treatments, but can be effectively treated with an appropriate antiemetic in most cases. Intractable nausea and vomiting beyond the first few days should arouse suspicion of recurrent tumor or other causes of bowel obstruction, as it is not commonly seen as a result of radiation alone.

Increased bowel activity with diarrhea can be expected fairly routinely after the first two weeks of pelvic radiation. It is recommended that instructions be given to patients for low-fiber, low-fat, bland diet. Most patients will require anti-diarrheal medications such as diphenoxylate HCL with atropine sulfate (Lomotil) or loperamide HCL to control diarrhea.

4.6122 Hematological toxicity of a mild nature will be seen frequently with a decline in WBC and platelet count.

4.613 Radiation Therapy Quality Control and Documentation **(06/14/2010)**
IROC Houston is funded by the NCI to support clinical trials employing radiation therapy and will supervise the dosimetry quality control for this clinical trial. To participate in the trial, the institutions must demonstrate the ability to achieve an accuracy of ±3% in measuring the output of their sources and ±5% in delivering the prescribed dose. **(04/28/2014)**

4.614 Radiation Therapy – ECOG and RTOG Institutions **(06/14/2010)**
Please follow the Radiation Therapy instructions as detailed above and in Section 4.5. All films and calculations should be sent directly to GOG Statistical and Data Center unless otherwise specified: **(06/07/2010)**

4.7 Pathology Requirements

4.71 Eligible Patients: All patients with FIGO 2009 Surgical Stage III or IVA endometrial carcinoma, including clear cell and serous papillary and undifferentiated carcinomas. Patients with FIGO 2009 Stage I and II clear cell or serous papillary uterine cancer with positive peritoneal cytology are eligible. **(01/03/2011)**

4.72 Ineligible Patients:
4.721 Patients with carcinosarcoma.
4.722 Patients with recurrent endometrial cancer.
4.723 Patients with Stage I and II endometrioid cancer with positive peritoneal cytology **(01/03/2011)**:
4.724 Patients with Stage IVB endometrial cancer **(01/03/2011)**:

4.73 Stained pathology slides are required for central review by the GOG Pathology Committee to confirm eligibility. At least one representative H&E stained slide (or slides) demonstrating primary site and histologic cell types will be required. At least one representative H&E stained slide documenting the most advanced stage of disease will be required. See Section 7.2 and 10.2 for additional instructions for submitting the stained pathology slides to the GOG Statistical and Data Center in Buffalo, NY.

4.8 Quality of Life Surveys

Four instruments will be used to assess QOL changes during the treatment plan and one year post-treatment.

4.81 FACT-G: FACT-G is a general QOL instrument that has been developed by David Cella and includes the following domains: physical well being, social/family wellbeing, treatment satisfaction, emotional well-being, and fulfillment and contentment. In this study, physical and functional well being, the areas most likely to be impacted by treatment, will be measured.

4.82 FACT-En: This will represent a compilation of additional concerns that patients with endometrial cancer receiving treatment have, and this was piloted in GOG 209.

4.83 Four (4)-item subscale of FACT GOG neuropathy: Patient reported neurotoxicity will be assessed using a four-item subscale embedded in FACT GOG neuropathy. Based upon data collected in both GOG-0177

and 0209, the first four questions on the subscale (NTX 1-4) were able to classify best the majority of patients and this will greatly shorten the number of questions patients will have to answer. The specific questions are: I have numbness or tingling in my hands, I have numbness or tingling in my feet, I have discomfort in my hands, and I have discomfort in my feet.
The summation of these first three QOL surveys represents the Trial Outcome Index that was piloted in GOG 209.

4.84 FACT-C (2 items): Two questions will be used from this survey and they are as follows (C3, C5): "I have control of my bowels"; "I have diarrhea."

5.0 TREATMENT PLAN AND ENTRY/RANDOMIZATION PROCEDURE **(04/28/2014)**

5.1 IROC Houston (formerly the Radiological Physics Center [RPC]) Credentialing Requirements **(04/28/2014)**

5.11 Credentialing for this protocol will be handled by IROC Houston. All information regarding credentialing can be found on the IROC Houston website [redacted] by selecting "Credentialing", then "GOG."

5.12 Before ANY patient is enrolled on this study, the treating radiation oncologist must complete on-line a Knowledge Assessment Questionnaire found on the IROC Houston (RPC) website.

5.13 <u>IMRT credentialing requirements when IMRT is planned</u>:

Institutions must be credentialed for IMRT by IROC Houston for this protocol prior to enrolling patients into this study when IMRT is planned. Each institution must successfully irradiate a standardized phantom available from IROC Houston. Instructions for requesting and irradiating the phantom are available at the IROC Houston web site. The treatment plan for irradiation of the phantom must be submitted electronically via TRIAD. (See Section 5.14.) Institutions that have been previously credentialed for IMRT via the head and neck phantom or the pelvic phantom can determine what additional requirements must be completed by filling out the "Credentialing Status Inquiry" form on the IROC Houston website. IROC Houston will issue credentials for this protocol to the institution and notify the GOG Statistical and Data Center.

Each Institution must complete the IMRT Facility Questionnaire available on the RPC web site by selecting "Protocol GOG-0258." Each institution must submit the completed IMRT Facility Questionnaire online.

Institution and/or peer-reviewed documentation of target position reproducibility [planning treatment volume (PTV) and clinical target volume (CTV)] must be consistent with Section 4.643.

5.14 Digital RT Data Submission Using TRIAD **(04/28/2014)**

TRIAD is the American College of Radiology's (ACR) image exchange application and it is used by IROC Houston. TRIAD provides sites participating in clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred. The following process must be completed prior to enrolling patients on the trial.

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. To submit images, the site physics user must have been assigned the 'TRIAD site user' role on the relevant Group or CTSU roster, and should follow their procedures for assignment of roster roles.

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 IROC- Houston web site.

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 e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

5.2 Registration Procedures **(04/28/2014)**

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

5.21 CTEP Associate Registration Procedures / CTEP-IAM Account

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 above 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>.

5.22 CTSU Registration Procedures

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

5.221 IRB Approval:

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 be approved to 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 members' website by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

5.222 Downloading Site Registration Documents:

Site registration forms may be downloaded from the GOG-0258 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

Go to https://www.ctsu.org and log in to 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 *NCTN NRG* link to expand, then select trial protocol # 0258
Click on the Site Registration Documents link

5.223 Requirements For GOG-0258 Site Registration:

- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)
- CTSU RT Facilities Inventory Form
  NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in IROC Houston monitoring program. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility

5.224 Submitting Regulatory Documents:

Submit completed forms along with a copy of your IRB Approval and Model 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)

5.225 Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)
Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
Click on the Regulatory tab at the top of your screen
Click on the Site Registration tab
Enter your 5-character CTEP Institution Code and click on Go

5.3 Patient Entry and Registration **(04/28/2014)**

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. It is integrated with the CTSU Enterprise System for regulatory and roster data. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

All site staff will use OPEN to enroll patients to this study. OPEN can be accessed on the GOG web menu page by clicking on the OPEN link.

Prior to accessing OPEN, site staff should verify the following:

All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group web site as a tool to verify eligibility.
All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access requirements for OPEN:

- 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 perform registrations, the site user must have been assigned the 'Registrar' role on the GOG or CTSU roster.
- To perform registrations you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member.

  Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

  Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions

contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

5.4 Treatment Plan

5.41 Patients can be registered when eligibility criteria have been met and informed consent obtained. Upon registration, each participant's protocol treatment will be randomized to one of the following two arms: **(06/07/2010)**

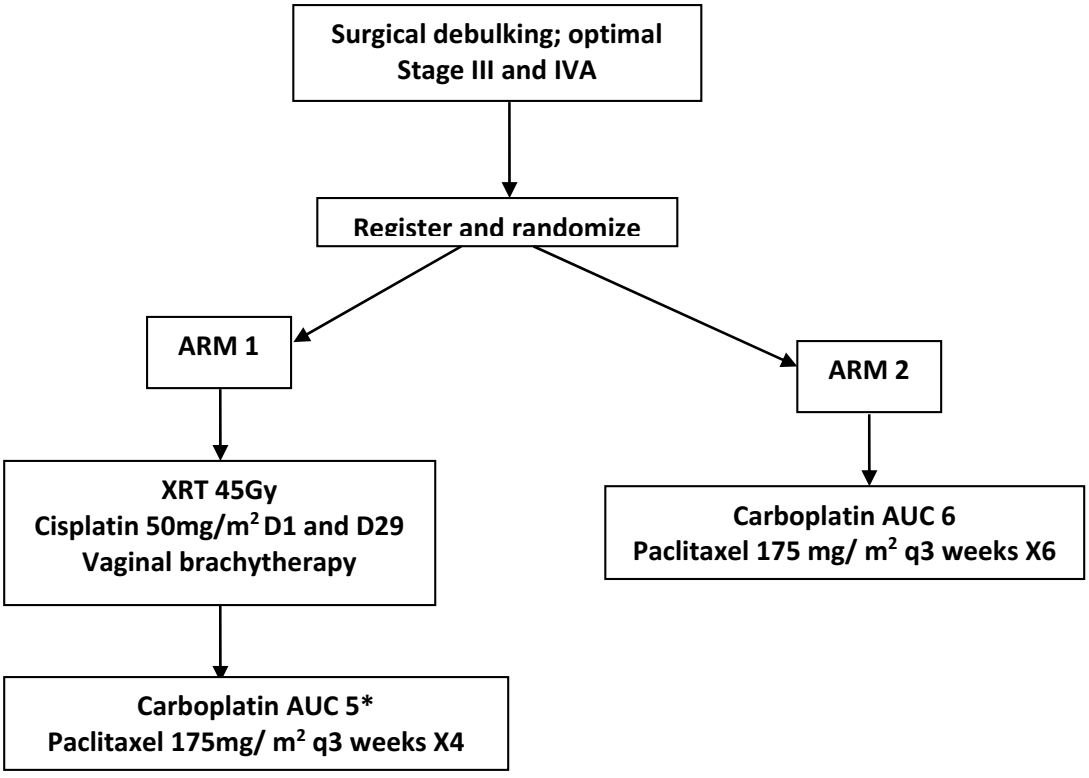
Regimen I: Cisplatin 50mg/m^2 IV on Day 1 and Day 29 (2 doses) given concomitantly with volume-directed RT, followed by Carboplatin/Paclitaxel given intravenously for 4 cycles at 3-week intervals. **(06/07/2010)**

OR

Regimen II: Carboplatin/Paclitaxel given intravenously for 6 cycles at 3-week intervals.

