

**GYNECOLOGIC ONCOLOGY GROUP/
AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK**

GOG-0233/ACRIN 6671

**UTILITY OF PREOPERATIVE FDG-PET/CT SCANNING PRIOR TO PRIMARY CHEMORADIATION
THERAPY TO DETECT RETROPERITONEAL LYMPH NODE METASTASIS IN PATIENTS WITH
LOCOREGIONALLY ADVANCED CARCINOMA OF THE CERVIX (IB2, IIA \geq 4 CM, IIB-IVA) OR
ENDOMETRIUM (GRADE 3 ENDOMETRIOID ENDOMETRIAL CARCINOMA; SEROUS PAPILLARY
CARCINOMA, CLEAR CELL CARCINOMA, OR CARCINOSARCOMA (ANY GRADE); AND GRADE 1
OR 2 ENDOMETRIOID ENDOMETRIAL CARCINOMA WITH CERVICAL STROMAL INVOLVEMENT
OVERT IN CLINICAL EXAMINATION OR CONFIRMED BY ENDOCERVICAL CURETTAGE)
(11/16/09)**

(11/16/09)

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STUDY PARTICIPANTS: ALL GYNECOLOGIC ONCOLOGY GROUP MEMBERS AND AFFILIATE GYNECOLOGIC SURGEONS WHO HAVE MET THE QUALIFICATION REQUIREMENTS FROM ACRIN. **(06/09/08)**

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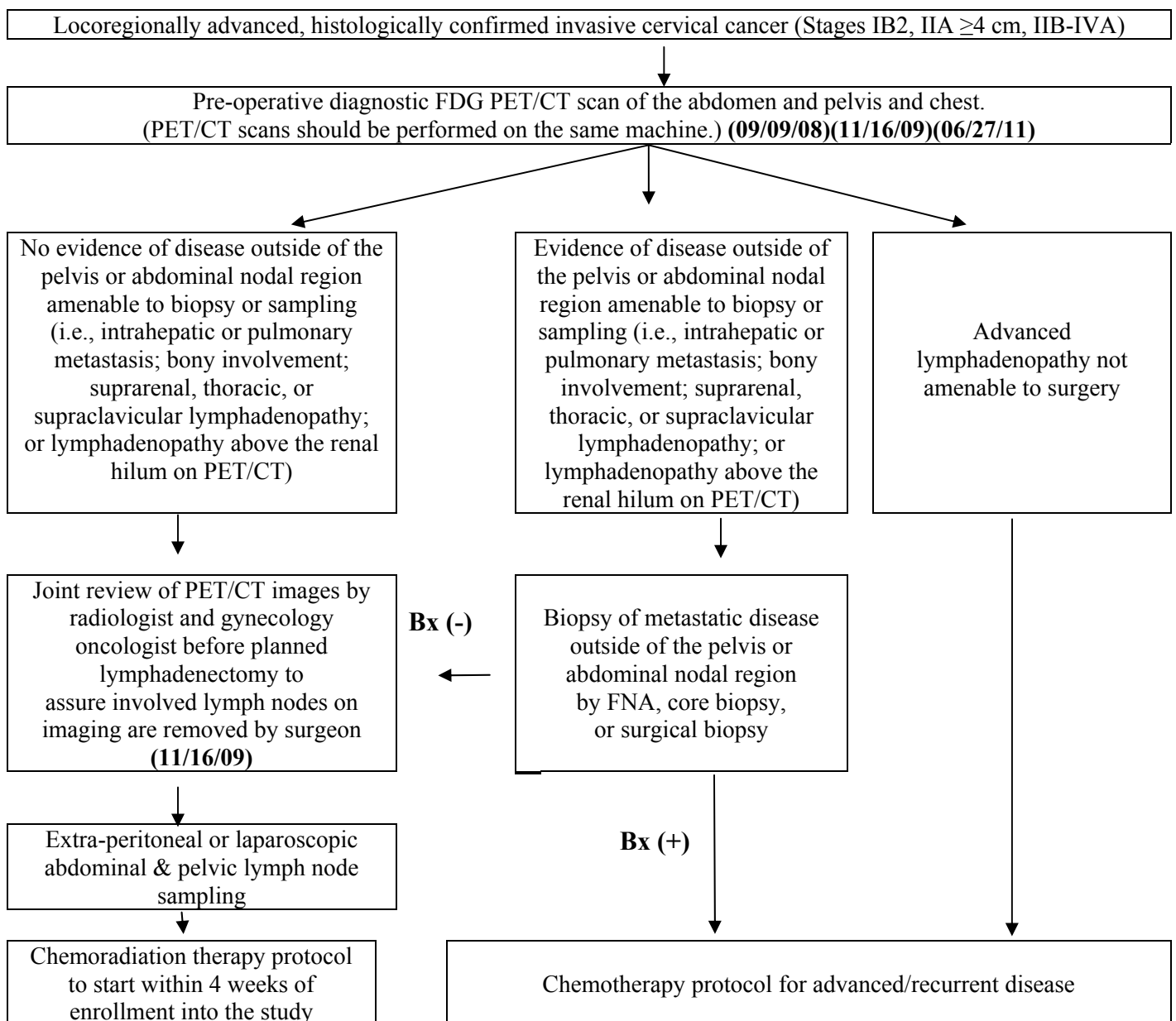
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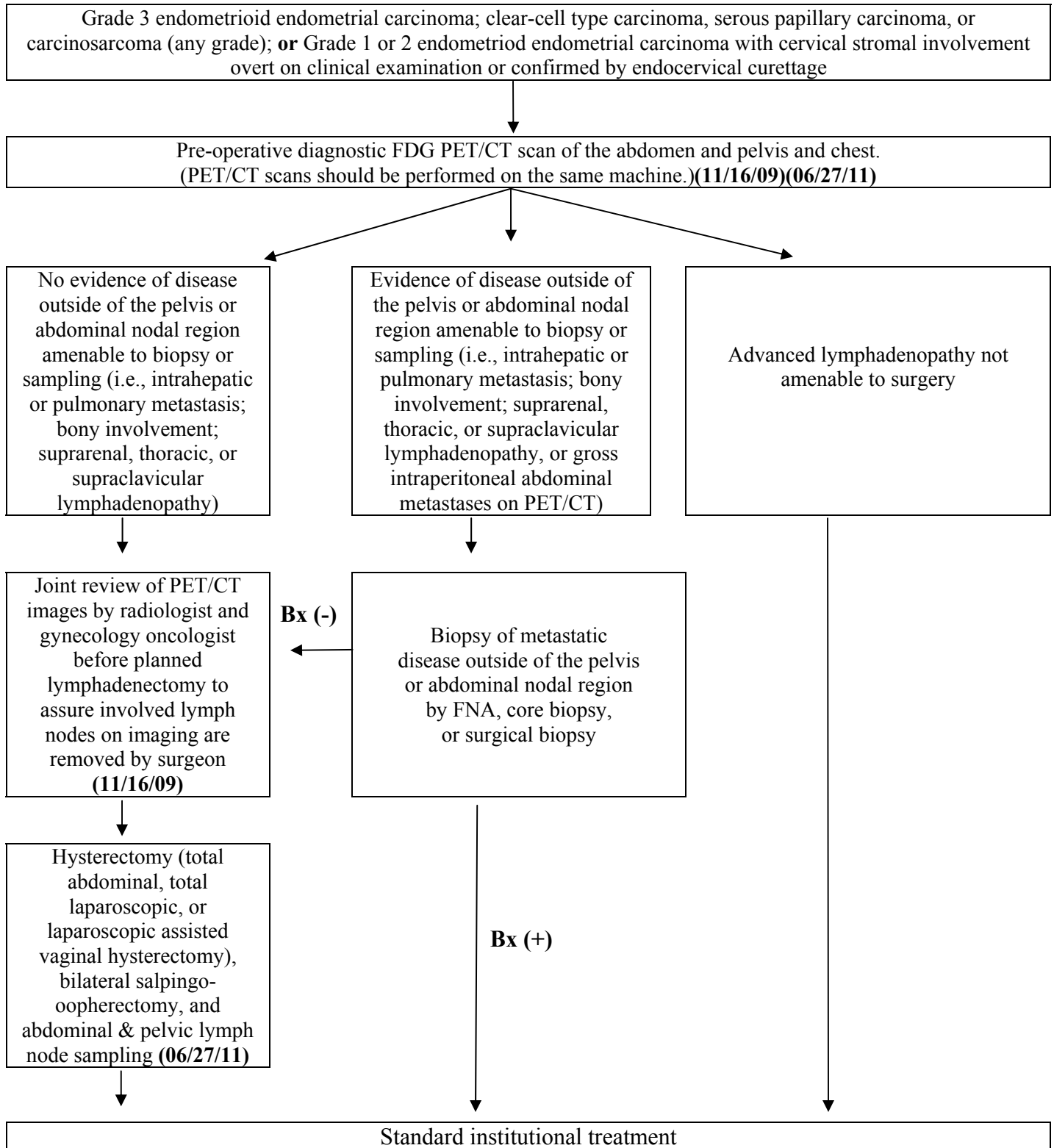
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UTILITY OF PREOPERATIVE FDG-PET/CT SCANNING PRIOR TO PRIMARY CHEMORADIATION THERAPY TO DETECT RETROPERITONEAL LYMPH NODE METASTASIS IN PATIENTS WITH LOCOREGIONALLY ADVANCED CARCINOMA OF THE CERVIX (IB2, IIA ≥4 CM, IIB-IVA) OR ENDOMETRIUM (GRADE 3 ENDOMETRIOID ENDOMETRIAL CARCINOMA; SEROUS PAPILLARY CARCINOMA, CLEAR CELL CARCINOMA, OR CARCINOSARCOMA (ANY GRADE); AND GRADE 1 OR 2 ENDOMETRIOID ENDOMETRIAL CARCINOMA WITH CERVICAL STROMAL INVOLVEMENT OVERT IN CLINICAL EXAMINATION OR CONFIRMED BY ENDOCERVICAL CURETTAGE) (11/16/09)

SCHEMA: CERVICAL CANCER (06/09/08)(11/16/09)



SCHEMA: ENDOMETRIAL CANCER (11/16/09)



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SPECIFIC AIMS/OBJECTIVES (11/16/09)

The primary aim of this study is:

- ❖ to define the utility of preoperative FDG-PET/CT scanning prior to primary chemoradiation therapy to detect retroperitoneal lymph node metastasis in participants with locoregionally advanced carcinoma of the cervix.(11/16/09)
- ❖ to define the utility of preoperative FDG-PET/CT scanning to detect retroperitoneal lymph node metastasis in participants with endometrial cancer (Grade 3 endometrioid endometrial carcinoma; clear-cell type carcinoma, serous papillary carcinoma, or carcinosarcoma [any grade]; and Grade 1 or 2 endometrioid endometrial carcinoma with cervical stromal involvement overt on clinical examination or confirmed by endocervical curettage).(11/16/09)

METHODS/METHODOLOGY(11/16/09)

In this study, a total of 380 women will be enrolled, including 165 patients with cervical cancer and 215 patients with endometrial cancer. Enrollment will take place in at least 10 sites. Interim analysis is planned when there are 40 positive cases enrolled from the two cohorts combined.(11/16/09)

ELIGIBILITY (see Section 5.0 for details)

PATIENTS WITH CERVICAL CANCER (11/16/09)

1. Patients must have primary, previously untreated, histologically confirmed, locoregionally advanced invasive carcinoma of the cervix and be considered for chemoradiation therapy.
2. Patients that qualify with the above credentials must be able to undergo extra-peritoneal or laparoscopic lymph node sampling.
3. Patients are suitable candidates for surgery.
4. Patients of child-bearing potential must have a negative urine or serum pregnancy test result within 7 days prior to undergoing PET/CT. In addition, they would undergo a urine pregnancy test on the day of PET/CT examination. The urine pregnancy test at the institution should detect hCG at the sensitivity of 25 mIU/mL. If the urine pregnancy test does not have the required sensitivity, a negative serum test is required. Postmenopausal women must have been amenorrheic for at least 12 consecutive months to be considered not of child-bearing potential.(11/16/09)
5. Patients must sign an IRB-approved informed consent form that allows access to prior medical records.
6. Patients must be accrued at an ACRIN-affiliated institution that is accredited by GOG.
7. Patients cannot have recurrent invasive carcinoma of the uterine cervix regardless of previous treatment.
8. Patients cannot have known metastases to the lungs, scalene lymph nodes, or metastases to other organs outside of the pelvis or abdominal lymph nodes at the time of the original clinical diagnosis.
9. Patients cannot have had previous pelvic or abdominal lymphadenectomy.
10. Patients cannot have evidence of prior pelvic radiation therapy for any reason.
11. Patients cannot have outside circumstances that interfere with the completion of the imaging studies or required follow-up.