Protocol treatment will start within 4 weeks from study entry. **(06/07/2010)**

5.42 Treatment Schema **(06/07/2010)**



*First dose of carboplatin will be at AUC of 5, in subsequent cycles the dose will be escalated to AUC 6, as described in Section 6.2. G-CSF use is required in Regimen I along with the four cycles of carboplatin/paclitaxel. **(08/12/09) (06/07/2010)**

5.43 Methods of chemotherapy administration:

5.431 Regimen I

5.4311 Treatment Sequence:
Day 1 and Day 29 Cisplatin 50 mg/m^2 IV, two doses. For reporting purposes Day 1 of cisplatin will be referred to as Cycle 1 and Day 29 will be referred to as Cycle 2. Drug will be diluted in 250 ml 0.9% sodium chloride and administered at a rate no more than 1 mg/minute. Details of pre- and post-hydration are left to the discretion of the treating physician, but at least cisplatin can be administered with hydration and supportive medications per institutional guidelines. One suggested regimen is 1000 ml 0.9% sodium chloride administered prior to cisplatin and another 1000 ml 0.9% sodium chloride administered following cisplatin are suggested. Mannitol may also be mixed with cisplatin at the discretion of the treating physician. Electrolyte monitoring and replacement will be done based on individual assessment. **(06/07/2010)**

5.4312 BSA Calculation: Maximum body surface area used for dose calculations will be 2.0 m^2 as per GOG Chemotherapy Procedures Manual.

5.4313 Antiemetic therapy is indicated. Details are left to the discretion of the treating physician. However, a suggested regimen would include dexamethasone and a 5HT3 antagonist (ondansetron or granisetron). Suggested prophylaxis for delayed nausea induced by cisplatin consists of dexamethasone and metoclopramide.

5.4314 Radiotherapy will be administered as detailed in Section 4.6.

Patients with pathologically negative para-aortic lymph nodes will be treated with pelvic irradiation. If any para-aortic lymph node is positive, the patient will receive extended field pelvic/para-aortic radiotherapy. As described in Section 4.58, patients are allowed to receive

para-aortic RT in the absence of para-aortic nodal staging information if pelvic lymph nodes are positive.

If there is tumor extension into the vagina, the external beam fields will be modified to include the disease volume with a 2 cm margin. If the patient's tumor extends into the cervix, or invades deeply and extends into the lower uterine segment, or if the tumor has extended into the vagina, such a patient will receive intra-vaginal boost brachytherapy (HDR or LDR) at the discretion of the radiation oncologist.

After volume-directed concurrent chemo-radiation is completed, patients randomized to this arm will receive four additional cycles of chemotherapy (carboplatin/paclitaxel). Use of G-CSF support for the last part of treatment is recommended.

5.4315 Post-radiation chemotherapy:

Chemotherapy will be initiated once all radiation-related toxicity recovered to less or equal to Grade 1 toxicity. A **maximum of 8 weeks** is allowed between the end of chemo-radiation therapy and re-initiation of chemotherapy. Patients who do not recover organ function to the required parameters will be discontinued from protocol.

Systemic chemotherapy will be administered after the completion of concurrent chemo-radiation and will consist of four cycles of carboplatin and paclitaxel. (See Section 5.332 regarding administration and specific recommendations for preparative regimen for this regimen.)

Because of the high risk for myelosuppression following chemo-radiotherapy, the recommended starting dose for carboplatin will be calculated for an AUC of 5 (see Section 5.3323 for dose calculation) and the recommended starting dose of paclitaxel will be 175 mg/m2. (See Section 6.2 regarding dose levels and treatment modification recommendations)

5.4316 Prophylactic G-CSF will be administered to patients randomized to Regimen I during the **post-radiation chemotherapy portion of the study.** Prophylactic G-CSF **should not be administered during radiotherapy.**

Filgrastim (Neupogen) can be administered at a dose of 5 mcg/kg subcutaneously Days 2-11, at the discretion of the treating physician. Rounding of the G-CSF dose to the nearest vial size is acceptable. Longer periods of G-CSF administration beyond 10 days are accepted at the discretion of the treating physician. G-CSF must be discontinued at least 24 hours prior to administration of subsequent doses of chemotherapy. For convenience, package insert recommendations regarding G-CSF use are printed below. These are not, however, protocol requirements, and clinical judgment as to duration (or re-institution of) G-CSF use should be exercised. Some investigators prefer to discontinue G-CSF after nadir and two successive ANC measurements over 1500/mcl. **(08/12/09)**

Filgrastim should be administered daily for up to two weeks until the ANC has reached 10,000/mcl following the expected chemotherapy-induced neutrophil nadir. The duration of Filgrastim therapy should be discontinued if the ANC surpasses 10,000/mm^3 after the expected chemotherapy-induced neutrophil nadir. **(08/12/09)**

Peg-filgrastim (Neulasta) may be used as an alternative to Filgrastim and should be administered as a single subcutaneous dose of 6 mg on Day 2, 24 hours after administration of the chemotherapy. Pegfilgrastim should not be administered within 14 days of subsequent chemotherapy. **(08/12/09)**

5.4317 Treatment interval: Treatments are administered every 21 days. A maximum of four cycles will be administered.

5.432 Regimen II- Paclitaxel/Carboplatin

5.4321 Paclitaxel: 175 mg/m^2, 3-hour infusion, Day 1, q 21 days followed by Carboplatin: dosed to an AUC of 6.0, Day 1, q 21 days for 6 cycles.

5.4322 BSA calculation: Maximum body surface area used for dose calculations will be 2.0 m^2 as per GOG Chemotherapy Procedures Manual.

5.4323 Dosing of Carboplatin – See Appendix IV for current dose calculation instructions. (01/03/2011)

Note that carboplatin dose will be recalculated if patient has weight change of greater than or equal to 10% from baseline. **(03/14/2011)**

5.4324 Sequence of Chemotherapy Administration: Paclitaxel will be administered in a three-hour infusion followed by carboplatin. An antiemetic regimen is recommended. The antiemetic regimen used should be based on peer-reviewed consensus guidelines and is left up to the discretion of the treating physician. Additionally, for all cycles where paclitaxel is to be administered, it is recommended that a preparative regimen be employed to reduce the risk associated with hypersensitivity reactions. This regimen should include dexamethasone (either IV or PO), anti-histamine H1 (such as diphenhydramine), and anti-histamine H2 (such as cimetidine, ranitidine, or famotidine).

5.4325 For patients randomized to Regimen I, prophylactic filgrastim (or peg-filgrastim) will be used during administration of carboplatin/paclitaxel. Filgrastim will not be used during radiotherapy, for patients randomized to Regimen I. For patients randomized to Regimen II, use of filgrastim should follow published ASCO guidelines[59]. Erythropoietin should be used according to published ASCO guidelines.[60]

5.433 Chemotherapy Guidelines

See Appendix IV for General Chemotherapy Guidelines. **(04/28/2014)**

6.0 TREATMENT MODIFICATIONS

Early and late toxicities encountered during treatment will be evaluated and graded according to the NIH common toxicity criteria outlined in CTCAE v3.0.

6.1 Radiation Therapy

6.11 GI Toxicity:

Gastrointestinal toxicity greater than Grade 2 requires temporary discontinuation of treatment until toxicity resolves to Grade 1 or less.

6.12 Hematological Toxicity:

CBC should be obtained weekly during radiation therapy. If the ANC falls below 1,000 /mcl or the platelet count below 50,000/mcl, the CBC should be obtained twice weekly. If the ANC falls below 500/mcl or the platelet count below 25,000/mcl, then treatments should be stopped temporarily to allow recovery to ANC > 500/mcl and platelet count > 50,000/mcl. Radiotherapy should be temporarily halted if on successive measurements the platelet count declines rapidly below 50,000. **(06/22/09)**

6.13 Recurrent Disease:

Treatment will be discontinued in patients with progressive disease. Consideration for other therapies should be given.

6.2 Chemotherapy-Hematological Toxicity

6.21 REGIMEN I: Cisplatin dose modifications **(06/07/2010)**

6.211 Dose reduction levels: **(06/07/2010)**

DRUG	INITIAL DOSE	Dose Reduction	UNITS
Cisplatin	50	40	Mg/m2

6.212

Treatment modifications will be based on the absolute neutrophil count (ANC) rather than the total white blood cell count (WBC). Administration of the second dose of cisplatin on Day 29 will be a dose Level 1 if the ANC is $\geq$ 1,500 cells/mcl and the platelet count is $\geq$ 100,000 cells/mcl, or at dose Level 2 if ANC 1,000 to 1,500 cells/mcl and/or platelet count is 70,000-100,000 cells/mcl. The second dose on Day 29 will be held until Day 36 if these parameters are not met. If on Day 36, the hematological parameters are not met, the second dose of cisplatin will be omitted. **(06/07/2010)**

6.213 G-CSF and erythropoietin should not be used during chemo-radiation treatment. Transfusions can be administered at the discretion of the treating physician.

6.22 REGIMENS I and II: Carboplatin and paclitaxel dose modifications: **(06/07/2010)**

6.221 Dose reduction levels: **(06/07/2010)**

DRUG	INITIAL DOSE	1ST DOSE REDUCTION	2ND DOSE REDUCTION	UNITS
Carboplatin	6.0*	5.0	4.0	AUC
Paclitaxel	175	175	135	Mg/m2

* For patients randomized to Regimen I, the initial dose of carboplatin will start at an AUC of 5. The first dose reduction for patients receiving carboplatin at an AUC of 5 will correspond to the second dose reduction described in the table above. Subsequent carboplatin doses will be escalated to an AUC of 6 as outlined below in Section 6.229. **(06/07/2010)**

6.222 Treatment modifications will be based on the absolute neutrophil count (ANC) rather than the total white cell count (WBC). Subsequent cycles of therapy will not begin until the ANC is ≥ 1,500/mcl and the platelet count is ≥100,000/mcl. Therapy will be delayed on a week-by-week basis until these values are achieved.

6.223 Treatment modifications will be employed in a sequential manner using cycle delay and dose reduction.

6.224 Patients who experience Grade 4 thrombocytopenia (≤10,000 plts/mcl) will have a 1-level dose reduction of carboplatin, without a change in paclitaxel dosage.

6.225 There will be no dose modifications based on uncomplicated ANC nadirs. **(06/07/2010)**

6.226 On Regimen II, patients who experience febrile neutropenia will receive G-CSF with subsequent cycles according to ASCO guidelines and no dose reduction. As all patients in Regimen I will receive G-CSF with systemic chemotherapy, if febrile neutropenia occurs despite the use of G-CSF, then dose reduction will be necessary. **(08/12/09)**

6.227 Patients who require a delay of > 7 days will receive a dose reduction of one level in accordance with the table above and without addition of G-CSF.

6.228 Protocol therapy will be discontinued in patients who require a delay of > 21 days.

6.229 There will be no dose re-escalations in the study, except the following: Patients randomized to Regimen I will be started at a reduced dose of carboplatin after radiotherapy (AUC 5). Their subsequent carboplatin dose will be escalated to an AUC of 6, provided that these patients do not develop any of the following: Grade 4 thrombocytopenia; greater than Grade 3 neutropenia that does not recover to Grade 1 by Day 21 of the first cycle; or other Grade 3 or higher non-hematological toxicity that does not recover to Grade 1 by Day 21 of the first cycle (except alopecia). Individual assessment by the treating physician is recommended prior to dose escalation of patients randomized to Regimen I after the first cycle of carboplatin and paclitaxel. **(06/07/2010)**

6.2210 Transfusions and erythropoietin can be administered at the discretion of the treating physician.

6.3 Systemic Chemotherapy: Non-Hematologic Toxicity

6.31 Paclitaxel hypersensitivity reaction: If hypersensitivity reactions to paclitaxel or its vehicle (Cremophor) occur, it will usually be during the first few minutes of infusion. Appropriate symptomatic therapy should be given. Continued treatment may be considered if the reaction is not life threatening; however, patients must be cautioned about potential recurrences of the reaction. Should the patient decide to continue with treatment, it is preferable that this be done on the same day of the occurrence. A suggested procedure would be to administer the drug first with 1 ml of the original IV solution diluted in 100 ml over one hour, then 5 ml in 100 ml over one hour, then 10 ml in 100 ml over one hour, and finally, the original solution at the original speed. Patients who elect not to have continued treatment with paclitaxel after experiencing a hypersensitivity reaction may continue on protocol therapy with carboplatin only.

6.32 Cardiac arrhythmias: Asymptomatic bradycardia associated with paclitaxel treatment is not an indication to discontinue therapy. For symptomatic arrhythmia, paclitaxel infusion should be discontinued, and the arrhythmia managed according to standard practice. The patient will be removed from protocol treatment and will require further cardiac assessment.

6.33 Ototoxicity

For clinically significant hearing loss or tinnitus, cisplatin will be discontinued. Audiograms are indicated in patients with pre-treatment hearing loss.

6.34 Myalgias

Myalgias can occur during the several days following paclitaxel treatment and may be severe. They should receive aggressive symptomatic treatment, including NSAIDs, narcotics, or steroids, as deemed appropriate by the treating physician. Myalgias are not an indication for dose reduction.

6.35 Neurological toxicity

Grade 2 or greater peripheral neuropathy requires delaying therapy until symptoms resolve to ≤ Grade 1. When treatment is resumed, paclitaxel dose should be reduced one dose level to 135mg/m^2. Recurrent Grade 2 neurotoxicity will require delay of treatment until neuropathy resolves to Grade 1. A delay exceeding three weeks for neurological function recovery will require discontinuation of protocol treatment. Patients will be removed from protocol therapy for recurrent Grade 3 or for Grade 4 neurological toxicity. **(10/13/09)(01/03/2011)**

6.36 Renal toxicity

Serum creatinine will be obtained at enrollment and with each cycle of treatment.

For creatinine levels ≥1.6 mg/dl prior to treatment, cisplatin will be held. Patient may remain on protocol therapy with the omission of cisplatin at the discretion of the treating physician. If the creatinine level subsequently returns to < 1.6 mg/dl, cisplatin may be reinstated in subsequent cycles. Hydration before and after cisplatin infusion is recommended for all patients (2 liters of fluid). Use of mannitol is optional.

Selective renal tubular defects are observed with cisplatin. Hypocalcemia, hypomagnesemia, and hypokalemia are common and potentially severe. Replacement of calcium, magnesium, and potassium is usually effective. Severe defects, although uncommon, may require chronic replacement therapy. Discontinuation from protocol in cases of severe renal tubular dysfunction resulting in dyselectrolemia can be done at the discretion of the treating physician.

6.37 Gastrointestinal toxicity

Nausea and Vomiting: Increased antiemetic support, sedation, and prophylactic hospitalization should be performed. Dose reductions are generally not needed for nausea and vomiting. Stomatitis or diarrhea: If any grade mucositis is present on Day 21 of a cycle, the next cycle of treatment should be withheld until the mucositis has cleared. Grades 3 or 4 mucositis or diarrhea require one dose level reduction for paclitaxel.

6.38 Hepatic Toxicity

Liver function tests will be obtained prior to treatment and before each cycle of therapy (Bilirubin, SGOT and SGPT).

Bilirubin must return to ≤1.5 ULN prior to further therapy. **(10/13/09)**

Transaminases (AST and ALT) should be ≤ 2.5 times ULN prior to each cycle of treatment.

6.39 Other toxicities: For any other Grade 3 or 4 toxicities not mentioned above, protocol treatment should be withheld until patients recover completely or to Grade 1 toxicity status. The next dose of the agent believed responsible for the adverse event will be given at a one dose level reduction. In general, unusual toxicities should be discussed with the Study Chair.

6.4 Discontinuation from protocol

6.41 Patients may withdraw from the protocol at any time for any reason.

6.42 Patients whose treatment is delayed over three consecutive weeks because of any toxicity should be removed from protocol therapy.

6.43 At the discretion of the treating physician, protocol treatment may be withdrawn because of serious toxicity or lack of compliance.

7.0 STUDY PARAMETERS

7.1 Observations and Tests **(06/07/2010) (01/03/2011) (01/13/14)**

The following observations and tests are to be performed and recorded on the appropriate form(s). **See Section 7.3 for a description of the specimen requirements for translational research for this study. See Sections 4.7, 7.2, and 10.2 for a description of the stained pathology slides that are required for central review by the GOG Pathology Committee to confirm eligibility and for instructions for shipping that material to the GOG Statistical and Data Center.**

Tests & Observations	Prior to study	During radiation therapy weekly	At the end of radiotherapy, prior to starting combination chemotherapy (Regimen I only)	Prior to each cycle of chemo-therapy	Follow-up	Within 4 weeks of completion of protocol therapy
History	1		X	X	4, 12	X
Physical Examination	1		X	X	4	X
Toxicity assessment	1	X	X	X	14	X
Pelvic Examination	1		X	7	4	X
HGB or HCT	2	X	X	3	13	X
ANC	2	5	X	3	13	X
Differential	2	X	X	3	13	X
Platelets	2	5	X	3		X
Creatinine	2	8	X	3		X
Bilirubin	2		X	3	13	X
SGOT, SGPT	2		X	3	13	X
Alkaline Phosphatase	2		X		13	X
Chest X-ray	9				6	
Urinalysis	2					
Abdomen and pelvis CT	9				6	
Chest CT scan	10				10	
Quality of Life Assessments	11		11		11	

1. Must be obtained within 28 days of initiating protocol therapy.
2. Must be obtained within 14 days of initiating protocol therapy.
3. Must be obtained within 4 days of re-treatment with protocol therapy.
4. Every 3 months for first 2 years, then every 6 months until 5 years post treatment.
5. Weekly, and twice a week if ANC < 1,000 or platelet count < 50,000 mcl.
6. Must be obtained at the end of therapy, then every 6 months for first 2 years, and then annually for an additional 3 years **(01/03/2011)**
7. Every other cycle of chemotherapy, or as clinically indicated.
8. Within 3 days from Day 29 cisplatin **(06/07/2010)**
9. Must be obtained after surgery and within 28 days prior to initiating protocol therapy. **(01/03/2011)**
10. Must be obtained if Chest x-ray is abnormal. Chest CT is acceptable in place of CXR for baseline

screening; however, the same modality that was used for baseline imaging studies must be used for all follow-up studies. **(06/07/2010)**

11. The QOL assessments to be administered are as follows: FACT-G Physical Well-being (PWB) and Functional Well-being (FWB) subscales (14 items), FACT-En additional concerns subscale (16 items), FACT/GOG-NTX-4 subscale (4 items), and items C3 and C5 from the FACT-C.
    Patients will complete the QOL assessments at 4 times:
    1) At baseline (within 14 days prior to starting protocol therapy)
    2) 6 weeks from start of protocol treatment (1 week post completion of RT for Regimen I or three weeks post completion of 2 cycles of chemotherapy for Regimen II)
    3) 18 weeks from start of protocol treatment (three weeks after completion of protocol therapy)
    4) 70 weeks from start of protocol treatment (1 year from completion of protocol therapy)
    NOTE: QOL assessments should be administered at ALL 4 assessment times, regardless of whether the patient progresses or is removed from the study for any reason.
12. After 5 years, information about survival will be obtained yearly by phone calls. **(08/12/09)**
13. At the end of protocol-directed therapy and yearly for the first 5 years. **(06/07/2010)**
    If abnormal, evaluate with appropriate diagnostic testing to exclude the presence of systemic metastatic disease. **(01/03/2011)**
14. Every 6 months for 3 years (report on Form TLC). **(01/03/2011)**

7.2 Stained Pathology Slides for Central Pathology Review to Confirm Eligibility

Stained pathology slides are required for central review by the GOG Pathology Committee to confirm eligibility for the protocol. At least one representative stained slide (or slides) documenting the primary site, histologic cell type, grade, and one slide to show the most advanced stage of disease. Peritoneal cytology slides are required for those patients with stage I and II clear cell or serous papillary uterine carcinoma, enrolled on the basis of positive cytology. **(01/03/2011)**

When submitting pathology material to the GOG SDC, individual slides must be labeled with GOG Patient ID, patient initials and the surgical / pathology accession number (e.g., S08-2355) and block identifier (e.g., A6). Don't not label with disease site or collection date. Pack the labeled slides into plastic slide cassette(s). Tape plastic slide cassettes shut and wrap in bubble wrap or another type of padded material prior to shipping. Please include the GOG Patient ID, patient initials, and protocol number on all pages of the pathology report and black out the patient's name. Ship pathology slides, three copies of both the Pathology Form F and the official pathology report directly to the **Pathology Materials Coordinator at the GOG Statistical and Data Center,** [redacted] The GOG Upload Application in SEDES is an alternative method for submitting pathology reports and Form F. Please see sec. 4.7 and 10.2 for additional requirements and instructions.

7.3 Translational Research **(01/13/14)**

7.31 Specimen Requirements

If the patient gives permission for her specimens to be collected and used for this optional translational research component, then participating institutions within the United States are required to submit the patient's translational research specimens as outlined below (unless otherwise specified).

A detailed description of the translational research specimen procedures can be found in Appendix III.

Required Specimen (Specimen Code)	**Collection Time Point**	**Ship To**
FFPE Primary or Metastatic (FT01[1])* 1st Choice: block 2nd Choice: 15 unstained slides (charged, 5µm)	Prior to all treatment	GOG Tissue Bank within 8 weeks of registration[2]
Whole Blood (WB01) 7-10mL drawn into purple-top (EDTA) tube(s)	Prior to or after starting study treatment	GOG Tissue Bank the day the blood is collected[2]

* A copy of the corresponding pathology report must be shipped with all tissue specimens sent to the GOG Tissue Bank
1 If submitting both, label primary as FT01 and metastatic as FT02. If only metastatic is submitted, it should be labeled FT01.
2 GOG Tissue Bank / Protocol GOG-0258, Nationwide Children's Hospital, [redacted]

7.32 Laboratory Testing

The GOG Tissue Bank will coordinate with the GOG Committee on Experimental Medicine and the GOG Statistical and Data Center to distribute appropriate specimens to approved laboratories for approved projects.

Investigators must submit a GOG concept or a GOG Tissue Bank Application to access GOG-0258 specimens and resources. If approved, a GOG-8000 series protocol will be developed for review and approval.

7.33 Future Research

Details regarding the banking and use of translational research specimens for future research can be found in Appendix III.