PATIENTS WITH ENDOMETRIAL CANCER (11/16/09)

1. Patients must have either histologically confirmed Grade 3 endometrioid endometrial carcinoma; clear cell carcinoma, serous papillary carcinoma or carcinosarcoma (of any grade); **or** histologically confirmed Grade 1 or 2 endometrioid endometrial carcinoma with cervical stromal invasion. Histologic type and grade must be histologically confirmed. Cervical stromal invasion may be documented by clinical examination or confirmed by histological examination.
2. Patients must be suitable candidates for surgery.

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3. Patients must sign an IRB-approved informed consent form that allows access to prior medical records.
4. Patients of child-bearing potential must have a negative urine or serum pregnancy test result within 7 days prior to undergoing PET/CT. In addition, they will undergo a urine pregnancy test on the day of PET/CT examination. The urine pregnancy test at the institution should detect hCG at the sensitivity of 25 mIU/mL. If the urine pregnancy test does not have the required sensitivity, a negative serum test is required. Postmenopausal women must have been amenorrheic for at least 12 consecutive months to be considered not of child-bearing potential.
5. Patients must be accrued at an ACRIN-affiliated institution that is accredited by GOG.
6. Patients cannot have known metastases to the lungs, scalene lymph nodes, or metastases to other organs outside of the pelvis or abdominal lymph nodes at the time of the original clinical diagnosis. Patients with known intraperitoneal disease may be enrolled as long as they and their surgeon are planning a pelvic and para-aortic lymphadenectomy per protocol.
7. Patients cannot have recurrent invasive carcinoma of the uterus regardless of previous treatment.
8. Patients cannot have had previous pelvic or abdominal lymphadenectomy.
9. Patients cannot have evidence of prior pelvic radiation therapy for any reason.
10. Patients cannot have outside circumstances that interfere with the completion of the imaging studies or required follow-up.

REQUIRED SAMPLE SIZE (11/16/09)

A total of 380 participants will be enrolled into the study: 165 participants will have histologically-confirmed cervical cancer and 215 participants will have histologically-confirmed endometrial cancer. (11/16/09)

1.0 ABSTRACT

This protocol for human research study is conducted according to US and international standards of Good Clinical Practice (International Conference on Harmonisation [ICH] Guidelines), applicable government regulations (Code of Federal Regulations), the American College of Radiology Imaging Network (ACRIN) and Gynecological Oncology Group (GOG) research policies and procedures. **(09/09/08)**

In the United States, cervix cancer is the third most common gynecologic malignancy, with approximately 11,000 new cases and 3,700 deaths annually. Primary radiotherapy (RT) fails to control locoregional disease in 20% to 85% of patients with locally advanced carcinoma. **(11/16/09)** These estimates are based on stage, tumor bulk, and nodal status. When compared with surgical findings, clinical staging is accurate in only 60% of cases. In many instances, errors in staging are related to undiagnosed lymph node metastases.

Endometrial cancers are the most common gynecologic cancers in the U.S., with more than 35,000 women diagnosed each year. Involvement of both pelvic and para-aortic lymph nodes predicts significantly worse disease with poorer outcomes. Currently, an accurate non-invasive test is not available for the detection of lymph node metastases, and surgical staging is the most accurate method to determine lymph node involvement. Although controversy continues over the necessity of surgical staging to evaluate the status of lymph nodes in patients with early-stage endometrial cancer, risk of extra-uterine disease is sufficiently high in the high-risk patients for whom surgical staging appears justified (1). High-risk stage I patients include women with Grade 3 endometrioid, serous papillary, clear cell, and carcinosarcoma, as well as with Grade 1 or 2 with deep myometrial and cervical involvement. **(11/16/09)**

More recently, fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) imaging has demonstrated its utility in detecting nodal involvement in a few small series in cervical and endometrial cancers. **(11/16/09)** The diagnostic sensitivity and specificity of the currently performed imaging modalities have been less than optimal in the evaluation of lymph node metastasis from cervical or endometrial cancer. The preliminary results of FDG-PET/CT for detection of lymph node metastasis have been encouraging. The primary objective of this study is to evaluate the diagnostic sensitivity and specificity of FDG-PET/CT imaging in identifying metastases to abdominal (common iliac, para-aortic, and para-caval) lymph nodes in patients with cervical cancer (stages IB2, IIA \geq 4 CM, IIB-IVA) and abdominal (common iliac, para-aortic, and para-caval) and pelvic lymph nodes in patients endometrial cancer (Grade 3 endometrioid or non-endometrioid endometrial carcinoma, any grade carcinosarcom, or Grade 1 or 2 with cervical involvement). **(11/16/09)**

Three-hundred eighty participants meeting the inclusion criteria will be enrolled in this multi-center study. The reference standard for confirmation or exclusion of lymph node metastasis will be pathological assessment of the lymph nodes removed at surgery. The diagnostic sensitivity and specificity of FDG-PET/CT will be evaluated in a central reader study including seven (7) expert readers. **(11/16/09)**

2.0 BACKGROUND AND SIGNIFICANCE

2.1 Cervical Cancer (11/16/09)

Cancer of the uterine cervix is the second most common cancer in females, representing 15% of all female cancers, 80% of which are diagnosed in underdeveloped countries (2). In the United States, cervical cancer is the third most common gynecologic malignancy, with approximately 11,000 new cases and 3,700 deaths annually (3). Though incidence and mortality in the United States dropped steadily from 1940 through 1990, there has recently been a plateau, arresting the decline (2, 4). The vast majority of cases are diagnosed with early-stage disease, but some with locally advanced disease require radiation therapy (5). Unfortunately, primary RT fails to control locoregional disease in 20% to 85% of patients with locally advanced carcinoma, depending on stage, tumor bulk, and nodal status (6–10).

One reason for the high failure rate may be that cervical cancer remains the only major gynecologic malignancy that is clinically staged (11). When compared with surgical findings, clinical staging is accurate in only 60% of cases (12, 13). A recent study by ACRIN/GOG cooperative group (14) shows improved clinical staging for local extent of disease, which appears to be influenced by reduction in the use of projectional imaging and increasing use of cross sectional imaging such as CT and MRI (14, 15). In many instances, errors in staging are related to undiagnosed lymph node metastases (12, 13). It is commonly accepted that patients with lymph node metastases have lower overall survival, disease-free survival, and survival after recurrence (14–16). Although not permitted to alter FIGO staging (17), many modalities have been employed to determine the extent of disease prior to therapy. In a clinical-pathologic study performed by the GOG, sensitivity and specificity of CT was only 34% and 96%, respectively (18). However, a more recent meta-analysis found the positive predictive value of CT to be 60% and the negative predictive value to be 91% for detection of retroperitoneal lymph node metastasis (19).

2.2 Endometrial Cancer (11/16/09)

Unlike cervical cancer, endometrial cancer is most commonly staged surgically via hysterectomy. Complete surgical staging for endometrial cancer also includes pelvic and para-aortic lymphadenectomy. Pre-operative imaging often plays a role by predicting the extent of myometrial invasion, involvement of the cervix, presence of metastatic disease in the lymph nodes, and presence of disease outside the uterus—all of which may lead to surgical lymphadenectomy for confirmation.

Involvement of both pelvic and para-aortic lymph nodes in endometrial cancer predicts significantly worse disease with poorer outcomes. Lymphatic drainage of the uterus is complex, and multiple lymphatic chains are at risk. They are found along the obturator, iliac (external, internal, and common), caval and aortic vessels, and also in the parametrial tissue and the presacral space. Therefore, unlike in cervical carcinoma, para-aortic and para-caval lymph nodes may be involved without involvement of pelvic lymph nodes.

The GOG conducted a surgical pathologic study of the spread patterns of endometrial cancer (20). The GOG study demonstrated that lymph node positivity was associated with grade, histologic subtype, and cervical involvement. Specifically, Grade 3 endometrioid cancers were found to have pelvic lymph node metastases in 18% of cases and para-aortic metastases in 11%; serous papillary and clear-cell histologies had pelvic lymph node metastases in 9% and para-

aortic metastases in 18%; and those with cervical stromal involvement had pelvic lymph node metastases in 16% and para-aortic metastases in 14%. Of participants with metastatic disease to the lymph nodes, 49% had involvement of the para-caval lymph nodes and 17% had metastases only to the para-caval lymph nodes. The actual rate of abdominal lymph node metastases may have been underestimated in this study since a thorough left para-aortic lymph node dissection was not performed. In a subsequent manuscript from the GOG (21), the incidence of lymph node metastases associated with cervical stromal involvement in 66 participants was reported as 30% pelvic lymph nodes, 17% para-aortic lymph nodes, and 38% pelvic and para-aortic lymph nodes.

Reported accuracy of CT and MRI to detect lymph node metastasis in endometrial cancer, based on short axis diameter of 8 or 10 mm, is between 18% and 66% sensitivity, and between 73% and 99% specificity (22–27).

2.3 PET Imaging in Assessing Lymph Node Metastases (11/16/09)

More recently, FDG-PET imaging has demonstrated its utility in detecting nodal involvement in a number of malignancies other than cervical cancer. In one study involving 48 patients with primary esophageal carcinoma, the participants were evaluated with PET, CT, and ultrasound (US) prior to undergoing complete lymphadenectomy (28). PET demonstrated 57% sensitivity, 97% specificity, and 86% accuracy compared to CT, which was only 18% sensitive ($p < 0.0001$), 99% specific ($p = 0.03$), and 78% accurate ($p = 0.003$). Overall, for N staging, PET was correct in 83% of cases, whereas CT and US were correct in 60% ($p = 0.006$) and 57% ($p = 0.003$), respectively. Similarly, in a study comparing PET with CT for diagnosing small (<1 cm), intermediate (1–3 cm), and large (>3 cm) mediastinal lymph node metastases from lung cancer, PET was equally reliable and accurate for detecting all sizes of lymph node lesions with better efficacy than CT (29). Overall sensitivity, specificity, and accuracy were 96%, 93%, and 94%, respectively, with a positive and negative predictive value of 86% and 98%. In summarizing the results from another study evaluating PET, CT, MRI, and US in the detection of lymph node metastases from head and neck cancer, the authors concluded that PET was the “procedure with the highest sensitivity and specificity” (30). (11/16/09)

Several reports also have demonstrated the utility of FDG-PET imaging in the diagnosis of lymph node metastases from cervical carcinoma. Rose et al. (31) pre-operatively evaluated 32 patients with IIB–IVA cervical cancer with no evidence of extra-pelvic disease. FDG was taken up by 91% of the cervical tumors and accurately diagnosed six of eight participants with positive para-aortic lymph node metastases. The sensitivity was 75%, the specificity 92%, the positive predictive value 75%, and negative predictive value 92%. Similarly, Sugawara et al. (32) correctly identified six of seven (86%) participants with known lymph node metastases using PET, compared to only four with CT. Reinhardt et al. (33) compared the diagnostic accuracy of MRI with that of PET in a group of 35 participants with stage IB and II cervical cancer. Eleven participants had surgically proven lymph node metastasis. FDG-PET had a sensitivity of 91%, a specificity of 100%, a negative predictive value of 96%, and an accuracy of 97% for depicting lymph node metastases, while the respective values for MRI were 73%, 83%, 67%, 87%, and 80%. A recent analysis of 15 published PET studies in cervical cancer by Havrilesky et al. (34) demonstrated that pooled sensitivity and specificity for detection of pelvic lymph node metastasis were 79% (95% CI, 65%–90%) and 99% (96%–99%), respectively for FDG-PET; 72% (53%–87%) and 96% (92%–98%), respectively for MRI; and 47% (21%–73%) for CT (the pooled specificity for CT not available) (27). In this review, the pooled sensitivity of FDG-PET

for para-aortic lymph nodes were 84% (95% CI, 68%–94%) and 95% (89%–98%), respectively (the pooled sensitivity and specificity for CT or MRI are not available). **(11/16/09)**