7.4 Quality of Life

7.41 Patients will complete the QOL Survey at four times:
1) At baseline (within 14 days prior to starting protocol therapy)
2) 6 weeks from start of protocol treatment (1 week post completion of RT for Regimen I or three weeks post completion of 2 cycles of chemotherapy for Regimen II)

3) 18 weeks from start of protocol treatment (three weeks after completion of protocol therapy)
4) 70 weeks from start of protocol treatment (1 year from completion of protocol therapy)

NOTE: **QOL assessments should be administered at ALL four assessments times, REGARDLESS of whether the patient progresses or is removed from study for any reason.**

7.42 The QOL survey is available in Spanish and French and has been translated into Korean for use on this study as of March 2010 (full validation of the Korean translation of En1 and En2 are pending). Requests for non-English versions should be made to the Statistical and Data Center. **(06/07/2010)**

7.43 Whenever possible, the QOL survey should be administered at the clinic visit before the patient is seen by the physician, before evaluations are performed, and before test results are shared with her. In the event that the questionnaires are not administered at the clinic visit, the QOL data can be collected by telephone or mail as back-up methods, with telephone data collection being the preferred back-up method.

7.44 The Quality of Life Liaison (GOG Nurse/Data Manager) at each institution has overall responsibility for the administration of the study questionnaire.

7.45 The GOG Nurse/Data Manager should read the instructions printed on the questionnaire to the patient and ensure that the patient understands the instructions. It is important to assure the patient that all material on the questionnaire is confidential and will not be shared with the health care team, and that it will not become part of the medical record.

7.46 Assistance in reading the questionnaire is permitted if the patient is unable to complete the questionnaire on her own (e.g., difficulty in reading, elderly). It is important not to influence the response of the patient. Note why the patient required assistance and what assistance was given.

7.47 Patients should be instructed to answer all the questions regardless of whether the symptoms or conditions asked about are related to the cancer or cancer treatment. Discourage family members from being present during questionnaire completion or from influencing the patient's response.

7.48 Review the questionnaire for completeness before the patient leaves.

7.481 If the patient has marked more than one answer per question, ask the patient which answer best reflects how she is feeling.

7.482 If the patient has skipped a question or questions, assure that she noted in the space provided that she has chosen not to answer those questions.

7.49 It is essential that the questionnaires be completed according to the schedule described in Section 7.41.

7.410 If the patient refuses or cannot complete the questionnaire at any time, she should be asked to do so at the next scheduled administration time.

7.411 Prior to submitting the QOL Scantron to the GOG Statistical and Data Center, be sure the following information is recorded and coded in:

a) patient's complete GOG number
b) date of form completion
c) study time point for which the form is being completed

8.0 EVALUATION CRITERIA

8.1 Parameters of Response – GOG RECIST Criteria

8.11 Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest dimension to be recorded). Each lesion must be ≥ 20 mm when measured by conventional techniques, including palpation, plain x-ray, CT, and MRI, or ≥ 10 mm when measured by spiral CT.

8.12 Baseline documentation of "Target" and "Non-Target" lesions

All measurable lesions, up to a maximum of 5 lesions per organ and 10 lesions in total representative of all involved organs, should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest dimension) and their suitability for accurate repetitive measurements by one consistent method of assessment (either by imaging techniques or clinically). A sum of the longest dimension (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

All other lesions (or sites of disease) should be identified as *non-target* lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as "present" or "absent."

All baseline evaluations of disease status should be performed as close as possible to the start of treatment and never more than four weeks before the beginning of treatment.

8.13 Recurrence (non-measurable disease studies) is defined as increasing clinical, radiological, or histological evidence of disease since study entry. CA125 rise, if measured, will not count as recurrence, unless there is clinical or radiological evidence of disease recurrence.

8.14 Survival is the observed length of life from entry into the study to death or the date of last contact.

8.15 Recurrence-Free Survival (non-measurable disease studies) is the period from study entry until disease recurrence, death, or date of last contact.

8.16 Subjective Parameters including performance status, specific symptoms, and side effects are graded according to CTCAE v3.0.

9.0 DURATION OF STUDY

9.1 Patients will continue on protocol for a maximum of six cycles of chemotherapy or until disease progression or adverse effects necessitate removal from protocol therapy.

9.2 Patients will be followed every three months for two years, then every six months for the next three years. After five years follow-up information will be obtained annually. All subsequent anti-cancer therapies will be reported. **(08/31/2009)**

9.3 A patient is considered off study therapy when the patient has either completed the prescribed number of cycles or fractions of study therapy, has progressed or died prior to completion of study therapy, a non-protocol drug or therapy (directed at the disease) is initiated, or ***all*** study therapy is totally discontinued. Report all chemotherapy treatment received on Form D2R, radiation therapy received on Form G, HDRV or LDRV and adverse events on Form T until the patient qualifies as being off study therapy**. (08/12/09)**

10.0 STUDY MONITORING AND REPORTING PROCEDURES

10.1 ADVERSE EVENT REPORTING FOR ALL REGIMENS (COMMERCIAL AGENTS AND RADIATION THERAPY ADMINISTRATION) **(04/28/2014)**

10.11 Definition of Adverse Events (AE)

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease that occurs in a patient administered a medical treatment, whether the event is considered related or unrelated to the medical treatment.

10.12 Reporting Expedited Adverse Events

Depending on the phase of the study, the use of investigational or commercial agents, and the role of the pharmaceutical sponsor, an AE report may need to reach multiple destinations. For patients participating on a GOG trial, all expedited AE reports should be submitted by using the CTEP Adverse Event Reporting System (AERS). All CTEP-AERS submissions are reviewed by GOG. Submitting a report through CTEP-AERS serves as notification to GOG and satisfies the GOG requirements for expedited AE reporting. All adverse reactions will be immediately directed to the Study Chair for further action.

The requirement for timely reporting of AEs to the study sponsor is specified in the Statement of Investigator, Form FDA-1572. In compliance with FDA regulations, as contained in 21 CFR 312.64, AEs should be reported by the investigator.

10.13 Phase 2 and 3 Trials Utilizing a Commercial Agent: CTEP-AERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days of the Last Dose of Any Commercial Study Agent

Reporting Requirements for Adverse Events that occur within 30 Days[1] of the Last Dose of the Commercial Agent on Phase 2 and 3 Trials

From the period of protocol activation through September 30, 2011, Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (CTCAE v3.0) are utilized for defining and grading specific adverse events reported through the CTEP-AERS system. **(09/26/11)**

Beginning October 1, 2011, the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 will be utilized for AE reporting through the CTEP-AERS system. CTCAE v 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 this Version of CTCAE. CTCAE v 4.0 definition is also available on the GOG member web site [redacted]. **(09/26/11)**

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	7 Calendar Days	Not Required	7 Calendar Days	Not Required	7 Calendar Days	7 Calendar Days
Possible Probable Definite	Not Required	7 Calendar Days	Not Required	7 Calendar Days	7 Calendar Days	7 Calendar Days	Not Required	24-Hrs; 3 Calendar Days	7 Calendar Days

[1] Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with a commercial agent require reporting as follows:

CTEP-AERS 24-hour notification followed by complete report within 3 calendar days for:

- Grade 4 and Grade 5 unexpected events

CTEP-AERS 7 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although a CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Please see exceptions below under the section entitled, "Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercial Agent." March 2005

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 3 calendar days" – The investigator must initially report the AE via CTEP-AERSwithin 24 hours of learning of the event followed by a complete CTEP-AERS report within 3 calendar days of the initial 24-hour report.
    "7 calendar days" – A complete CTEP-AERS report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE Grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported, regardless of

attribution and designation as expected or unexpected, with the exception of any events identified as protocol-specific exclusions for expedited adverse event reporting.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported to GOG via CTEP-AERS if the event occurs following treatment with a commercial agent.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exceptions to CTEP-AERSExpedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercial Agent:

There are no additional instructions or exceptions to CTEP-AERS expedited reporting requirements for this protocol.

10.14 Procedures for Expedited Adverse Event Reporting:

10.141 CTEP-AERS Expedited Reports: Expedited reports are to be submitted using CTEP-AERS available at http://ctep.cancer.gov. The CTEP, NCI Guidelines: Adverse Event Reporting Requirements for expedited adverse event reporting requirements are also available at this site.

AML/MDS events must be reported via CTEP-AERS (in addition to your routine AE reporting mechanisms). In CTCAE v4.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment-related secondary malignancy. **(03/14/2011)**

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to NCI by telephone at: 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper CTEP-AERS forms have been removed from the CTEP website and will NO LONGER be accepted. **(01/03/2011)**

10.2 GOG DATA MANAGEMENT FORMS **(09/21/2009) (01/03/2011) (01/13/14)**

The following forms must be completed for all patients registered and submitted to the GOG Statistical and Data Center (SDC) in accordance with the schedule below. Protocol forms and instructions can be submitted through or printed from the SDC Electronic Data Entry System (SEDES) online application found at the GOG Web Menu page. All amendments to forms submitted through SEDES must also be submitted through SEDES. The original form and required copies for forms NOT submitted online must be mailed to the GOG SDC. **Note: Pathology materials (Form F, path report, and slides) may be submitted together via postal mail or by using the upload feature of SEDES. Stained slides must be submitted via postal mail. See 7.2 for additional mailing instructions. Additionally, radiation materials (forms, copies, films, reports, etc) must be submitted together via postal mail. (09/21/2009) (03/14/2011)**

Form	**Due within**		**Copies***	**Comments**
	Weeks	**Event**		
Knowledge Assessment **(04/28/2014)**	0	Prior to Registration	1	Available at http://irochouston.mdanderson.org under 'Credentialing.'
Form R (Registration Form)	2	Registration	1	Mandatory submission via SEDES
Specimen Consent Application	1	Registration	NA	Complete Online
Form OSU (Uterine Cancer On-Study Form)	2	Registration	1	Mandatory submission via SEDES
Form DR (Pre-Treatment Summary Form)	2	Registration	1	Mandatory submission via SEDES
Form D2M (Solid Tumor Reporting Form) - baseline	2	Registration	1	Mandatory submission via SEDES
Form C (Surgical Reporting Form) Operative report Discharge summary	6 6 6	Registration Registration Registration	1 2 2	Mandatory submission via SEDES Submit via postal mail to SDC or upload via SEDES
Quality of life: *** Scantron Form – baseline Scantron Form – 6 weeks Scantron Form – 18 weeks Scantron Form – 70 weeks	 2 10 22 74	 Treatment Start Treatment Start Treatment Start Treatment Start	 1 1 1 1	Submit Scantron form via postal mail to SDC***
Pathology requirements Primary diagnosis: Form F (Pathology Form) Pathology Report Stained path slides to confirm eligibility	 6 6 6	 Registration Registration Registration	 2 2 **	 Submit together via postal mail to GOG SDC in Buffalo, NY, or submit using the report upload feature of SEDES**

Cytology Report Positive cytology slides	6 6	Registration Registration	2 **	
Radiation Materials: External beam: - daily treatment reports - CT/MRI showing relevant target volume Δ - simulation films or digitally reconstructed radiograph - portal films - dosimetry calculation - Isodose distribution curves - Form G (Radiation Treatment Form) - 3D Plan electronically submitted to ITC. Brachytherapy: - Treatment record for HDR - orthogonal simulation films for each intracavitary placement - dosimetry calculation - isodose distribution curves for the first intracavitary implant and each subsequent intracavitary implant if different from earlier implants - Form HDRV (Vaginal HDR Intracavitary Radiation Oncology Form) or Form LDRV (Vaginal LDR Intracavitary Radiation Oncology Form) IMRT Plan electronically submitted to ITC - DDSI - Digital treatment planning data - Color isodose distribution	4	Completion of radiation therapy	 2 1 1 1 2 2 2 1 1 2 2 2	Form G, HDRV and LDRV must be submitted via SEDES. Paper copies should also be submitted with radiation materials via postal mail. Submitted electronically via TRIAD **(04/28/2014)** Submitted electronically via TRIAD **(04/28/2014)**
Form D2R (Cycle Dose Drug Form)	2	Completion of each cycle of combination chemotherapy and each cycle of cisplatin	1	Mandatory submission via SEDES

Form T (Common Toxicity Form)	2	Start of each subsequent cycle of chemotherapy and cycle of cisplatin and 3 weeks after last cycle of chemotherapy	1	Mandatory submission via SEDES
Form D2M (Solid Tumor Evaluation Form)	2	Each disease evaluation	1	Mandatory submission via SEDES At completion of study therapy, semi-annually for 2 years, annually for 3 years or until disease progression is documented.
Form TLC (Follow-Up Period Adverse Event Reporting Form)	2	Each follow-up toxicity assessment following completion of study therapy	1	Mandatory submission via SEDES until non-protocol therapy is initiated or disease progression is documented. Every 6 months for 3 years.
Form SP-FT01-0258***** FFPE primary or metastatic tumor	8	Registration	NA	Submit via SEDES*ƒ*
Form SP-FT02-0258***** 2nd FFPE primary or metastatic tumor (optional)	8	Registration	NA	Submit via SEDES*ƒ*
Form SP-WB01-0258 whole blood	26	Treatment Start	NA	Submit via SEDES*ƒ*
Form QO (Treatment Completion Form)	2	Completion of study treatment	1	Mandatory submission via SEDES
Form Q (Follow-Up Form)	2	Disease progression; death; normal follow-up	1	Mandatory submission via SEDES quarterly for 2 years, semi-annually for 3 more years, annually thereafter for 5 years. Report cause of death.

* The number of required copies including the original form, which must be sent to the Statistical and Data Center (SDC). No copies are required for forms submitted through SEDES. Additionally, forms submitted through SEDES should not be sent through postal mail or fax, with the exception of Form G, Form HDRV, and Form LDRV.

** Stained pathology slides are required for central review by the GOG Pathology Committee to confirm eligibility. See Sections 4.7 and 7.2 for additional requirements and mailing instructions.

*** QOL assessments should be administered at ALL four assessments times, REGARDLESS of whether the patient progresses or is removed from study for any reason. Use only Scantron forms with the header of "GOG Protocol #258." Quality of life forms will be provided by the SDC upon request. A form must be submitted whether or not the assessment is performed. Please note: A QOL coversheet will not be collected. The coversheet questions have been included on the Scantron Form

**** For all patients assigned to the treatment arm with radiation, Regimen I, the brachytherapy materials and forms will appear on the patient form schedule. Forms HDRV and LDRV are both required to be submitted through SEDES for all patients whether or not brachytherapy is given and no matter what dose rate is used. The materials will be addressed based on these completed treatment forms. **(06/07/2010)**

***** A copy of the corresponding pathology report must be shipped with all tissue specimens sent to the GOG Tissue Bank.

ƒ Form SP must be submitted via SEDES regardless of whether the specimen is submitted for research.

Δ CT/MRI showing relevant target volume is from the treatment planning system. A print-out of one of the following will show the relevant tumor volume: CT/MRI slices with volumes on them (can obtain this with the isodose lines also on the slices), the DRR (Digital Reconstructed Radiograph - where all the slices are

put together. Looks like an x-ray of the body, except it includes volumes and is from a CT/MRI scanner) or BEV (Beams Eye View – this shows the tumor volume from the perspective of each beam given, as well as the blocking used). Best to submit the CT/MRI slices, but the others are fine. **(01/03/2011)**

This study will be monitored by the Abbreviated Clinical Data System (CDUS) Version 3.0. CDUS data will be submitted quarterly to CTEP by electronic means.

This study utilizes the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) for defining and grading adverse events to be reported on GOG case report forms. A GOG CTCAE v3.0 Manual is available on the GOG member web site [redacted] and can be mailed to the institution registering a patient to this study if requested. **(09/26/11)**

11.0 STATISTICAL CONSIDERATIONS

11.1 Overview, Study Registration and Randomization*:*

This study is a two-arm, open-label, randomized Phase III trial. The control arm for this trial is combination chemotherapy consisting of six, cycles of paclitaxel and carboplatin. This regimen will be compared to a regimen of tumor-directed radiation with concurrent cisplatin followed by four cycles of paclitaxel and carboplatin combination chemotherapy. The treatment regimens will be allocated so that the same number of patients will be treated with each treatment regimen. All patients will be registered centrally at the GOG Statistical and Data Center. The randomized treatment assignment will be revealed following patient registration. Reports and publications will include a complete accounting of all patients registered to this study.

11.2 Relevant data:

The principal items to be collected analyzed and reported to determine the therapeutic effect of treatment are outlined below.

11.21 ***Outcome variables:*** recurrence-free survival (RFS), overall survival, cumulative incidence of local recurrence (limited to the pelvis or vagina) and cumulative incidence of distant metastases (beyond the pelvis and vagina).

11.22 ***Tumor characteristics*****:** pelvic and para-aortic node status, FIGO surgical stage, maximum diameter of residual disease, cell type, depth of myometrial invasion and tumor grade.

11.23 ***Patient characteristics*****:** age, race, and performance status. Race will be evaluated as a prognostic factor; however, no specific hypothesis test of an interaction between race and treatment is planned.

11.24 ***Adverse effects of therapy*****:** the frequency and severity of acute and late adverse effects will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

11.25 ***Therapy administered*****:** total amount in mg/m^2 of each chemotherapy agent delivered, the number of cycles of chemotherapy completed, and the total dose and number of fractions of radiation delivered to the pelvis, extended field, and vagina. The reason for discontinuation of study regimen will also be captured.

11.26 ***Quality of life***: FACT-G Physical Well-being (PWB) and Functional Well-being (FWB) subscales (14 items), FACT-En additional concerns subscale (16 items), FACT/GOG-NTX-4 subscale (4 items) and items C3 and C5 from the FACT-C.

11.3 Accrual rate, sample size and study duration:

The anticipated annual accrual is 180 patients. This estimate is based upon the accrual to GOG-0184 and 0209. The expected accrual period will be 54 months for a total of 804 patients. This accrual duration accounts for a 5% ineligibility rate. The post-accrual follow-up period for maturity of RFS and survival will require up to 12 months for RFS and 34 months for survival depending on the accrual rate and event rates in each arm.

11.4 Hypotheses, planning parameters, method of analysis and sample size justification:

The primary hypothesis of this study is whether the addition of volume-directed radiation to adjuvant platinum and paclitaxel chemotherapy improves recurrence-free survival in patients with optimally debulked Stage III or IVA endometrial adenocarcinoma. Secondary endpoints include overall survival, cumulative incidence of local recurrence, cumulative incidence of distant metastases, acute and late adverse effects, and patient-reported quality of life.

***RFS and survival*:** For the purpose of planning this study, the death rate for survival and the recurrence or death rate for the RFS endpoint in the control regimen are estimated using the data from the doxorubicin and cisplatin arm of GOG-0122. Data from that trial suggests that the hazard of first recurrence or death (RFS events) does not remain constant over time, but rather is greatest at the beginning of the study and decreases with time on study. The hazard rates have been estimated assuming a Gompertz model (hazard function $h(t)= \alpha\exp(\beta t)$ for $t\geq 0$). The Gompertz model parameter estimates for RFS are, $\alpha=0.0196$ per month (initial hazard) and $\beta= -0.0217$ (hazard decay factor). The Gompertz model parameter estimates for survival are, $\alpha=0.0114$ per month and $\beta= -0.0120$. These models assume that the recurrence or death rate is initially high, but declines rapidly over time, while the death rate starts lower and decays at a slightly slower rate.

A 28.5% decrease (relative hazard=1.4) in the first recurrence or death rate would be considered clinically significant. This relative decrease in recurrence or death rate translates into increasing the three-year recurrence-free survival from 61% to 70% and the three-year survival from 72% to 79%. This difference will require observing a total of at least 252 failures to permit at least 85% statistical power when the probability of Type I error for a one-tail comparison will be set at 0.05.[51] Overall Type I error is limited to 0.05 for RFS and survival separately. Independence between the two endpoints, RFS and survival, and randomized treatment will be assessed with a stratified logrank test for an intent-to-treat analysis of eligible patients. The stratification will be defined by the covariates gross residual tumor (none or microscopic versus. gross) and age (65 and under versus over 65 years).

***Toxicity*:** The maximum grade over the entire course of therapy for any individual effect will be used as a summary of acute toxicity. The Kruskal-Wallis test corrected for ties will be used to compare the maximum grade of acute adverse effects of therapy by treatment arm. The CTCAE v3.0 grading system will be used (i.e., scale from 0 for none to 5 for death). A significance level of 0.01 will be used for each tested AE term or category. No correction for multiple testing will be employed, since it is very important to identify moderate increases in the severity of toxicity at the risk of increasing the Type I error. Since some of these toxicities are correlated, the overall Type I error is less than calculations would indicate when assuming complete independence.

The maximum grade over the follow-up period (prior to initiation of subsequent therapy) for any individual effect will be used as summary of late adverse effects. The cumulative incidence of Grade 3 or higher bowel-related gastrointestinal adverse events will also be estimated using the date of onset and will account for competing events of death, progression, and non-protocol cancer treatment.

Quality of Life: The following assessment tools will be used to measure the quality of life prior to, during, and following treatment:

- FACT-G Physical Well-being (PWB) and Functional Well-being (FWB) subscales (14 items),
- FACT-En additional concerns subscale (16 items),
- FACT/GOG-NTX-4 subscale (4 items) and
- Items C3 and C5 from the FACT-C.

Each tool will be evaluated at baseline (prior to therapy), 6 weeks from start of protocol therapy (1 week post completion of RT for Regimen I or three weeks post completion of 2 cycles of chemotherapy for Regimen II), 18 weeks from start of protocol therapy (three weeks after completion of protocol therapy), and then 70 weeks from start of protocol therapy (1 year from completion of protocol therapy).

Each item in the subscales listed above are scored using a five-point scale (0=not at all; 1=a little bit; 2=somewhat; 3=quite a bit; 4=very much). Within an individual assessment, one or more items may not be answered. A subscale score will be computed as long as more than 50% of subscale items have been answered. A subscale score S_i with N_i items will be calculated as:

$$S_i = N_i \times \frac{\sum_{j=1} \left(\delta_{ij} \times s_{ij} \right)}{\sum_{j=1} \delta_{ij}}$$

Where δ_{ij} is equal to 1 when the jth item has a valid response, otherwise it is equal to 0 and s_{ij} is the response score of the jth item. The total score for the PWB and FWB is the sum of the two subscale scores if at least 80% of PWB and FWB items have been answered. The total FACT-En TOI score is the sum of the

FACT-En PWB, FWB and FACT-En additional concerns subscale scores if at least 80% of TOI-En items have been answered.