There are limited data available on the utility of PET/CT on the evaluation of lymph node metastases in cervical cancer. Sironi et al. studied 47 participants with cervical cancer. Fifteen had metastatic lymph nodes at histopathologic examination, and 32 had no histopathologically confirmed nodal metastasis (35). Of the total 1081 pelvic lymph nodes histopathologically sampled, 18 were found to be positive for metastatic disease. The overall lymph node-based sensitivity, specificity, and accuracy of PET/CT were 72%, 99.7%, and 99.3%, respectively. The overall patient-based sensitivity, specificity, and accuracy of PET/CT were 73%, 97%, and 89%, respectively. To date, no PET/CT study is available in cervical cancer that has compared PET with PET/CT. However, in various types of cancers, this comparison has been made, and these studies have demonstrated improvement of PET performance when fused PET/CT images were used (36). For example, in a study of 260 participants with various types of cancers, Antoch et al. reported that PET/CT is more accurate in lymph node staging than PET alone with sensitivities of 92% for PET/CT and 85% for PET and specificities of 93% and 88%, respectively (37). Thus, an improvement of approximately 10% in the performance of PET is expected when PET/CT is used. **(11/12/08)(11/16/09)**

To date, there are limited data available in cervical or endometrial cancer that have compared PET/CT with MRI in the detection of metastatic lymph nodes (38–40). Park et al. retrospectively studied 36 participants with cervical cancer prior to radical surgery (38). The sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) for detecting metastatic disease in the pelvic lymph nodes were 41%, 100%, 82%, 100%, and 79%, respectively for FDG-PET/CT and 55%, 80%, 72%, 55%, and 80%, respectively for MRI. Choi et al. studied 22 participants with FIGO stages of IB to IVA prior to lymphadenectomy (39). The sensitivity, specificity, and accuracy for detection of pelvic and para-aortic lymph nodes were 30%, 93%, and 73%, respectively for MRI and 58%, 93%, and 85%, respectively for FDG-PET/CT. While FDG-PET/CT was statistically more sensitive than MRI ($p = 0.02$), the specificity and accuracy of these two imaging modalities were not statistically different. In endometrial cancer, Park et al. studied 53 participants with endometrial cancer (40). In detecting primary uterine corpus cancer, there was no significant difference between MRI and FDG-PET/CT. The sensitivity, specificity, accuracy, PPV, and NPV for detecting primary cancer were 91.5%, 33.3%, 84.9%, 91.5%, and 33.3%, respectively for MRI and 89.4%, 50.5%, 84.9%, 93.3%, and 37.5%, respectively for FDG-PET/CT. For extrauterine distant metastatic disease (such as liver, lung, bone, peritoneum, mesentery, etc.) on a patient-by-patient basis, PET/CT had sensitivity, specificity, accuracy, PPV, and NPV of 100%, 93.8%, 92.5%, and 100%, respectively. MRI of the chest and abdomen were not performed and thus, the performance of this modality for detection of distant extrauterine disease was not evaluated. With MRI, the sensitivity, specificity, accuracy, PPV, and NPV for detecting pelvic and para-aortic metastatic lymph nodes on lymph node area-by-area analysis were 46.2%, 87.9%, 83.9%, 28.6%, and 94.0%, respectively for MRI; and were 69.2%, 90.3%, 88.3%, 42.9%, and 96.6%, respectively for PET/CT. PET/CT showed higher sensitivity for detecting lymph node metastasis, but it did not reach statistical significance ($p = 0.250$). **(11/16/09)**

There are limited data on the performance of PET and PET/CT alone or in comparison with MRI in the evaluation of lymph node metastasis in endometrial cancer. Table 1 summarizes the available data in the literature (38, 41–44). (11/16/09)

Table 1. Available data in the literature—comparison of PET or PET/CT with MRI in evaluating lymph node (LN) metastases (11/16/09)

Patients/LNs	Sensitivity	Specificity	Reference/Modality
Node-based	23/45 (51%)	1,927/1,931 (99.8%)	PET (41)
Patient-based*	6/12 (50%)	30/33 (90.9%)	
Node-based	32/60 (53%)	1,419/1,424 (99.6%)	PET/CT (42)
Pelvic	17/31 (55%)	916/918 (99.8%)	
Para-aortic	15/29 (52%)	503/506 (99.4%)	
Patient-based	5/10 (50%)	26/30 (86.7%)	
Node-based	2/3 (60%)	68/70 (98%)	PET (43)
Patient-based	2/2 (100%)	15/16 (94%)	
Patient-based [†]			PET (44)
Pelvic	0/5 (0%)	21/21 (100%)	
Para-aortic	0/1 (0%)	18/18 (100%)	
Extra LN	5/6 (83%)	24/24 (100%)	
Patient-based [‡]			PET/CT & MRI (38)
Pelvic & para-aortic LNs			
PET/CT	9/13 (62%)	112/124 (90%)	
MRI	6/13 (50%)	109/124 (88%)	
Extrauterine PET/CT	100%	93.8%	

* cervix and endometrium combined; pelvis and abdomen combined

[†] all positive LNs < 6mm

[‡] total lymph node area

2.4 Surgical Staging (11/16/09)

At present, the routine use of extra-peritoneal surgical staging prior to radiation therapy in patients with bulky or locally advanced disease remains controversial. Proponents of surgical staging cite the ability to detect and then treat metastatic disease beyond the standard radiation fields (45, 46). Recent evidence suggests a survival advantage both in patients with para-aortic lymph node metastases who receive radiation (18, 47) and in patients who receive prophylactic para-aortic radiation, despite having negative or unevaluated para-aortic lymph nodes (48). Beyond this is the potential therapeutic benefit of the debulking of large lymph node metastases that are beyond the ability of standard radiotherapy doses to sterilize (49, 50). (11/16/09)

Those opposed to the routine use of pre-treatment surgical staging in cervical carcinoma argue that only a small number of patients will benefit from extended field radiation. This is based on the belief that most patients with advanced disease will die of local failure, making distant

control irrelevant (51, 52). With the use of multimodal treatments, however, and with improved brachytherapy, there is a trend toward improved local control, thus increasing the importance of measures that preferentially might improve distant control (53, 54). Pre-irradiation surgical staging also has been associated with an increase in late radiation related morbidity and mortality, although principally this is for transperitoneal surgical approaches combined with extended-field radiation in doses exceeding 5000 centigray (cGy) (50, 55, 56). **(11/16/09)**

Several studies have suggested survival advantages for patients undergoing extraperitoneal staging laparotomy prior to definitive radiation therapy. Downey et al. reported similar survival for patients with completely resected lymph nodes, whether microscopically or macroscopically involved (57% and 51%, respectively) (57). In a follow-up report, Cosin et al. again demonstrated equivalent survival for patients with completely resected microscopically or macroscopically involved lymph nodes. They also showed a significant improvement in survival for those with macroscopically involved lymph nodes who underwent complete resection compared to those with unresectable lymph nodes (58). In addition to surgical debulking, Goff et al. (59) suggested that surgical lymphadenectomy provided more accurate information than CT scans, allowing for better individualization of therapy and resulting in treatment modifications in 43% of their patients. Similar results have been reported by others (54, 55, 60, 61). **(11/16/09)**

PET/CT is thought to have a higher sensitivity and specificity to detect retroperitoneal lymph node metastasis as compared to the current cross-sectional imaging modalities.**(11/16/09)**

The study will primarily focus on two critical areas. It is important to evaluate the diagnostic sensitivity and specificity of pre-operative FDG-PET/CT scan imaging in identifying metastases to abdominal (common iliac, para-aortic, and para-caval) lymph nodes in patients with locoregionally advanced cervical carcinoma and abdominal (common iliac, para-aortic, and para-caval) and pelvic lymph nodes in high-risk endometrial cancer.**(11/16/09)**

In addition to achieving the primary objectives, the study also has secondary goals that are essential to the overall success of the study. The secondary aims will address additional aspects of the reader study data. These include examining the sensitivity and specificity of detection of pelvic lymph node metastasis, the analysis of the original scan interpretations performed at the participating sites, and the analysis of data on complications from surgery and imaging. **(11/16/09)**

3.0 SPECIFIC AIMS/OBJECTIVES (11/16/09)

3.1 Primary Objectives

- 3.1.1** To evaluate the diagnostic sensitivity and specificity of preoperative FDG-PET/CT imaging in identifying metastases to abdominal (common iliac, para-aortic, and para-caval) lymph nodes in participants with locoregionally advanced cervical carcinoma.

- 3.1.2** To evaluate the diagnostic sensitivity and specificity of preoperative FDG-PET/CT imaging in identifying metastases to retroperitoneal abdominal lymph nodes in participants with high-risk endometrial cancer.

3.2 Secondary Objectives

- 3.2.1** To evaluate the diagnostic sensitivity and specificity of preoperative FDG-PET/CT imaging in identifying metastases to pelvic lymph nodes (obturator, external iliac) and pelvic and abdominal lymph nodes combined in participants with locoregionally advanced cervical carcinoma.
- 3.2.2** To evaluate the diagnostic sensitivity and specificity of preoperative FDG-PET/CT imaging in identifying metastases to pelvic lymph nodes and pelvic and abdominal lymph nodes combined in participants with high-risk endometrial cancer.
- 3.2.3** To evaluate the additive diagnostic value of CT fusion (PET/CT) compared with PET scanning alone in the identification of metastases to pelvic (obturator, external iliac), abdominal (common iliac, para-aortic, and para-caval), and combined (all regions) lymph nodes in participants with locoregionally advanced cervical carcinoma or high-risk endometrial carcinoma.
- 3.2.4** To determine the percentage of participants with locoregionally advanced cervical carcinoma or high-risk endometrial cancer in whom PET/CT detects biopsy-proven disease outside the abdominal or pelvic lymph nodes.
- 3.2.5** To determine complications associated with extra-peritoneal or laparoscopic abdominal and pelvic lymphadenectomy in participants with locoregionally advanced cervical cancer.
- 3.2.6** To determine the cause(s) of delay in the initiation of radiation therapy or interruption in radiation therapy in participants with cervical cancer.
- 3.2.7** To evaluate the diagnostic sensitivity and specificity of PET/CT in the identification of metastases to pelvic (obturator, external iliac), abdominal (common iliac, para-aortic, and para-caval), and combined (all regions) lymph nodes in a combination of locoregionally advanced cervical cancer and high-risk endometrial cancer cohorts.

The primary metrics of diagnostic accuracy for all of the above will be sensitivity and specificity. The reference standard is the result of pathological evaluation of pelvic and abdominal lymph nodes. Objectives 3.1.1, 3.1.2, 3.2.1, 3.2.2, 3.2.3, 3.2.4, and 3.2.7 will be evaluated primarily through central reader studies.

4.0 STUDY OVERVIEW (11/16/09)

A total of 380 women will be enrolled in this study from at least 10 sites. Eligible participants are women who have met the pre-entry requirements for either cervical or endometrial cancer as specified in the Eligibility Criteria sections of the protocol specific to each disease cohort. Participants must be accrued at GOG member institutions or affiliates who are also accredited by ACRIN.

Assuming that approximately 20% of the enrolled women in both cancer cohorts will actually have positive abdominal nodes, with 8% of the cervical cancer cohort and 15% of the endometrial cancer cohort without reference standard, the expected number of women with positive nodes in the abdomen in the study sample is 30 in the cervical cancer cohort and 36 in the endometrial cancer cohort. The enrollment figure may need to be revised if the number of positive nodes is below the above projected numbers. Interim analysis will be done when 40 positive nodes from the two cohorts combined are available for assessment.