The QOL objectives in this study are to compare treatment regimens with respect to the patient-reported quality of life as measured with PWB+FWB score, TOI of FACT-En, and patient-reported neurotoxicity as measured with FACT/GOG-Ntx-4 subscale. A difference of 2~3 points is considered the minimally clinically important difference (MCID) for PWB and FWB respectively.[52] For this study an observed difference of 4 points for the total score of PWB and FWB will be considered as the MCID in terms of QOL between the treatment groups. This magnitude of difference is equivalent to an effect size of 0.38 assuming that the standard deviation (SD) is 10.4 for the total score of PWB and FWB as observed in GOG-0209.

A difference of 1.5 points in FACT-GOG/Ntx-4 subscale (4 items) is considered the MCID between the treatment groups for this study. This size of difference is equivalent approximately to an effect size of 0.35 assuming a SD of 4.3 as observed in GOG-0209.

It has been suggested by the FACIT author[53] that the Trial Outcome Index (TOI) which is the sum of the PWB, FWB, and "additional concerns" of a specific cancer is more responsive to change in QOL outcomes in cancer clinical trials. However, limited data are available on the validation of the TOI of FACT-En in terms of psychometric properties. For the purposes of this study, the TOI of FACT-En will be assessed as an exploratory endpoint. Currently the FACT TOI-En scale is being used in GOG-0209 and will be validated once the study is completed. By the time of the final QOL report, if the TOI of FACT-En is validated to be a reliable scale and sensitive to treatment and change over time, it will be assessed as a definitive endpoint in place of PWB+FWB to measure the quality of life. The TOI of FACT-En is computed by summating the FWB, PWB and En subscale if at least 80% of TOI-En items have been answered. A difference of 6 points for TOI of FACT-En will be considered as the MCID in terms of QOL between the treatment groups. [52]

The treatment differences of QOL scores that are expected to be observed in this study and their corresponding effect sizes are listed in table below.

	Lower limit of MCID	Estimated SD	Effect size	Study or reference
PWB+FWB	4	10.4	0.38	GOG-0209
TOI of FACT-En	6	15.4	0.39	GOG-0209
FACT-GOG/Ntx-4 subscale	1.5	4.3	0.35	GOG-0209

With the multiple QOL measures, the Type I error is set at $0.017=1-(1-0.05)^{1/3}$ for each two-tail comparison between treatments to ensure the overall Type I error to be 0.05. The sample size required for detecting an effect size of 0.35 with a statistical power of 90% is 220 eligible patients in each randomized group. Patient death, illness, noncompliance, and missed appointment can cause missing information that increases over time. In GOG-0209, approximately 68% of eligible patients who participated in QOL component completed the assessment at 26 weeks post randomization. Assuming the completion rate for the QOL assessment at 70 weeks post start of protocol therapy in this trial is 65%, then the primary sample size of 766 eligible patients (383 per arm) will provide a statistical power of at least 93.5%.[54] The statistical power will be higher if correlation among repeated measures exists.

Linear mixed models adjusted for baseline score, age, and performance status at enrollment will be used to test the hypothesis of no difference in PWB+FWB scores and FACT-GOG/NTX-4 scores between assigned treatment arms in an intent-to-treat analysis of eligible patients. These models will account for the correlation among scores measured over time. The interaction between treatment and assessment time on QOL scores will be tested initially in each model. If this interaction is found to be statistically significant (at level of 0.05), treatment comparisons for each assessment tool will be carried out individually at each point using the model parameter estimates. If there is no evidence of an interaction, then a weighted average of estimates over the three points will be compared between assigned treatment arms. The empirical sandwich variance will be used to estimate the precision of the parameter estimates. Satterthwaite's DF approximation will be used in significance testing to adjust the degrees of freedom for unequal group variances.

An exploratory data analysis is planned to assess patient-reported gastrointestinal symptoms between the two groups using similar methods described above. The gastrointestinal symptoms are evaluated with items C3 and C5 in combination with En1, O1, O3 and Cx6 in TOI of FACT-En. A subscale score of gastrointestinal symptoms is computed using the same method described above for PWB and FWB subscales.

One or more of the QOL assessments may be missing for an individual on any occasion. Missing information is troublesome, particularly in studies involving repeated patient assessments. Data management procedures will be used to reduce missing data. At selected semi-annual group meetings, the data managers and nurses will be given presentations that describe the goals of this study and stress the importance of obtaining complete assessment. A study contact person will be designated to answer questions that arise throughout the study. A calendar of events that lists the dates of required QOL assessments for each patient will be made available to the patient's health care provider as soon as the patient has been registered onto this study. Also, the clinic staff will use the GOG Web-based forms tracking system to obtain reminders of the upcoming QOL assessments.

In case an assessment is missed, the reasons for missed QOL assessments will be collected. The distribution of these reasons/missed assessments will be evaluated over time between the treatment arms for comparability. Assessment completion rates will be summarized and monitored by the Quality of Life Committee every 6 months.

11.5 Interim analysis*:*

An initial interim analysis of RFS will be performed when there are at least 105 events (recurrence or death) reported among all enrolled eligible patients. It is projected that 105 events will be observed within 36 months of accrual. The second planned interim analysis will be performed when there are at least 210 events reported (estimated to occur at least 3 months after target accrual is reached). Each interim analysis will be scheduled to coincide with the GOG Data Monitoring Committee (DMC) meetings that are held at each GOG semi-annual group meeting. Overall survival, the accrual rate, adverse events of treatment, treatment compliance, and results of external studies will be included in the interim analysis report to the DMC to be taken into consideration when reaching a decision. This planned interim analysis will include both an efficacy and a futility analysis. The possibility of additional unplanned interim analyses of efficacy is taken into consideration in the plans below.

***Interim analysis for efficacy*:** The previously described stratified logrank test will be used to compare recurrence-free survival distributions between the experimental regimen and the control regimen at each interim analysis. If the null hypotheses can be rejected with $p \leq 0.001$ (one-tail test), terminating the accrual will be considered given that the study has not yet reached the target accrual goal. If the study is closed early, an additional period of follow-up for data maturity will also be considered prior to releasing the final report. This will require evaluating the benefit of observing additional failures with the cost of postponing the release of the final report to observe these failures. There will be no correction to the nominal p-value in the final report. It has been shown that there is only a very small increase in Type I error associated with this type of interim analysis plan, even in the event of additional (unplanned) interim analyses using the 0.001 nominal p-value. [55]

***Interim analysis for futility*:** A futility analysis will be performed only at the first planned interim analysis. If the observed rate of recurrence or death of the chemotherapy and radiation regimen is greater than the observed rate of recurrence or death of the chemotherapy-only arm when stratified by residual tumor and age, then accrual termination will be considered (if still active) with a conclusion that an advantage for the chemotherapy and radiation regimen has not been established. The increase in Type II error due to this interim analysis is less than 1% if only one interim analysis is performed at 50% information time. [56]

Under the null hypothesis, this procedure has a 50% chance of resulting in early termination.

***Safety monitoring*:** The GOG Data Safety and Monitoring Board (DSMB) reviews accumulating summaries of adverse event reports and all serious adverse event (SAE) reports submitted during the interval between group meetings. This committee also reviews deaths in which treatment may have contributed to the cause. Based upon these reviews, the DSMB may recommend study amendments to the DMC pertaining to patient safety.

***Design assumptions*:** Assumptions made to determine sample size will be checked prior to the planned time of closing the study to patient entry. This will not involve a comparison of treatment arms but will be based upon aggregated data.

11.6 Planned gender, minority and ethnic inclusion:

The following are the race and ethnicity distributions anticipated for this trial based upon historical data. All patients in this study will be female by definition of disease. Prior GOG studies in this population have not indicated that there is substantial heterogeneity of treatment effects among racial/ethnic subgroups. Therefore, the study design does not incorporate specific hypotheses concerning treatment interactions involving race or ethnicity**.**

Ethnic Category	**Number of patients anticipated**
Hispanic or Latino	23 (2.8%)
Not Hispanic or Latino	726 (90.3%)
Undeclared	55 (6.9%)
Total	804 (100.0%)
Racial Category	**Number of patients anticipated**
American Indian/Alaskan Native	2 (0.3%)
Asian	16 (2.0%)
Native Hawaiian or Other Pacific Islander	8 (1.0%)
Black or African American	42 (5.2%)
White	732 (91.0%)
Undeclared	4 (0.5%)
Total	804 (100.0%)

12.0 BIBLIOGRAPHY

1. Mariani A, Webb MJ, Keeney GL, Aletti G, Podratz KC. Endometrial cancer: predictors of peritoneal failure. *Gynecol Oncol*. 2003; 89: 236-242.

2. McMeekin DS, Lashbrook D, Gold M, Johnson G,Walker JL , Mannel R. Analysis of FIGO Stage IIIc endometrial cancer patients. *Gynecol Oncol*. 2001; 81: 273-278.

3. McMeekin, DS, Lashbrook D, Gold M, et al. Nodal distribution and its significance in FIGO stage IIIc endometrial cancer. *Gynecol Oncol*. 2001; 82: 375-379.

4. Stewart KD, Martinez AA, Weiner S, et al.. Ten-year outcome including patterns of failure and toxicity for adjuvant whole abdominopelvic irradiation in high-risk and poor histologic feature patients with endometrial carcinoma. *Int J Radiat Oncol Biol Phys*. 2002; 54: 527-535.

5. Sood B, Jones J, Gupta S, et al. Patterns of failure after the multimodality treatment of uterine papillary serous carcinoma. *Int J Radiat Oncol Biol Phys*. 2003; 57: 208-216.

6. Mariani A, Webb MJ, Keeney GL, Aletti G, Podratz KC. Assessment of prognostic factors in stage IIIA endometrial cancer. *Gynecol Oncol*. 2002; 86:38-44.

7. Mariani A, Webb MJ, Keeney GL, Haddock MG, Aletti G, Podratz KC. Stage IIIC endometrioid corpus cancer includes distinct subgroups. *Gynecol Oncol*. 2002; 87: 112-117.

8. Aoki Y, Kase H, Watanabe M., Sato T, Kurata H, Tanaka K. Stage III endometrial cancer: analysis of prognostic factors and failure patterns after adjuvant chemotherapy. *Gynecol Oncol*. 2001; 83:1-5.

9. Randall ME, Filiaci VL, Muss H, et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol.* 2006; 24:36-44.

10. Thigpen, JT, Buchsbaum HJ, Mangan C, Blessing JA. Phase II trial of Adriamycin in the treatment of advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. *Cancer Treat Rep.* 1979; 63: 21-27.

11. Thigpen JT, Blessing JA, Homesley H, Creasman WT, Sutton G. Phase II trial of cisplatin as first-line chemotherapy in patients with advanced or recurrent

endometrial carcinoma: a Gynecologic Oncology Group Study. *Gynecol Onco*. 1989; 33: 68-70.

12. Thigpen JT, Blessing JA, DiSaia PJ, et al. A randomized comparison of doxorubicin alone versus doxorubicin plus cyclophosphamide in the management of advanced or recurrent endometrial carcinoma: A Gynecologic Oncology Group study. *J Clin Oncol*. 1994;12:1408-1414.