5.0 PARTICIPANT SELECTION

5.1 Inclusion Criteria: Cervical Cancer Only (11/16/09)

- 5.1.1 Participants must have primary, previously untreated, histologically confirmed, locoregionally advanced (IB2, IIA \geq 4cm, IIB-IVA), invasive carcinoma of the cervix (any cell type) and be considered for chemoradiation therapy. All patients must have had appropriate surgery for cervical carcinoma with appropriate tissue available for histologic evaluation to confirm diagnosis and stage. **(06/09/08)(06/27/11)**
- 5.1.2 Participants must be appropriate surgical candidates to undergo extra-peritoneal or laparoscopic lymph node sampling.
- 5.1.3 Participants must have GOG performance status of 0, 1, or 2.
- 5.1.4 Participants should have creatinine within normal institutional limits OR, in participants with creatinine levels above institutional normal, glomerular filtration rate (GFR) must be >60 mL/min/1.73 m²; there is no lower limit of normal for serum creatinine for this protocol. GFR should be determined within 28 days prior to the FDG-PET/CT for the trial. **(11/12/08)(06/01/09)(06/27/11)**
- 5.1.5 Participants of child-bearing potential must have a negative urine or serum pregnancy test result within 7 days prior to undergoing PET/CT. In addition, they would undergo a urine test on the day of PET/CT examination. The urine test at the institution should detect hCG at the sensitivity of 25 mIU/mL. If the urine test does not have the required sensitivity, a negative serum test is required. Postmenopausal women must have been amenorrheic for at least 12 consecutive months to be considered not to be of child-bearing potential. **(11/16/09)**
- 5.1.6 Participants must sign an IRB-approved informed consent and authorization permitting release of personal health information.
- 5.1.7 Participants must be enrolled at an ACRIN-affiliated institution that is accredited by GOG. **(06/27/11)**

5.2 Exclusion Criteria: Cervical Cancer Only (11/16/09)

- 5.2.1 Patients with recurrent invasive carcinoma of the uterine cervix regardless of previous treatment.
- 5.2.2 Patients who have known metastases to lungs, scalene lymph nodes, or metastases to other organs outside of the pelvis or abdominal lymph nodes at the time of the original clinical diagnosis.
- 5.2.3 Patients with any stage of cervical cancer other than IB2, IIA \geq 4cm, and IIB-IVA.
- 5.2.4 Patients who had a prior pelvic or abdominal lymphadenectomy performed for any reason.

- 5.2.5 Patients who have received prior pelvic radiation therapy for any reason. (06/01/09)
- 5.2.6 Patients with circumstances that will not permit completion of the imaging studies or required follow up.
- 5.2.7 Patients with renal abnormalities, such as a pelvic kidney, horseshoe kidney, or renal transplantation, which would require modification of the lymphadenectomy. (06/01/09)
- 5.2.8 Patients with a history of anaphylactic or life-threatening allergic reactions to any contrast media.
- 5.2.9 Patients who are pregnant or lactating or who suspect they might be pregnant. (11/16/09)
- 5.2.10 Patients with GOG performance status of 3 or 4.
- 5.2.11 Patients with other invasive malignancies, with the exception of non-melanoma skin cancer, who had (or have) any evidence of the other cancer within the last 5 years or whose previous cancer treatment contraindicates this protocol therapy. (11/16/09)
- 5.2.12 Patients with a history of cirrhosis. (11/16/09)
- 5.2.13 Patients with poorly controlled, insulin-dependent diabetes (fasting blood glucose level >200 mg/dL).
- 5.2.14 Patients weighing greater than that allowable by the PET/CT scanner. (09/09/08)(06/27/11)

5.3 Inclusion Criteria: Endometrial Cancer Only (11/16/09)

- 5.3.1 Participants must have histologically confirmed Grade 3 endometrioid or non-endometrioid endometrial carcinoma (clear cell or serous papillary) or carcinosarcoma as diagnosed from an endometrial biopsy or dilation and curettage **or** histologically confirmed Grade 1 or 2 endometrioid endometrial carcinoma **with** cervical stromal involvement overt on clinical examination or confirmed by endocervical curettage. All patients must have had appropriate surgery for endometrial carcinoma with appropriate tissue available for histologic evaluation to confirm diagnosis and stage. (06/27/11)
- 5.3.2 Participants must be appropriate surgical candidates to undergo hysterectomy and lymph node sampling.
- 5.3.3 Participants must have GOG performance status of 0, 1, or 2.
- 5.3.4 Participants should have creatinine within normal institutional limits OR, in participants with creatinine levels above institutional normal, GFR must be >60 mL/min/1.73 m²; there is no lower limit of normal for serum creatinine for this protocol. GFR should be determined within 28 days prior to the FDG-PET/CT for the trial. (06/27/11)
- 5.3.5 Participants of child-bearing potential must have a negative urine or serum pregnancy test result within 7 days prior to undergoing PET/CT. In addition, they would undergo a urine test on the day of PET/CT examination. The urine test at the institution should detect hCG at the sensitivity of 25 mIU/mL. If the urine test does not have the required sensitivity, a negative serum test is required. Postmenopausal women must have been amenorrheic for at least 12 consecutive months to be considered not to be of child-bearing potential. (11/16/09)

- 5.3.6 Participants must sign an IRB-approved informed consent and authorization permitting release of personal health information.
- 5.3.7 Participants must be enrolled at an ACRIN-affiliated institution that is accredited by GOG.

5.4 Exclusion Criteria: Endometrial Cancer Only (11/16/09)

- 5.4.1 Patients with recurrent invasive carcinoma of the uterus regardless of previous treatment.
- 5.4.2 Patients who have known metastases to lungs, scalene lymph nodes, or metastases to other organs outside of the pelvis or abdominal lymph nodes at the time of the original clinical diagnosis. Patients with known intraperitoneal disease may be enrolled as long as they and their surgeon are planning a pelvic and para-aortic lymphadenectomy per protocol.
- 5.4.3 Patients who had a prior pelvic or abdominal lymphadenectomy performed for any reason.
- 5.4.4 Patients who have received prior pelvic radiation therapy for any reason.
- 5.4.5 Patients with circumstances that will not permit completion of the imaging studies or required follow up.
- 5.4.6 Patients with renal abnormalities, such as a pelvic kidney, horseshoe kidney, or renal transplantation, which would require modification of the lymphadenectomy.
- 5.4.7 Patients with a history of anaphylactic or life-threatening allergic reactions to any contrast media.
- 5.4.8 Patients who are pregnant or lactating or who suspect they might be pregnant. (11/16/09)
- 5.4.9 Patients with GOG performance status of 3 or 4.
- 5.4.10 Patients with other invasive malignancies, with the exception of non-melanoma skin cancer, who had (or have) any evidence of the other cancer within the last 5 years or whose previous cancer treatment contraindicates this protocol therapy. (11/16/09)
- 5.4.11 Patients with a history of cirrhosis. (11/16/09)
- 5.4.12 Patients with poorly controlled, insulin-dependent diabetes (fasting blood glucose level >200 mg/dL).
- 5.4.13 Patients weighing greater than that allowable by the PET/CT scanner.(06/27/11)

5.5 Recruitment and Screening

Potential study participants will be seen by a GOG investigator as part of their standard care for their cervical or endometrial cancer. At the time of their visit, the standard of care treatment will be discussed along with possible participation in the GOG-0233/ACRIN 6671 trial. If the patient agrees to participate, they will be consented by the GOG investigator or investigator-designee. More information about study participant enrollment is available on the GOG and ACRIN web sites.(11/16/09)

Investigators who wish to participate in the trial are required to complete an ACRIN Protocol Specific Application (PSA) found on the ACRIN web site (<http://www.acrin.org/PROTOCOLSUMMARYTABLE/PROTOCOL6671/6671ProtocolApplicationandSiteActivation>)

[/tabid/416/Default.aspx](#)). (06/09/08) The PSA requires the collaboration of the ACRIN and GOG researchers to complete the following information:

1. Documentation of the number of patients treated in the previous two years who would meet protocol eligibility;
2. Documentation of the site’s recruitment potential;
3. Detailed description of how the patients will be identified, informed about the study, and consented into the trial.

ACRIN will work with the protocol team and site investigators to determine materials that would be helpful for participant recruitment. Site investigators will be responsible for obtaining IRB approval recruitment materials provided by ACRIN.

5.6 Inclusion of Women and Minorities

The GOG/ACRIN participating institutions will not exclude potential participants from participating in this or any study solely based on 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 cervix and endometrial cancer population treated by participating institutions.

Women of all ethnic groups are eligible for this trial. In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research the projected gender and minority accruals are shown below:

Gender and Minority Accrual Estimates: Cervical Cancer (11/16/09)

Ethnic Category	Sex			
	Females	Males	Unknown	Total
Hispanic or Latino	20	N/A	N/A	20
Not Hispanic or Latino	145	N/A	N/A	145
Ethnic Category: Total of all patients	165	N/A	N/A	165
Racial Category				
American Indian or Alaskan Native	2	N/A	N/A	2
Asian	7	N/A	N/A	7
Black or African American	45	N/A	N/A	45
Native Hawaiian or other Pacific Islander	0	N/A	N/A	0
White	111	N/A	N/A	111
Racial Category: Total of all patients	165	N/A	N/A	165

Gender and Minority Accrual Estimates: Endometrial Cancer (11/16/09)

Ethnic Category	Sex			
	Females	Males	Unknown	Total
Hispanic or Latino	25	N/A	N/A	25
Not Hispanic or Latino	190	N/A	N/A	190
Ethnic Category: Total of all patients	215	N/A	N/A	215
Racial Category				
American Indian or Alaskan Native	2	N/A	N/A	2
Asian	9	N/A	N/A	9
Black or African American	49	N/A	N/A	49
Native Hawaiian or other Pacific Islander	0	N/A	N/A	0
White	155	N/A	N/A	155
Racial Category: Total of all patients	215	N/A	N/A	215

6.0 SITE SELECTION**6.1 Investigator & Institutional Requirements***GOG Requirements*

Protocol requirements will be sent out to GOG sites. GOG investigators must be willing to perform pre-treatment surgical staging in cervical or endometrial carcinoma, and the other responsibilities outlined in the GOG investigator letter of participation that is sent as part of the GOG-0233/ACRIN 6671 PSA.(11/16/09)

ACRIN Requirements

The ACRIN Biostatistics and Data Management Center (BDMC) will monitor participant accrual. The gynecological surgeons at each participating site must sign a letter of agreement to facilitate recruitment of participants and to comply with the protocol. During the first year, accrual will be reviewed monthly with the intention of discovering and resolving any barriers. The trial PI will designate members for a "Patient Enrollment Support Committee." Committee members will be responsible for monitoring the accrual rates for individual institutions and developing corrective action plans for institutions that fall below 75% of a site's expected accrual after a six-month start up period from the time the site is open for participant enrollment.

6.2 IRB Approval and Informed Consent

All institutions must have study-specific Institutional Review Board (IRB) approval for the protocol and informed consent form(s). The informed consent form templates are included in this protocol as Appendix III.(11/16/09) The investigator and the investigator-designated research staff must follow OHRP-approved consent procedures (Title 45, Part 46 Code of Federal Regulations), as well as those set by the local IRB at the institution. A copy of the IRB approval letter and a copy of the IRB approved, institutional study-specific consent forms must be on file at ACRIN Headquarters (fax: 215-717-0936,

ATTN: Protocol Development and Regulatory Compliance [PDRC] Department) prior to registering the first participant.(11/16/09)

ACRIN PDRC will review the IRB documentation and grant sites approval after conducting the IRB review process. After the site is approved for participant enrollment, ACRIN PDRC will forward a copy of the institution's IRB approval letter and IRB-approved informed consent forms to the GOG Regulatory Office (ATTN: Shawn Griffin, email: sgriffin@gog.org; fax: 215-854-0716).(11/16/09) GOG staff will enter the approval into the GOG regulatory database. The IRB approval information will appear in the web registration system, allowing the approved site to complete web registration.

7.0 ONLINE REGISTRATION SYSTEM

7.1 Using the Online Registration System

- 7.1.1 The institution must register the participant using the web-based registration application available at www.gog.org. Instructions for web-based registration can be found by going to the GOG Web Menu page, selecting "Start/finish a patient registration" and then selecting "Directions" found in the left side of the page. Call (800) 523-2917 for any questions regarding participant registration. (06/09/08)
- 7.1.2 The institution will enter the participant's name, GOG number, and assigned regimen in the appropriate place in their Log Book to verify the participant's entry. Participants will be registered at GOG only. ACRIN will be notified of each registration after GOG completes the registration process.(11/16/09)
- 7.1.3 GOG will notify ACRIN and the primary investigators of enrollment/registration via Mercury.
- 7.1.4 If a data manager is unable to complete a Fast Fact Sheet (FFS) because the patient is ineligible, the randomization is not to be completed.

8.0 SURGICAL TREATMENT & PET/CT SCAN EVALUATION

8.1 Pathologic Evaluation Prior to Pelvic and Abdominal Lymph Node Sampling

- Any evidence of disease outside of the pelvis or abdominal nodal region amenable to biopsy or sampling (i.e. intrahepatic or pulmonary metastasis; bony involvement; or suprarenal, thoracic or supraclavicular lymphadenopathy; or lymphadenopathy above the renal hilum) on PET/CT needs to be pathologically evaluated prior to performance of the pelvic and abdominal lymph node sampling. Unless biopsy is positive on a non-image guided biopsy, an imaging-guided biopsy or lymphadenectomy would be required, as applicable. If surgical approach is required, this may be performed during the same surgery as the lymph node sampling, as long as frozen-section diagnosis is used in order to abort the lymph node sampling if the disease outside of the pelvis or abdominal nodal regions is found to be positive. Otherwise, percutaneous biopsy will be performed.(06/09/08) **At the discretion of the participant and her surgeon**, women with endometrial cancer with lymphadenopathy above the renal hilum or extensive abdominal/pelvic lymphadenopathy who are still planning to undergo a complete pelvic and para-aortic

lymphadenectomy may proceed to surgery without performing a percutaneous biopsy of the supra-renal adenopathy.(11/16/09)

- If metastatic disease is confirmed, the participant will not undergo lymph node dissection but rather will go on to palliative chemotherapy protocols at the investigator's discretion.
- All participants will remain in the study regardless of metastases, and all appropriate forms and follow-up information will need to be completed.
- Those unable to be confirmed (either biopsy not technically feasible or pathologically negative) may proceed with lymph node sampling at the investigator's discretion.

8.2 Pelvic and Abdominal Lymph Node Sampling

Lymph node dissection will be performed in accordance with strict anatomic boundaries.

NOTE: This differs from the standard GOG definitions. (06/09/08)

- External Iliac Lymph Nodes: From bifurcation of common iliac artery cranially to the point at which the deep circumflex iliac vein crosses over the external iliac artery caudally. Lateral boundary is the psoas muscle and genito-femoral nerve. Medial boundary is the ureter and superior vesical artery. Deep boundary is the inferior border of the external iliac vein.
- Obturator Lymph Nodes: Similar to the external iliac lymph node boundaries only extending between the inferior borders of the external iliac vein superiorly and the obturator nerve inferiorly.
- Common Iliac Lymph Nodes: from bifurcation of the common iliac artery caudally to the bifurcation of the aorta cranially. Lateral boundary is the psoas muscle and medial boundary the common iliac artery. At the surgeon's discretion, these may be arbitrarily divided in the middle into "high" and "low" common iliac lymph nodes and be sent as separate specimens.
- Left Para-aortic Lymph Nodes: The caudal boundary is the bifurcation of the aorta. Lateral boundary is the psoas muscle and medial boundary the aorta. The cranial boundary is the point at which the inferior mesenteric artery (IMA) exits the aorta. Positive lymph nodes above the IMA may be resected at the surgeon's discretion. Abdominal lymph nodes from above the IMA are to be sent as a separate specimen.
- Right Para-Caval Lymph Nodes: The caudal boundary is the bifurcation of the aorta. Lateral boundary is the psoas muscle and medial boundary the aorta. The deep boundary is the Vena Cava. The cranial boundary is the point at which the inferior mesenteric artery (IMA) exits the aorta. Positive lymph nodes above the IMA may be resected at the surgeon's discretion. Abdominal lymph nodes from above the IMA are to be sent as a separate specimen.
- Any lymph node sitting at the boundary between two regions will be considered to belong to the more cranial region by convention (i.e. a palpable lymph node at the bifurcation of the common iliac artery will be considered a common iliac lymph node and one at the bifurcation of the aorta will be considered para-aortic or para-caval).

Lymph nodes overlying the aorta will be divided into left para-aortic and right para-caval based upon their relationship to the midline of the aorta.

8.3 Treatment Modifications (06/09/08)

8.3.1 Surgery will not be performed if there is advanced lymphadenopathy not amenable to surgery.

8.3.1.1 Joint review of PET/CT images by radiologists and gynecology oncologist before planned lymphadenectomy to assure involved lymph nodes on imaging are considered in surgical planning and removed by surgeon.(11/16/09)

8.3.2 Lymph Node Sampling

- Surgery may be terminated if it is judged to be in the best interest of the participant. The reason for termination will be explained in the operative report.
- Successful completion of a lymph node sampling in all eight lymph node “regions” (left obturator, right obturator, left external iliac, right external iliac, left common iliac, right common iliac, right para-caval, and left para-aortic) is an endpoint of the study.
- If lymph nodes appear clinically negative in a particular region, then complete lymphadenectomy in that region is required.
- If lymph nodes appear overtly suspicious, the investigator may choose to perform anything from a complete lymphadenectomy to a biopsy.
- If anything less than a complete lymphadenectomy is performed, then frozen section confirmation of disease must be performed.
- If the frozen section is unable to confirm disease, then complete lymphadenectomy is required.
- Each lymph node “region” is to be considered independently of one another.
- Therefore, even if a biopsy is positive in one region, a complete lymph node dissection is required in all other regions not independently proven to be positive by intra-operative confirmation of metastatic disease.
- For participants with **cervical carcinoma**, it is inappropriate to convert an extra-peritoneal or laparoscopic lymph node dissection to a trans-peritoneal approach for the sake of removing lymph nodes.(11/16/09)
- Participants with **endometrial carcinoma** may undergo a trans-peritoneal, extra-peritoneal, or laparoscopic lymphadenectomy and may be converted from one to another if necessary in the opinion of the surgeon.(11/16/09)

8.3.3 Laparoscopic Lymphadenectomy

8.3.3.1 Technical Difficulty (11/16/09)

- If the lymph node sampling is performed by a laparoscopic approach and cannot be completed successfully due to technical difficulties (i.e., inadequate exposure):

- an extra-peritoneal lymphadenectomy must be attempted in participants with **cervical carcinoma**, or
- a trans-peritoneal or extra-peritoneal lymphadenectomy must be attempted in participants with **endometrial carcinoma**.

8.3.3.2 Unresectable Lymph Nodes (11/16/09)

- In participants with **cervical carcinoma**, if the laparoscopic lymph node sampling was unsuccessful due to unresectable lymph nodes, extra-peritoneal lymphadenectomy is not required but may be attempted at the surgeon's discretion. At the very least, intra-operative documentation of metastatic disease to the unresectable lymph node region must be documented.
- In participants with **endometrial carcinoma**, an unsuccessful laparoscopic lymphadenectomy due to unresectable lymph nodes may be converted to a trans-peritoneal or extra-peritoneal lymphadenectomy at the surgeon's discretion. At the very least, intra-operative documentation of metastatic disease to the unresectable lymph node region must be documented.

8.3.3.3 Retroperitoneal Fibrosis (11/16/09)

- In the event of an inability to develop the retroperitoneal spaces (i.e., retroperitoneal fibrosis or adhesions), the procedure should be terminated.
- If, in a participant with **cervical carcinoma**, in the investigator's opinion, an extra-peritoneal lymph node dissection would be similarly unsuccessful, an extra-peritoneal attempt at lymph node sampling is not necessary.
- If, in a participant with **endometrial carcinoma**, in the investigator's opinion, a trans-peritoneal or extra-peritoneal lymph node dissection would be similarly unsuccessful, an extra-peritoneal attempt at lymph node sampling is not necessary.
- Every reasonable attempt should be made to perform a biopsy of any available lymph nodes. Trans-peritoneal lymph node sampling will not be performed for participants with **cervical carcinoma**, but may be performed in participants with **endometrial carcinoma**.

8.3.4 Modified or Aborted Lymph Node Sampling

- In the event of a modified or aborted lymph node sampling (i.e., sampling from less than all eight regions), the surgeon must clearly document in the operative report precisely why the procedure could not be completed.
- Any operative procedure other than an eight-region staging as outlined above will be considered a "failed procedure," but not a protocol violation unless the operative note fails to provide sufficient detail explaining the deviation from the defined surgical objective.

NOTE: If the physical constraints of the participant prevent the lymphadenectomy from being performed per the protocol or if the extent of tumor spread discovered at laparotomy would render the lymphadenectomy not the standard of care for therapy, the investigator will not be in violation of the protocol. However, if the procedure was not done or done incorrectly when it could have been done, it will be considered a protocol violation. **(11/16/09)**

- “Failed procedures” and instances when participant physical constraints prevent lymphadenectomy will be documented on the Pelvic and Abdominal Lymphadenectomy form.**(11/16/09)**
- Again, each lymph node region is to be evaluated independently of one another.
- Therefore, even if a biopsy is positive in one region, a complete lymph node dissection is required in all other regions not independently proven to be positive by intra-operative confirmation of metastatic disease.

8.4 PET/CT Identification of Advanced Disease

8.4.1 If the PET/CT identifies advanced disease outside of the pelvis or abdominal nodal region (i.e., intrahepatic, pulmonary, or thoracic or supraclavicular lymph nodes) that is amenable to biopsy, tissue confirmation (pathologically by tissue acquisition) must be obtained from the most technically accessible site.

8.4.1.1 Positive imaging findings unrelated to the cervical or endometrial cancer (i.e. axillary lymph nodes) should not be considered as requiring biopsy as per the protocol.**(11/16/09)** It is, however, a clinical decision as to whether these need to be biopsied. If they are, that data should be provided to the study.

8.4.1.2 Should non-image guided biopsy return with negative findings, an imaging-guided biopsy or lymphadenectomy (as appropriate) will be required to rule out false-negative result for biopsy.**(06/27/11)**

8.4.2 Once metastatic disease is biopsy proven, the lymphadenectomy is to be abandoned and clearly documented on the Pelvic and Abdominal Lymphadenectomy form. **(06/09/08)**

8.4.2.1 Among participants with **endometrial carcinoma**, if intraperitoneal or supra-renal lymph node disease is detected on PET/CT, then the healthcare team may proceed with lymphadenectomy per protocol if agreed upon by both the participant and her surgeon. In this situation, pre-operative tissue confirmation will not need to be obtained.**(11/16/09)**

8.4.3 In the case of a lesion seen on PET but not seen on dedicated diagnostic images (i.e. lung or liver metastasis), biopsy will not be required unless this involves the

supraclavicular lymph nodes. In this case, supraclavicular lymph node dissection should be performed.

- 8.4.4** Participants with suspicious PET/CT findings unamenable to biopsy will undergo protocol-specified lymphadenectomy followed by repeat imaging with conventional radiographs, CT, MRI, or bone scintigraphy at the time of the 6-month follow-up.(11/16/09)
- 8.4.5** These lesions will be considered false-positive results if they remain unchanged over a follow-up interval of 6 months.
- 8.4.6** Otherwise, they will be considered true positive. If imaging reveals a lesion that is not amenable to biopsy (or if a biopsy is negative), these participants should go on to lymphadenectomy.

8.5 Evaluation Criteria

8.5.1 All procedures will be evaluated according to disease-specific schema for surgical evaluation and for pathologic evaluation.(11/16/09)

8.5.2 All PET/CT scans will be required to undergo centralized/decentralized review to be organized by ACRIN (see Section 12.1.5 for instructions on submitting images to ACRIN).(11/16/09) The central reading for PET/CT will be conducted at the ACRIN headquarters (Philadelphia, PA).(11/16/09)

8.5.2.1 Suspicious lymphadenopathy on PET/CT scans will be defined as: visible lymph nodes ≥ 10 mm in the short axis if the node is oval shaped and > 8 mm in diameter if rounded. In addition, necrotic lymph nodes on contrast-enhanced CT will be considered abnormal. (11/16/09)

(06/09/08)

8.5.2.2 FDG-PET/CT images will be evaluated qualitatively for focal areas of abnormally increased FDG uptake. The likelihood of the spread of disease in pelvic lymph nodes, para-aortic lymph nodes, and other sites is according to the following scale: definitely benign, most likely benign, probably benign, probably malignant, most likely malignant, definitely malignant. A positive finding is defined as the presence of abnormal FDG uptake (when accumulation of the tracer is moderately to markedly increased relative to the uptake in comparable normal structures or surrounding tissues, with the exclusion of physiologic bowel and urinary activity), even when the lymph node has normal size (see above Section 8.5.2.1 for criteria used to characterize lymph node based on size).(11/16/09) A negative finding is defined as no detectable FDG uptake, even when the lymph nodes are enlarged. Semiquantitative analysis of selected lesions (primary tumor and up to five additional lesions involving each lymph node group and/or distant organs) using the standardized uptake value (SUV) method also will be performed.