13. Seski JC, Edwards CL, Herson J, Rutledge FN. Cisplatin chemotherapy for disseminated endometrial cancer. *Obstet Gynecol*. 1982; 59: 225-228.

14. Muss HB. Chemotherapy of metastatic endometrial cancer. *Semin Oncol*. 1994;21: 107-113.

15. Thigpen T, Vance, R., Lambuth, B., et al. Chemotherapy for advanced or recurrent gynecologic cancer. *Cancer*. 1987; 60: 2104-2116.

16. Woo HL, Swenerton KD, Hoskins PJ. Taxol is active in platinum-resistant endometrial adenocarcinoma. *Am J Clin Oncol*. 1996;19: 290-291.

17. Ball HG, Blessing JA, Lentz SS, Mutch DG. A phase II trial of paclitaxel in patients with advanced or recurrent adenocarcinoma of the endometrium: a Gynecologic Oncology Group study. *Gynecol Oncol*. 1996; 62: 278-281.

18. Lissoni A, Zanetta G , Losa G, Gabriele A, Parma G, Mangioni C. Phase II study of paclitaxel as salvage treatment in advanced endometrial cancer. *Ann Oncol*. 1996; 7: 861-863.

19. Fleming GF. Systemic therapy for advanced or recurrent endometrial carcinoma. *Curr Oncol Rep*. 1999;1:47-53.

20. Fleming GF, Fowler JM, Waggoner SE, et al. Phase I trial of escalating doses of paclitaxel combined with fixed doses of cisplatin and doxorubicin in advanced endometrial cancer and other gynecologic malignancies: a Gynecologic Oncology Group study. *J Clin Oncol*. 2001; 19: 1021-1029.

21. Thigpen T, Blessing J, Homesley H et al. Phase III trial of doxorubicin +/- cisplatin in advanced and recurrent endometrial carcinoma: A Gynecologic Oncology Group study. *Proc Am Soc Clin Oncol*. 1993; 12: 261.

22. Mundt AJ, McBride R, Rotmensch J, Waggoner SE, Yamada SD, Connell PP. Significant pelvic recurrence in high-risk pathologic stage I--IV endometrial carcinoma patients after adjuvant chemotherapy alone: implications for adjuvant radiation therapy. *Int J Radiat Oncol Biol Phys*. 2001: 50*:* 1145-1153.

23. Sartori E, Laface B, Gadducci A, et al. Factors influencing survival in endometrial cancer relapsing patients: a Cooperation Task Force (CTF) study. *Int J Gynecol Cancer.* 2003;13: 458-465.

24. Fleming GF, Brunetto VL, Cella D, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol*. 2004; 22: 2159-2166.

25. Hoskins PJ, Swenerton KD, Pike JA, et al. Paclitaxel and carboplatin, alone or with irradiation, in advanced or recurrent endometrial cancer: a phase II study. *J Clin Oncol.* 2001; 19: 4048-4053.

26. Nakamura T, Onishi Y, Yamamoto F, Kouno S, Maeda Y, Hatae M. Evaluation of paclitaxel and carboplatin in patients with endometrial cancer[in Japanese]. *Gan To Kagaku Ryoho*. 2000; 27: 257-262.

27. Price FV, Edwards RP, Kelley JL, Kunschner A J, Hart LA. A trial of outpatient paclitaxel and carboplatin for advanced, recurrent, and histologic high-risk endometrial carcinoma: preliminary report. *Semin Oncol.* 1997; 24: S15-78-S15-82.

28. Weber B, Mayer P, Bougnoux P et al. What is the best chemotherapy regimen in recurrent or advanced endometrial carcinoma? Preliminary results. *Proc of Am Soc Clin Oncol*. 2003; 22: 453a.

29. Mundt AJ, Murphy KT, Rotmensch J, Waggoner SE, Yamada SD, Connell PP. Surgery and postoperative radiation therapy in FIGO Stage IIIC endometrial carcinoma. *Int J Radiat Oncol Biol Phys*. 2001;50: 1154-1160.

30. Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. *Lancet*. 2000; 355:1404-1411.

31. McMeekin DS, Tillmanns T. Endometrial cancer: treatment of nodal metastases. *Curr Treat Options Oncol*. 2003; 4:121-130.

32. Nelson G, Randall M, Sutton G, Moore D, Hurteau J, Look K. FIGO stage IIIC endometrial carcinoma with metastases confined to pelvic lymph nodes: analysis of treatment outcomes, prognostic variables, and failure patterns following adjuvant radiation therapy. *Gynecol Oncol*. 1999; 75: 211-214.

33. Greven KM, Curran WJ Jr., Whittington R, et al.. Analysis of failure patterns in stage III endometrial carcinoma and therapeutic implications. *Int J Radiat Oncol Biol Phys.* 1989; 17: 35-39.

34. Schorge JO, Molpus KL, Goodman A, Nikrui N, Fuller AF Jr. The effect of postsurgical therapy on stage III endometrial carcinoma. *Gynecol Oncol*. 1996; 63:34-39.

35. Onda T, Yoshikawa H, Mizutani K, et al. Treatment of node-positive endometrial cancer with complete node dissection, chemotherapy and radiation therapy. *Br J Cancer.* 1997; 75: 1836-1841.

36. Bruzzone M, Miglietta L, Franzone P, Gadducci A, Boccardo F. Combined treatment with chemotherapy and radiotherapy in high-risk FIGO stage III-IV endometrial cancer patients. *Gynecol Oncol*. 2004; 93: 345-352.

37. Greven K, Winter K. Underhill K, Fontenesci J, Cooper J, Burke T. Final analysis of RTOG 9708: adjuvant postoperative irradiation combined with cisplatin/paclitaxel chemotherapy following surgery for patients with high-risk endometrial cancer. *Gynecol Oncol*. 2006; 103:155-159.

38. Mangili G, De Marzi P, Beatrice S, et al. F. Paclitaxel and concomitant radiotherapy in high-risk endometrial cancer patients: preliminary findings. *BMC Cancer.* 2006; 6: 198.

39. The Department of Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med*. 1991; 324:1685-1690.

40. Schaake-Koning C, van den Bogaert W, Dalesio O, et al.. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. *N Engl J Med.* 1992; 326: 524-530.

41. Herskovic A, Martz K, al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med.* 1992; 326: 1593-1598.

42. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med.* 2003; 349: 2091-2098.

43. Keys HM., Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med.* 1999; 340:1154-1161.

44. Thomas GM. Improved treatment for cervical cancer--concurrent chemotherapy and radiotherapy. *N Engl J Med*.1999; 340:1198-1200.

45. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med.* 1999; 340:1144-1153.

46. Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med.* 1999;340:1137-1143.

47. Homesley HD, Filiaci V, Gibbons SK, et al. A randomized phase III trial in advanced endometrial carcinoma of surgery and volume-directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: A Gynecologic Oncology Group study. SGO, March 2008, Tampa, FL.

48. Bruner DW, Barsevick A, Tian C, et al. Randomized trial results of quality of life comparing whole abdominal irradiation and combination chemotherapy in advanced endometrial carcinoma: a gynecologic oncology group study. *Quality of Life Research.* 2007;16:89-100.

49. Cella DF, Tulsky DS, Gray G, et al. The functional assessment of Cancer Therapy Scale: Development and validation of the general measure. *J Clin Oncology.* 1993;11: 570-579.

50. Ward WL, Hahn EA, Mo F, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) quality of life instrument. *Quality of Life Research.* 1999; 8:181-195.

51. Schoenfeld DA. Sample size formula for the proportional hazards regression model. *Biometrics.* 1983; 39:499-503.

52. Yost KJ, Eton DT. Combining distribution- and anchor-based approaches to determine minimally important differences: the FACIT experience. *Eval Health Prof.* 2005; 28:172-191.

53. Webster K, Cella D, Yost K. The functional assessment of chronic illness therapy (FACIT) measurement system: properties, applications, and interpretation. *Health Qual Life Outcome.* 2003.1: 79.

54. Hintze J. *NCSS and PASS. Number Cruncher Statistical Systems*. Kaysville, UT: [www.ncss.com], 2001.

55. Freidlin B, Korn EL, George SL. Data monitoring committees and interim monitoring guidelines. *Control Clin Trials*. 1999; 20:395-407.

56. Wieand S, Schroeder G, O'Fallon JR. Stopping when the experimental regimen does not appear to help. *Stat Med*. 1994; 13:1453-1458.

APPENDIX I

CARCINOMA OF THE ENDOMETRIUM
FIGO CLASSIFICATION
2009

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

*Either G1, G2, or G3.

**Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II.

[#]Positive cytology has to be reported separately without changing the stage.

APPENDIX II **(04/28/2014)**

Translational Research Specimen Procedures **(01/13/14)**

I. Summary of Specimen Requirements

If the patient gives permission for her specimens to be collected and used for this optional translational research component, then participating institutions within the United States are required to submit the patient's specimens as outlined below (unless otherwise specified).

Required Specimen (Specimen Code)	**Collection Time Point**	**Ship To**
FFPE Primary or Metastatic (FT01[1])* 1st Choice: block 2nd Choice: 15 unstained slides (charged, 5µm)	Prior to all treatment	GOG Tissue Bank within 8 weeks of registration[2]
Whole Blood (WB01) 7-10mL drawn into purple-top (EDTA) tube(s)	Prior to or after starting study treatment	GOG Tissue Bank the day the blood is collected[2]

* A copy of the corresponding pathology report must be shipped with all tissue specimens sent to the GOG Tissue Bank
If submitting both, label primary as FT01 and metastatic as FT02. If only metastatic is submitted, it should be labeled FT01.
GOG Tissue Bank / Protocol GOG-0258, Nationwide Children's Hospital, [redacted]

II. Obtaining a GOG Bank ID for Translational Research Specimens

Only one GOG Bank ID (# # # # - # # - G # # #) is assigned per patient. All translational research specimens and accompanying paperwork must be labeled with this coded patient number. A GOG Bank ID can be obtained online via the Tissue Bank Portal on the GOG website (under Tools on the Web Menu page).

Obtain the patient's study ID (GOG #) for all protocols with translational research specimen requirements before requesting a Bank ID from the Tissue Bank Portal. **Be sure to indicate if the patient has a previous GOG # when registering.** This will ensure the patient is only assigned one Bank ID. The GOG ID – Bank ID Lookup on the Tissue Bank Portal can be used to search for an existing Bank ID.

Please contact GOG User Support if you need assistance or have assigned more than one Bank ID to a patient [redacted]

III. Requesting Translational Research Specimen Kits

Kits are not provided for this protocol.

IV. Labeling Translational Research Specimens

A waterproof permanent marker or printed label should be used to label each translational research specimen with:

GOG Bank ID (# # # # - # # - G # # #)
GOG protocol number (GOG- # # # #)
specimen code (see section I)
collection date (mm/dd/yyyy)
surgical pathology accession number (tissue specimens only)
block number (tissue specimens only)

Note: If labeling slides, only label on the top, front portion of the slide. Do not place a label on the back of the slide or over the tissue. The label must fit on the slide and should not be wrapped around the slide or hang over the edge.