The SUV is the ratio of the decay-corrected concentration of FDG within the tumor ($\mu\text{Ci/g}$) to the average concentration of FDG in the body (i.e. the administered activity divided by the body weight). This will be performed by visually identifying the region or regions of the tumor on the PET images that qualitatively appear to have the most intense FDG uptake. A circular region of interest 1 cm in diameter centered on the maximum-value pixel will be drawn to calculate the mean SUV within the region. This value will be reported as peak SUV. Initially, attenuation-corrected and non-attenuation-corrected PET images will be evaluated for presence of primary cervical or endometrial cancer and nodal and distant metastasis, which will be recorded on the data form.(11/16/09) The SUV data obtained from this trial will be used to directly compare SUVs of the primary and nodal disease in comparison to biopsy proven metastatic deposits.

(11/16/09)

- 8.5.3** For participants with **cervical carcinoma**, all participants are expected to initiate chemoradiation therapy within 4 weeks of their enrollment in the study as outlined in Section 9.4.(11/16/09) Delays in initiation of radiation therapy as well as delays during treatment will be documented in order to assess the impact of the surgical procedure. Initiation date will be recorded on the Pelvic & Abdominal Lymphadenectomy Form. Any delay in initiation of therapy beyond 4 weeks must be clearly documented and an explanation provided. In addition, any subsequent delays in treatment must also be documented and an explanation provided. The date of completion of radiation therapy must also be documented.

NOTE: For participants with **endometrial carcinoma**, no such therapeutic requirements exist for this study.(11/16/09)

9.0 STUDY PROCEDURES: DISTINCT FOR CERVICAL OR ENDOMETRIAL CANCER (11/16/09)

CERVICAL CANCER (Sections 9.1 through 9.9) (11/16/09)

9.1 Patient Entry & Registration Visit

- Obtain prior medical history, including allergy history;
- Perform a physical examination;
- Perform a urine or serum pregnancy test, as applicable (see Eligibility Criteria Section 5.1.5);(06/27/11)
- Obtain labs, including confirming GFR, if not completed within 28 days prior to the FDG-PET/CT for the trial, per Eligibility Criteria;(06/27/11)
- Perform a chest X-ray (if a chest CT has been completed for metastasis assessment, it may be used in place of the chest X-ray);(11/16/09)
- Conduct an electrocardiogram (ECG);(11/12/08)

- Determine if patient meets all cervical cancer–specific eligibility requirements according to Section 5.0 (slides and reports from the initial biopsy will need to be submitted within 6 weeks after enrollment to GOG for retrospective histopathologic confirmation); **(11/16/09)(06/27/11)**
- Obtain cervical cancer–specific, signed consent on an IRB-approved informed consent form prior to performing any study related procedures, including those not considered standard of care for the treatment/evaluation of cervical cancer;**(11/16/09)**
- Gather the Fast Fact Sheet (FFS);
- Register the participant using the web-based registration application or by phone (800-523-2917). Instructions for web-based registration and randomization can be found by going to the GOG Web Menu page or in Section 7.0, Online Registration System.

9.2 Visit 1: FDG PET/CT (11/16/09)(06/27/11)

Participants will undergo diagnostic FDG PET/CT scan as described in Section 12.0.**(11/16/09)**

- Conduct a urine or serum pregnancy test;**(11/12/08)**
- Perform the FDG PET/CT with SUV calculation. **(11/16/09)**

9.2.1 Imaging-Guided Biopsy (06/27/11)

If PET/CT shows a lesion outside the abdominal/pelvic lymph nodes (for cervical cancer). The decision to perform lymphadenectomy is at the discretion of the surgeon for abdominal organ involvement outside the lymph node. However, if the decision is not to perform lymphadenectomy, the surgeon needs to biopsy what is positive on PET/CT.

If a non-imaging guided biopsy is performed and the results are positive, no imaging-guided biopsy is needed. However, imaging-guided biopsy may be used for initial diagnosis of suspicious findings and is necessary should an initial non-imaging guided biopsy return a negative result. CT scan or ultrasound are acceptable imaging approaches.

For positive results on imaging-guided biopsy, the participant becomes ineligible for the trial. For negative results, the participant continues on trial but is required to have a follow-up CT scan after 6 months.

9.3 Visit 2: Lymph Node Sampling Within 2 Weeks after Visit 1 (11/16/09)

All participants will subsequently undergo pelvic and abdominal lymph node sampling by either an extra-peritoneal or a laparoscopic approach (Section 8.0). This will occur no more than 2 weeks from the date of the PET/CT scan.

- Joint review of PET/CT images by radiologist and gynecology oncologist before planned lymphadenectomy to assure involved lymph nodes on imaging are removed by surgeon. All participants in this review will document that this image review occurred, date of review, and any changes to the planned surgery resulting from the image review;**(11/16/09)**

- Assess for any study-related adverse event since Visit 1;(11/16/09)
- Perform the lymph node sampling surgical procedure.

9.4 Visit 3: Chemotherapy Begins Within 4 Weeks from Visit 1 (11/16/09)

- All participants are expected to initiate chemoradiation therapy within 4 weeks from PET/CT;(11/16/09)
- Initiate the administration of the chemotherapy regimen;(11/16/09)
- Assess for any study-related adverse events since Visit 2.(11/16/09)

NOTE: Initiation date of chemoradiation therapy will be recorded on the Post-Surgery Follow-Up Form. Any delay in initiation of therapy beyond 4 weeks from PET/CT must be clearly documented and an explanation provided. In addition, any subsequent delays in treatment must also be documented and an explanation must be provided. The date of completion of chemoradiation therapy must be documented. Delays in initiation of therapy will not be counted as protocol violations.

9.5 Visit 4: Within 6 Weeks after Visit 3 (11/16/09)

- Perform a physical examination to monitor the effects of all surgical procedures performed up to this time-point;(11/16/09)
- Assess for any study-related adverse events since Visit 3.(11/16/09)

9.6 Visit 5: 6 Months after Visit 1 (11/16/09)

- Review the results of the physical examination;
- Perform a CT scan or PET/CT if a finding is visible on PET/CT and was not able to be biopsied or imaging-guided biopsy returned negative results;(11/16/09) (06/27/11)
- Assess for any study-related adverse events since Visit 4.(11/16/09)

9.7 Visits 6–13: Every 3 Months for 2 Years after Visit 1—Per Standard of Care (11/16/09)

- Obtain routine blood tests at the discretion of the treating physician (no data collection is required);(11/12/08)
- Perform physical examinations;
- Perform x-rays, per discretion of the investigator;(11/16/09)
- Assess for any study related adverse events.

9.8 Visits 14–19: Every 6 Months for 3 Additional Years after Visit 13—Per Standard of Care (11/16/09)

- Obtain routine blood tests at the discretion of the treating physician (no data collection is required);(11/12/08)
- Perform physical examinations;
- Perform x-rays, per discretion of the investigator;(11/16/09)

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- Assess for any study related adverse events.

NOTE: Participant will receive standard of care as recommended by the participant's treating physician for 5 years following completion of their surgical evaluation. If enrolled on another GOG study, this can be done in conjunction. Follow-up information (Q-Forms) must be submitted per GOG requirements, if the participant is not enrolled in another GOG study.

9.9 Study Procedures Timetable: Cervical Cancer
(06/09/08)(11/12/08)(06/01/09)(11/16/09)(06/27/11)

Procedures	Registration Visit	Visit 1: Day of FDG PET/CT	Visit 2: Within 2 weeks after Visit 1	Visit 3: Within 4 weeks after Visit 1	Visit 4: Within 6 weeks Post-op	Visit 5: 6 months after Visit 1	Visits 6- 13: Every 3 months for 2 years after Visit 1	Visits 14-19: Every 6 months for 3 additional years after Visit 13
Informed Consent	X							
Eligibility/Registration (Submission of biopsy slide and report to GOG for histopathologic confirmation)	X							
Fast Fact Sheet	X							
Medical History (including allergy history)	X							
Physical Examination	X				X	X	X	X
Pregnancy Test (urine or serum): 7 days prior to PET/CT	X	X						
GFR (within 28 days prior to FDG-PET/CT)	X							
Chest X-ray (or alternate chest imaging)	X							
ECG	X							
FDG PET/CT Examination		X						
Review All Images (Radiologists and Surgeon)			X (Prior to Surgery)					
Imaging-Guided Biopsy (if Suspicious Lesion Found on PET/CT and Initial Biopsy Is Negative)			X (Prior to Surgery)					
Pelvic and Abdominal Lymph Node Sampling			X					
Chemoradiation Therapy				X				
CT (of the area with initial positive PET/CT outside abdomen and no biopsy proof of disease after imaging-guided biopsy)						X		
Chest X-ray (per investigator's discretion)							X	X
Adverse Event Assessment			X	X	X	X	X	X

(11/16/09)
(06/01/09)

ENDOMETRIAL CANCER (Sections 9.10 through 9.17) (11/16/09)

9.10 Patient Entry & Registration Visit (11/16/09)

- Obtain prior medical history, including allergy history;
- Perform a physical examination;
- Perform a urine or serum pregnancy test, as applicable (see Eligibility Criteria Section 5.3.5);(06/27/11)
- Obtain labs, including confirming GFR, if not completed within 28 days prior to the FDG-PET/CT for the trial, per Eligibility Criteria;(06/27/11)
- Perform a chest X-ray (if a chest CT has been completed for metastasis assessment, it may be used in place of the chest X-ray);
- Conduct an ECG;
- Determine if patient meets all endometrial cancer–specific eligibility requirements according to Section 5.0 (slides and reports from the initial biopsy will need to be submitted within 6 weeks after enrollment to GOG for retrospective histopathologic confirmation);(06/27/11)
- Obtain endometrial cancer–specific, signed consent on an IRB-approved informed consent form prior to performing any study related procedures, including those not considered standard of care for the treatment/evaluation of endometrial cancer;
- Gather the Fast Fact Sheet (FFS);
- Register the participant using the web-based registration application or by phone (800-523-2917). Instructions for web-based registration and randomization can be found by going to the GOG Web Menu page or in Section 7.0, Online Registration System.

9.11 Visit 1: FDG PET/CT (11/16/09)(06/27/11)
(11/16/09)

Participants will undergo diagnostic FDG PET/CT scan as described in Section 12.0.

- Conduct a urine or serum pregnancy test;
- Perform the FDG PET/CT with SUV calculation.(11/16/09)

9.11.1 Imaging-Guided Biopsy

If PET/CT shows a lesion outside the abdominal organs (for endometrial cancer). The decision to perform lymphadenectomy is at the discretion of the surgeon for abdominal organ involvement outside the lymph node. However, if the decision is not to perform lymphadenectomy, the surgeon needs to biopsy what is positive on PET/CT.

If a non-imaging guided biopsy is performed and the results are positive, no imaging-guided biopsy is needed. However, imaging-guided biopsy may be used for initial diagnosis of suspicious findings and is necessary should an initial non-imaging guided biopsy return a negative result. CT scan or ultrasound are acceptable imaging approaches.

For positive results on imaging-guided biopsy, the participant becomes ineligible for the trial. For negative results, the participant continues on trial but is required to have a follow-up CT scan after 6 months.

9.12 Visit 2: Lymph Node Sampling Within 2 Weeks after Visit 1(11/16/09)

All participants will subsequently undergo pelvic and abdominal lymph node sampling (Section 8.0). This will occur no more than 2 weeks from the date of the PET/CT scan.

- Joint review of PET/CT images by radiologist and gynecology oncologist before planned lymphadenectomy to assure involved lymph nodes on imaging are removed by surgeon. All participants in this review will document that this image review occurred, date of review, and any changes to the planned surgery resulting from the image review;(11/16/09)
- Assess for any study-related adverse event since Visit 1;(11/16/09)
- Perform the lymph node sampling surgical procedure.

9.13 Visit 3: Within 6 Weeks after Visit 2(11/16/09)

- Perform a physical examination to monitor the effects of all surgical procedures performed up to this time-point;(11/16/09)
- Assess for any study-related adverse events since Visit 2.(11/16/09)

9.14 Visit 4: 6 Months after Visit 1(11/16/09)

- Review the results of the physical examination;
- Perform a CT scan or PET/CT if a finding is visible on PET/CT and was not able to be biopsied or imaging-guided biopsy returned negative results;(06/27/11)
- Assess for any study-related adverse events since Visit 3.(11/16/09)

9.15 Visits 5–12: Every 3 Months for 2 Years after Visit 1—Per Standard of Care (11/16/09)

- Obtain routine blood tests at the discretion of the treating physician (no data collection is required);
- Perform physical examinations;
- Perform x-rays, per discretion of the investigator;
- Assess for any study related adverse events.

(06/27/11)

9.16 Study Procedures Timetable: Endometrial Cancer (11/16/09)(06/27/11)

Procedures	Registration Visit	Visit 1: Day of FDG PET/CT	Visit 2: Within 2 weeks after Visit 1	Visit 3: Within 6 weeks Post-op	Visit 4: 6 months after Visit 1	Visit 5- 12: Every 3 months for 2 Years after Visit 1
Informed Consent	X					
Eligibility/Registration (Submission of biopsy slide and report to GOG for histopathologic confirmation)	X					
Fast Fact Sheet	X					
Medical History (including allergy history)	X					
Physical Examination	X			X	X	X
Pregnancy Test (urine or serum): 7 days prior to PET/CT	X	X				
GFR (within 28 days prior to FDG-PET/CT)	X					
Chest X-ray (or alternative chest imaging)	X					
ECG	X					
FDG PET/CT Examination		X				
Review All Images (Radiologists and Surgeon)			X (Prior to Surgery)			
Imaging-Guided Biopsy (if Suspicious Lesion Found on PET/CT and Initial Biopsy Is Negative)			X (Prior to Surgery)			
Pelvic and Abdominal Lymph Node Sampling			X			
CT (of the area with initial positive PET/CT outside abdomen and no biopsy proof of disease after imaging-guided biopsy)					X	
Chest X-ray (per investigator's discretion)						X
Adverse Event Assessment			X	X	X	X

(11/16/09)

10.0 Data Collection and Management

10.1 General

10.1.1 The ACRIN web address is www.acrin.org.

10.1.2 Data collection and management will be performed jointly by the GOG Statistical and Data Center (SDC) and the Biostatistics and Data Management Center (BDMC) of ACRIN.

To minimize duplication of efforts and information, ACRIN BDMC will manage data elements related to imaging endpoints and the GOG SDC will manage data elements related to surgical endpoints and study monitoring.

To facilitate study obligations, there will be periodic transfers (between ACRIN BDMC and GOG SDC) of uniquely collected key data elements. Furthermore, the respective group will provide promptly elements deemed essential for interim and final analyses if these elements are not otherwise included in the periodic transfers. (06/09/08)

10.1.3 Participant enrollment and data collection occurs through a series of programmed screens accessed through the ACRIN web site to register participants, collect participant data, and maintain calendars of data submissions for each participant. By using the World Wide Web, ACRIN has made participant registration, data entry, and updated calendar information available to clinical sites 24 hours a day, seven days a week. Each successful case registration is confirmed through receipt of an e-mail containing a registration/randomization confirmation and a case specific calendar identifying timelines for data and image submission. If the confirmation e-mail is not received, the enrolling person should contact the Data Management Center before attempting a re-registration.

10.2 Clinical Data Submission

10.2.1 Upon successful participant registration, a confirmation e-mail containing the registration and case specific calendar is sent to the research staff enrolling the participant via the web. In addition, the investigator-designated research staff may download the participant specific data submission calendar, which lists all forms and designated reports required by protocol, along with the form due dates at the DMC. These calendars will be updated as the study proceeds to reflect data that have been received, reply to deadlines for queries about unclear data, deadlines for follow-up reports of adverse events, or changes in the protocol that change the data being collected or the timeframe. Updated calendars for each participant can be obtained 24 hours a day from the ACRIN website. The research associate may use the calendar as a case management tool for data submission and follow-up scheduling.

10.2.2 The investigative site is required to submit data according to protocol as detailed on each participant's calendar, as long as the case status is designated as

open/alive or until the study is terminated. The case is closed when all data have been received, reviewed, and no outstanding data query exists for the case.

10.2.3 To submit data via the ACRIN website, the appropriate investigator-designated research staff will log onto the ACRIN web site and supply the pre-assigned user name and password. Case report forms will be available on the web site through a series of links. Each web form is separated into modules; each module must be completed sequentially in order for the internal programming to be accurate. The user selects the link to the appropriate form and enters data directly into the web-based form. As information is entered into the web form application, various logic checks will be performed. These logic checks look for missing data, any out of range data, and data in the wrong format (e.g. character data in a field requiring numeric responses). Such errors will be detected as soon as the user attempts to submit the form or move to the next data element. They must be corrected before the form is transmitted to the DMC. The user will not be able to finalize form transmission to the DMC until all data entered passes these logic checks. Forms that are not completed in one sitting can still be submitted and completed at a later date. The form will remain available on the web until the “Complete Form Submission” button is depressed.

10.2.4 Once data entry of a form is complete, and the summary form reviewed for completeness and accuracy, the investigator or the research staff presses the “Complete Form Submission” button on the form summary screen and the data are transferred into the clinical database. No further, direct revision of the submitted data is allowed after this point. E-mail confirmation of web data entry is automatically generated and sent to the site investigator or research associate listing all of the data completed and just submitted. Should a problem occur during transmission and the e-mail confirmation of data submission is not received, the investigator or research associate should contact the Data Management Center for resolution of the submission.(11/12/08)

10.2.5 If a temporary problem prevents access to the Internet, all sites are notified of the event and estimated down time through an ACRIN broadcast message. The investigative site should wait until access is restored to submit data. The site RA or investigator should notify the DMC of the problem and the DMC will give an estimated time when access will be restored. If access will be unavailable for an extended period, sites must seek another Internet Service Provider (ISP). On a short-term basis, the ACR can serve as an ISP.

10.3 Data Security

The registration and data collection system has a built-in security feature that encrypts all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of identification codes and passwords.

10.4 Electronic Data Management

10.4.1 Data received from the web-based forms are electronically stamped with the date and time of receipt by the ACRIN server. The data are then entered into the database. A protocol-specific validation program is used to perform more extensive data checks for accuracy and completeness. Complimentary validation programs are initiated at the Brown Biostatistics Center and the Data Management Center. The logic checks performed on the data at this point are more comprehensive than those built into the web-based data entry screens. They include checking that answers are logical, based on data entered earlier in the current form and more thorough checks. Data elements that fail validation are followed up by the DMC research associate. The validation program generated by BC produces a log of errors, which is sent to the DMC Research Associate (RA) for resolution. The program is frequently updated to incorporate exceptions to rules so that subsequent validity checks minimize the time the DMC RA at the DMC needs to spend resolving problems. Additional data review will take place once the data are transferred to the BC. The BC will run thorough cross-form validations, frequency distributions to look for unexpected patterns in data, and other summaries needed for study monitoring. Any errors found at the BC will be reported to the DMC RA for resolution. All BDMC communication with the participating sites is normally done through the Data Management Center. (11/12/08)

10.4.2 If checks at DMC or BC detect missing or problematic data, the DMC RA sends a Request for Information (Z1 query letter) to the site RA or investigator specifying the problem and requesting clarification. The DMC RA updates the participant's data submission calendar with the due date for the site RA or investigator's response.

10.5 Missing and Delinquent Data Submission

In addition to providing the investigator a data collection calendar for each case, the DMC periodically prompts institutions for timely submission of data through the use of a Forms Due Report. Distributed at intervals via the electronic mail system directly to both the RA and the investigator at each site, this report lists data items (e.g. forms, reports, and images) that are delinquent and those that will be due before the next report date. In addition to prompting clinicians to submit overdue data, the Forms Due Report helps to reconcile the DMC's case file with that of the RA and/or investigator. Future Due Forms Report may be sent on an as needed basis in addition to past due reports. The site investigator or research associate may use the Forms Due and Future Due Reports as a case management tool.

10.6 Data Quality Assurance

10.6.1 The Biostatistical Center (BC) at Brown University will maintain a study database at its site for monitoring data quality and for performing analyses. These data are drawn directly from the permanent database of the Data Management Center (DMC). The transfer of data between the DMC and the BC

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has been validated through a series of checks consisting of roundtrip data verification in which data are sent back and forth to verify that the sent data are equivalent to the received data. These checks are repeated at random intervals during the course of a given study. Any discrepancies and other data quality issues will be referred to DMC for resolution, since only the DMC can correct the data file. No changes to the data will be made at the BC.

10.6.2 The goal of the monitoring of data is to assess compliance with the protocol and to look for unforeseen trends that may be indicative of procedural differences among clinical sites. If patterns are discovered in the data that appear to arise from causes specific to an institution, the Biostatistical and Data Management Center (BDMC) will apprise the ACRIN Headquarters and the site of the problem, and work with the site, along with ACRIN Protocol Development and Regulatory Compliance Department, until the problem has been resolved. If the BDMC, along with the Audit Group, cannot find a resolution to the problem, it will be brought to the Steering Committee for further discussion and resolution.

11.0 DATA COLLECTION FORMS (06/09/08)(11/16/09)(06/27/11)

The following forms must be completed for all participants 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 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. **Pathology material (Form F, pathology reports and slides) should be submitted together via mail. The GOG Uploader Application in SEDES is an alternate method for submitting the operative report, discharge summary, Form F, pathology reports and slides to the GOG SDC.**

Form[±]	Due Within		Copies*	Comments
Form R (Registration Form)	2	Registration	1	Mandatory submission via SEDES
Primary cervical cancer: Form OSC (Primary Cervical Cancer - On Study Form)	2	Registration	1	Mandatory submission via SEDES
Primary cervical cancer: Form F (Pathology Form) - Pathology Report - Stained Slides	6	Registration	4 Slides (2 minimum)	Path report: four copies of the institution’s dictated surgical pathology report, specifically the cervical biopsy documenting carcinoma. Slides: a representative H + E stained slide(s) to document the primary carcinoma and a representative H + E stained slide to confirm stage histologically. Must be submitted together.

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Primary endometrial cancer: Form OSE (Primary Endometrial Cancer - On Study Form)	2	Registration	1	Mandatory submission via SEDES
Primary endometrial cancer: Form F (Pathology Form) - Pathology Report - Stained Slides	6	Registration	4 Slides (2 minimum)	Path report: four copies of the institution's dictated surgical pathology report, specifically the cervical biopsy documenting carcinoma. Slides: a representative H + E stained slide(s) to document the primary carcinoma and a representative H + E stained slide to confirm stage histologically. Must be submitted together.
Form DR (Pre-treatment Summary Form)	4	Registration	1	Mandatory submission via SEDES
Form C (Surgical Reporting Form)	6	Surgery	2	Mandatory submission via SEDES
Operative report	6	Surgery	2	Submit via postal mail or upload via SEDES
Primary disease: Form F (Pathology Form)	6	Surgery	1	Submit together via postal mail to GOG SDC or upload via SEDES
Pathology Report	6	Surgery	2	
Stained Slides	6	Surgery	**	
Form PAL (Pelvic and Abdominal Lymphadenectomy)	6	Surgery	2	Mandatory submission via SEDES
Form PRLN (Pathology Review of Lymph Nodes)	12	Surgery	1	Mandatory submission via SEDES
Form PSF (Post Surgery Follow-up)	4	6 week post operative follow-up visit	1	Mandatory submission via SEDES
Form D2R (Cycle Dose Drug Form)	4	PET/CT	1	Mandatory submission via SEDES
Form T (Common Toxicity Reporting Form)	4	PET/CT	1	Mandatory submission via SEDES (see Section 21.1.2)
Form T (Common Toxicity Reporting Form)	4	6 week post operative follow-up visit	1	Mandatory submission via SEDES (see Section 21.1.2)
Form Q0 (Treatment Completion Form)	2	Completion of study Rx and change in Rx	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

± Use the SDC Electronic Data Entry System (SEDES), available on the GOG website, to view and print a copy of each form along with instructions, and to submit forms electronically. Check SEDES periodically as forms that are not currently available for electronic data entry will be made available for electronic data entry over time.

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- * The number of required copies including the original form which must be sent to the Statistical and Data Center.
- ** At least one representative stained slide (or slides) documenting the primary.

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 (<http://www.gog.org> under MANUALS) and can be mailed to the institution registering a patient to this study if requested. (06/27/11)

12.0 IMAGE PROCEDURES

(11/16/09)

12.1 FDG PET/CT Imaging (06/09/08)(11/12/08)(06/27/11)

Imaging examinations should be submitted to the ACRIN Imaging Core Laboratory after each time point/visit. A completed, signed Image Transmittal Worksheet (ITW) MUST accompany all imaging exams submitted to ACRIN for each time point. For exams submitted via the Internet, complete the ITW and e-mail it to imagearchive@acr-arrs.org or fax it to 215-923-1737. For exams submitted via media, complete the ITW and include it with the media shipment. Please affix a label to the jacket of the media that includes: study name, site name, case no., date of exam(s), time point, and type of imaging. **The ITW form MUST be completed in its entirety for the case to be credited.**

Participants must undergo whole-body PET and CT imaging with a PET/CT unit per institutional standard of care. ***Reminder for PET imaging: All PET exams should contain three trans-axial whole body series, attenuated and non-attenuated corrected PET scans, and the CT images.** The PET/CT unit should have a multi-slice CT (>1 slice) and BGO (Bismuth Germinate Oxide), LSO (Lutetium Oxyorthosilicate) or GSO only. Sodium Iodide (NaI) based scanners are not acceptable. The ability to calculate standardized uptake value (SUV) is also mandatory. The PET/CT scanner needs to be qualified by ACRIN before participating in this protocol.