V. Submitting Formalin-Fixed, Paraffin-Embedded Tissue

Formalin-fixed, paraffin embedded (FFPE) tissue should be the most representative of the specimen type (primary, metastatic). Primary and metastatic tumor should be collected prior to all treatment. Only one block may be submitted per tissue type.

Primary tumor is the 1st choice and metastatic tumor is the 2nd choice. If submitting both, label primary tumor with the specimen code FT01 and metastatic tumor with the specimen code FT02. If only metastatic tumor will be submitted, it should be labeled FT01.

Every attempt should be made to provide a FFPE block; however, if a block cannot be provided on a permanent basis, then 15 unstained slides (charged, 5µm) should be submitted. All tissue sections should be cut sequentially from the same block.

Note: If stained slides (required to confirm patient eligibility by central pathology review) will be cut from the same block that will be submitted for translational research, your pathology department should cut the slides for staining prior to submitting the block for translational research.

The type of specimen (block, slides) and the type of tumor tissue (primary, metastatic) should be specified on Form SP.

All FFPE tissue should be submitted with the corresponding pathology report.

VI. Submitting Whole Blood

1. Label the lavender/purple top (EDTA) collection tube(s) as described above. Multiple tubes may be used to collect the required amount.

2. Draw 7-10mL of blood into the labeled lavender/purple top tube(s). A minimum of 3mL is needed for processing.

3. Immediately after collection, gently invert the tube 5-10 times to mix the blood and EDTA.

4. Whole blood specimens should be refrigerated (4°C) until the specimens can be shipped. Ship whole blood to the GOG Tissue Bank the day the specimen is collected. If the whole blood absolutely cannot be shipped the day it is collected, the tube(s) should be refrigerated (4°C) until the specimen can be shipped.

VII. Submitting Form SP

Form SP must be submitted via SEDES for each required specimen regardless of whether the specimen is submitted for research.

A copy of the SEDES-completed Form SP must accompany each specimen shipped to the GOG Tissue Bank (or alternate laboratory). Handwritten forms will not be accepted.

Note: A copy does not need to be sent if the specimen is not collected.

Retain a printout of the completed form for your records.

Please contact GOG User Support if you need assistance [redacted]

VIII. Shipping Translational Research Specimens

A SEDES-completed copy of Form SP must be included for each translational research specimen.

FFPE Tissue

FFPE tissue and a copy of the corresponding pathology report should be shipped using your own container at your own expense to:

[redacted]

Do not ship FFPE tissue for Saturday delivery.

Whole Blood

Whole blood specimens should be shipped to the GOG Tissue Bank (address above).

Whole blood can be shipped to the GOG Tissue Bank **Monday through Friday for Tuesday through Saturday delivery**. Do not ship whole blood the day before a holiday. Use your own shipping container to ship specimens via **FedEx priority overnight**.

When shipping whole blood specimens, **your institution must comply with IATA standards** (www.iata.org). If you have questions regarding your shipment, contact the GOG Tissue Bank at [redacted]

To ship whole blood specimens you will need (1) a sturdy shipping container (e.g., a cardboard or styrofoam box), (2) a leak proof biohazard envelope with absorbent material*, (3) a puncture and pressure resistant envelope (e.g. Tyvek envelope), (4) an Exempt Human Specimen sticker, and (5) a pre-paid FedEx air bill.

**If you will be shipping whole blood specimens from more than one patient, please put each specimen in a separate plastic zip-lock bag before placing the specimens in the shipping bag. You may include up to four different blood specimens in one biohazard envelope.*

If you do not have these materials available at your institution, you may order them from any supplier [redacted]

Shipping Whole Blood Using Your Own Shipping Container

Place the whole blood specimen in a biohazard bag containing absorbent material. Expel as much air as possible before sealing the bag.

Wrap the biohazard bag in bubble wrap or another padded material.

Place the padded tube(s) into a Tyvek envelope. Expel as much air as possible before sealing the envelope.

Place the Tyvek envelope in a sturdy shipping container (e.g., cardboard FedEx box).

Insert a copy of Form SP for each specimen.

Attach an Exempt Human Specimen Sticker to the outside of the shipping container.

Print a pre-paid FedEx air bill using the Kit Management application (found under Data Entry on the Web Menu page). Attach the air bill.

Make arrangements for FedEx pick-up through your usual institutional procedure or by calling [redacted]

IX. Distributing Translational Research Specimens

The GOG Statistical and Data Center and Tissue Bank will coordinate the distribution of specimens to approved investigators.

Investigators will not be given access to any personal identifiers.

Investigators will be responsible for the direct supervision and oversight of translational research and for keeping accurate records of all specimen testing.

Investigators will ensure the results are linked to the appropriate specimen-specific identifiers and are responsible for transferring relevant laboratory data to the GOG Statistical and Data Center.

At the discretion of the Chair of the Committee on Experimental Medicine and the Director of the GOG Tissue Bank, investigators may be required to ship any specimens (or by-products) remaining after the completion of the translational research to the GOG Tissue Bank.

X. Banking Translational Research Specimens for Future Research

Specimens will remain banked in the GOG Tissue Bank and made available for approved research projects if the patient has provided permission for the use of her specimens for future health research. The patient's choices will be recorded on the signed informed consent document and electronically via the online Specimen Consent Application. (At the time of specimen selection for project distribution, the most recent consent information will be used.

GOG institutions can amend a patient's choices regarding the future use of her specimens at any time if the patient changes her mind.

If the patient revokes permission to use her specimens, the GOG Tissue Bank will be instructed to destroy or return any remaining specimens. The patient's specimens will not be used for any <u>further</u> research; however, any specimens distributed for research prior to revoking consent cannot be returned or destroyed. In addition, the patient cannot be removed from any research that has been done with her specimens distributed prior to revoking consent.

Note: If return of specimens is requested, shipping will be at the institution's expense.

APPENDIX III **(04/28/2014)**

CARBOPLATIN DOSE CALCULATION INSTRUCTIONS (03/14/11)

1) The Cockcroft-Gault formula will be used in GOG trials (not the Jelliffe formula).

2) Conversion of IDMS creatinine levels to "non-IDMS" values will not be permitted.

3) The carboplatin calculation tool on the GOG website has been updated. A legacy carboplatin calculator (using the Jelliffe formula and IDMS to "non-IDMS" conversion) is also available, if needed for dose modifications (see below).

Dosing of Carboplatin:
The carboplatin dose will be calculated to reach a target area under the curve (AUC) according to the Calvert formula using an estimated glomerular filtration rate (GFR) from the Cockcroft-Gault formula.

The initial dose of carboplatin must be calculated using GFR. In the absence of renal toxicity greater than or equal to CTCAE Grade 2 (serum creatinine >1.5 x ULN) or toxicity requiring dose modification, the dose of carboplatin **will not** need to be recalculated for subsequent cycles, but will be subject to dose modification for toxicity as noted in the protocol.

Carboplatin doses will be based on the subject's weight at baseline and will remain the same throughout the study. However, the doses will be recalculated if the patient has a weight change of greater than or equal to 10% from baseline.

In patients with an abnormally low serum creatinine (less than 0.7 mg/dl), the creatinine clearance should be estimated using a **minimum value of 0.7 mg/dl**. If a patient is currently being dosed using a creatinine value less than 0.7 mg/dl, adjust dose with next planned treatment.

For trials where patients enter and are treated within less than or equal to 12 weeks of surgery: If a more appropriate (higher) baseline creatinine value is available from the pre-operative period (within 4 weeks of surgery date), that value may also be used for the initial estimation of GFR.

CALVERT FORMULA:

Carboplatin dose (mg) = target AUC x (GFR + 25)

NOTE: the GFR used in the Calvert formula should not exceed 125 ml/min.

Maximum carboplatin dose (mg) = target AUC (mg/ml x min) x 150 ml/min.

The maximum allowed doses of carboplatin are:

AUC 6 = 900 mg
AUC 5 = 750 mg

AUC 4 = 600 mg

For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance. The estimated creatinine clearance (ml/min) is calculated by the method of Cockcroft-Gault using the following formula:

$$\textbf{Creatinine Clearance (mL/min)} = \frac{\textbf{[140-Age (years)] x Weight (kg) x 0.85}}{\textbf{72 x serum creatinine (mg/dl)}}$$

Notes:
1) Weight in kilograms (kg):
Body Mass Index (BMI) should be calculated for each patient. A BMI calculator is available at the following link: http://www.nhlbisupport.com/bmi/
Actual weight should be used for estimation of GFR for patients with BMI of less than 25.
Adjusted weight should be used for estimation of GFR for patients with **BMI of greater than or equal to 25**.
Adjusted weight calculation:
Ideal weight (kg) = (Height (cm)/2.54) – 60) x 2.3) + 45.5

Adjusted weight (kg) = ((Actual weight – Ideal weight) x 0.40) + Ideal weight

If a patient with BMI of greater than or equal to 25 is currently being dosed using actual weight, adjust dose with next planned treatment.

2) The Cockcroft-Gault formula above is specifically for women (it includes the 0.85 factor).

At the time of a dose modification for toxicity:

1) If the creatinine at the time of a dose modification is lower than the creatinine used to calculate the previous dose, use the previous (higher) creatinine; if the creatinine at the time of a dose modification is higher than the creatinine used to calculate the previous dose, use the current (higher) creatinine. This will ensure that the patient is actually receiving a dose reduction.

2) If the dose of carboplatin (mg) at the time of dose modification, is higher than the previous dose due to the use of the Cockcroft-Gault formula [when the previous dose was calculated using the Jelliffe formula and IDMS to "non-IDMS" conversion (if applicable)], use the same method that was used to calculate the previous dose [Jelliffe formula and IDMS to "non-IDMS" conversion (if applicable)], to calculate the dose of carboplatin (mg) at the time of dose reduction. A legacy carboplatin calculator is available on the GOG website for this purpose. This will ensure that the patient is actually receiving a dose reduction.

APPENDIX IV **(04/28/2014)**
General Chemotherapy Guidelines:

- For 21 or 28 day cycles, a patient will be permitted to have a new cycle of chemotherapy delayed up to 7 days (without this being considered to be a protocol violation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.
- It will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window before and after the protocol-defined date" for "Day 1" treatment of 21 or 28 day cycles. If the treatment due date is a Friday, and the patient cannot be treated on that Friday, then the window for treatment would include the Thursday (1 day earlier than due) through the Monday (day 3 past due).
- For weekly regimens, it will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window," for example; "Day 8 chemotherapy" can be delivered on Day 7, Day 8, or Day 9 and "Day 15 chemotherapy" can be given on Day 14, Day 15, or Day 16.
- Chemotherapy doses can be "rounded" according to institutional standards without being considered a protocol violation (most institutions use a rule of approximately +/- 5% of the calculated dose).
- Chemotherapy doses are required to be recalculated if the patient has a weight change of greater than or equal to 10%. Patients are permitted to have chemotherapy doses recalculated for <10% weight changes. **(04/28/2014)**
- Maximum body surface area used for chemotherapy dose calculations will be 2.0 m^2. For chemotherapy dose calculations that use mg/kg, there will be no maximum kilogram amount used (doses will be calculated on actual weight in kg).