Detailed information can be found on the ACRIN web site at: <http://www.acrin.org/PROTOCOLSUMMARYTABLE/PROTOCOL6671/6671ImagingMaterials/tabid/417/Default.aspx> under ACRIN 6671/GOG 0233 Imaging Materials.

PET Technical Assessment Form will be used to ensure protocol compliance. The PET Technical Assessment Form can be found on the ACRIN web site at: <http://www.acrin.org/PROTOCOLSUMMARYTABLE/PROTOCOL6671/6671ImagingMaterials/tabid/417/Default.aspx>.

There is no set criteria that requires the original institution to repeat a PET/CT study. However, considering that PET/CT is standard of care for initial staging of cervical and endometrial cancers, the study may be repeated if it is judged by the original institution that the study is suboptimal and does not provide clinical information to stage the patient prior to therapy.(11/16/09) The most common reasons that result in a suboptimal study can be found in Form C1.

Participant/FDG Preparation: Please refer to Section 13.0 for detailed drug (FDG) information.

The order of FDG-PET/CT study will be as follows:(11/12/08)

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1. Measure blood glucose level by glucometer. If it is below 150 mg/dL, continue. If blood glucose level is above 150 mg/dL, consult nuclear medicine physician.
2. If applicable, place Foley catheter.
3. Place an intravenous catheter. Give oral contrast to the participant.
4. Inject FDG, and flush catheter with 20-40 mL of normal saline solution. All participants will be well hydrated during the study (typically given an infusion of 500 mL 0.45% or 0.9% saline solution intravenously) or if intravenous hydration is not possible (e.g., if it is difficult to establish intravenous access), must drink a minimum of 4 cups of water.
5. See below (Section 12.1.1) for detailed information about two options for CT acquisition.**(11/16/09)** Approximately 60 minutes (+/- 10 minutes) after FDG injection, a diagnostic CT scan with contrast agents (oral and intravenous) or a low-dose CT (with oral contrast) will be performed. Patients must void prior to imaging. The diagnostic or low-dose CT of the chest, abdomen, and pelvis should be completed 60 minutes (+/- 10 minutes) after FDG injection, if it is performed before PET emission scan. The diagnostic or low-dose CT of the chest, abdomen, and pelvis should be initiated immediately after PET emission scan, if it is performed after PET emission scan. In either case, **the PET emission scan has to be performed approximately 60 minutes (+/- 10 minutes) after FDG injection.**
6. PET emission scan will be performed immediately after a low-dose CT or after the diagnostic CT depending on the CT option. At some sites, the diagnostic CT will be taken immediately after PET imaging without moving the patient (see options described in Section 12.1.1 below).**(11/16/09)**

Per one of the CT protocols described in Section 12.1.1 below, some centers may perform a second CT scan only for attenuation correction of the PET images.**(11/16/09)** Thus, a second low-energy CT scan can be performed just prior to emission PET scan (after completion of diagnostic CT) for attenuation correction of the PET images. In the alternative scenario described below, the low-dose CT scan must be performed prior to the PET scan if the diagnostic CT is to follow the PET imaging. The CT parameters for attenuation correction will be utilized according to imaging protocol at each center. We recommend effective mAs of 111, kVp of 130, 5-mm slice thickness and 4-mm interval.**(11/16/09)**

12.1.1 Diagnostic CT Imaging (06/09/08)(11/12/08)(11/16/09)

General: All PET/CT (including the diagnostic CT part of PET/CT) scans **must** be performed on the same scanner immediately before or after the PET emission scan, depending on the CT option (see below). In either case, **the PET emission scan has to be performed approximately 60 minutes (+/- 10 minutes) after FDG injection.** It is recommended (but not obligatory) to use a breathing technique already in place to diminish respiratory artifacts. Typically, participants will be instructed to hold their breath while scanning the diaphragm.

First option: Diagnostic CT before PET (with optional low-dose CT in between).

1. Diagnostic CT imaging (with oral and intravenous contrast) per institutional standard of care will be done approximately 60 minutes (+/- 10 minutes) after the FDG injection (see Section 12.1.4) beginning in a craniocaudal direction with the participant's upper neck. **(11/16/09)**
2. An optional low-dose CT can be conducted immediately after the diagnostic CT without moving the participant. The low-dose CT will take a minute or so.
3. The PET scan should follow immediately after the CT without moving the participant.

Second option: The low-dose CT (with oral contrast) will be performed before PET emission scan and the diagnostic CT will be performed immediately after completion of PET emission scan.

1. The low-dose CT, starting at approximately 60 minutes (+/- 10 minutes) after FDG injection immediately before the PET emission scan in a craniocaudal direction starting with the participant's upper neck. The low-dose CT will take a minute or so.
2. The PET emission scan should then be initiated at 60 minutes (+/- 10 minutes) immediately after the low-dose CT scan.
3. Diagnostic (intravenous contrast) CT should be performed immediately after the PET scan without moving the participant (it will be about 75 to 90 minutes after the FDG injection).

Intravenous contrast: Intravenous contrast is required in participants with adequate intravenous access and no contradictions to it. A nonionic contrast agent (such as Optiray 350) will be administered intravenously according to the participant's weight:

- For participants <180 pounds, 125 mL of Optiray[®] 350 (Mallinckrodt Inc.) or equivalent will be given at the rate of 3 mL/sec with a 55-sec delay in imaging.
- For participants ≥180 to <250 pounds, 150 mL Optiray 350 will be given at the rate of 3 mL/sec with a 70-sec delay in imaging.
- For participants 250 to 300 pounds, 175 mL Optiray 350 will be given at the rate of 3 mL/sec with an 85-sec delay in imaging. **(09/09/08)**

Oral contrast: A water-soluble, iodinated oral contrast such as MD-Gastroview[®] (Mallinckrodt Inc.) or equivalent is preferred over barium. Typically, a total dose of 600 mL of MD-Gastroview will be ingested prior to FDG injection.

MD-Gastroview (Diatrizoate Meglumine and Diatrizoate Sodium Solution) is a palatable lemon-vanilla flavored water-soluble iodinated radiopaque contrast medium for oral or rectal administration. Each mL contains 660 mg diatrizoate meglumine, 100 mg diatrizoate sodium, and approximately 4.8 mg sodium and 367 mg organically bound iodine. MD-Gastroview will be prepared according to the package insert – 25 ml of MD-Gastroview is diluted in 1L of tap water. A 600 mL dose is equal to 22.9 g of iodine.

12.1.2 PET Imaging (11/16/09)

All participants will begin fasting 4 hours prior to the FDG-PET/CT imaging. If the participant is receiving total parenteral nutrition and/or intravenous fluids containing glucose, it also should be discontinued for at least 4 hours prior to the FDG-PET imaging. To exclude fasting hyperglycemia in all participants regardless of history of diabetes or nutritional status (such as total parenteral nutrition), the blood glucose level should be determined prior to the FDG administration. No diabetic medications should be administered within 4 hours prior to checking the glucose level. Participants with poorly controlled diabetes can have a small dose of short-acting insulin (with dose determined by the referring physician) with a light meal and then fast for 4 hours prior to the PET study. PET imaging should not be performed if the blood glucose level is >200 mg/dL.

An intravenous catheter (typically, a 20- or 22-gauge Angiocath) will be placed, typically in the antecubital fossa, for participant hydration, contrast, and FDG administration. 10-20 mCi of FDG (0.14-0.21 mCi/kg) will be administered intravenously as a bolus. A dose at a higher end of the range is recommended, with appropriate reduction in the per kilogram dose for heavier patients (in accordance with the manufacturer's recommendation). All participants will be well hydrated during the study (typically given an infusion of 500 mL 0.45% or 0.9% saline solution intravenously) or a minimum of 4 cups of water, if intravenous hydration is not possible (e.g., if it is difficult to establish intravenous access). To ensure adequate clearance of bladder activity (which might obscure structures adjacent to the bladder), all participants should void immediately prior to imaging.

12.1.3 Optional Diuretic Treatment: (11/16/09)

Diuretics without Foley catheter: 20 mg of furosemide will be given before or at the time of FDG administration.

Diuretic with Foley catheter: 20 mg of furosemide will be given 20 minutes after FDG administration. Before the study, a Foley catheter (typically 16-french) will be placed using aseptic technique.

12.1.4 PET Technique (11/12/08)(11/16/09)

Imaging will begin approximately 60 minutes (+/- 10 minutes) after FDG injection (see above in Section 12.1.1 for the order options of diagnostic and low-dose CT and PET imaging).(11/16/09) The participant will be positioned supine, with arms comfortably positioned above the head, whenever possible. To minimize lower back discomfort, one or two pillows may be placed under the participant's knees. The region imaged should extend from the participant's upper/mid-neck to the upper thigh.

If the acquisition of diagnostic CT data (see Section 12.1.1 for CT technique) occurs prior to PET imaging, the imaging table will automatically be moved further into the imaging system and PET imaging will be initiated, covering the same field of view as the CT, beginning in a caudocranial direction with the participant's upper thigh. A series of sequential emission scans (3–5 minutes' duration, depending on the participant's size) will be performed. Images will be corrected for scatter and reconstructed using iterative reconstruction algorithm. Emission PET images will be reconstructed with and without attenuation data. Low-dose and/or diagnostic CT data will be used for attenuation correction of the PET data per the options outlined in Section 12.1.1 above. Image reconstruction will depend on the scanner manufacturer. We recommend an iterative reconstruction using OSEM algorithm in a 128 x 128 matrix with a Zoom of 1 and with a 5 mm Gaussian filter. Scatter, decay and deadtime correction, as provided by the manufacturer.(11/16/09)

12.1.5 Image Submission to ACRIN (11/12/08)(11/16/09)

All images collected from PET/CT are to be in digital format. ACRIN has developed software that allows for electronic transmission of images to the Image Management Center (IMC) that have been scrubbed of all participant identifiers.

ACRIN can provide software (TRIAD, see www.triad.acr.org) for installation on a PC at your site that collects and submits image sets.(11/16/09) This software anonymizes, encrypts and non-destructively compresses the images as they are transferred by FTP to the ACRIN database in Philadelphia. For further information or questions, email imagearchive@acr-arrs.org.(11/16/09)

Image Submission Software PC Requirements:

1. Network capability to transmit data from PET scanner to a linked workstation or PC? (11/16/09)
2. Do you have a PC available to transmit data (patient data, PET image data) to ACRIN? (11/16/09)
 - a. Operating System Windows XP Pro
 - b. Access to the Internet: Internet Explorer
 - c. Minimum of 50 GB available hard drive
 - d. At least 1 GB RAM
 - e. Ability to view PDF documents
3. Software utilities required to run image transmission software:
 - a. Windows Installer 3.1
 - b. Microsoft .NET framework 2.0
 - c. MDAC Type 2.8
 - d. MS SQL 2005 Express

Please contact ACRIN to arrange for installation of the TRIAD software prior to first participant accrual. Contact the TRIAD help desk by e-mailing Triad-Support@acr-arrrs.org or by calling 215-940-8820.(11/16/09)

For Imaging Core lab image submission questions contact the lead technologist for this trial at imagearchive@acr-arrrs.org or 215-940-8880.(11/16/09)

For submission on media, the media type must be limited to MOD, CD, or DVD. Media will not be returned unless specifically requested and unless return instructions and packaging are provided.

Send media to:(11/16/09)

American College of Radiology
1818 Market Street, 16th floor
Philadelphia, PA. 19103
ATTN: ACRIN 6671 – Core lab

Each site will be required to be qualified by ACRIN prior to participant accrual. For detailed information regarding site PET qualification and PET/CT requirements, visit the ACRIN web site at: <http://www.acrin.org/PROTOCOLSUMMARYTABLE/PROTOCOL6671/6671ImagingMaterials/tabid/417/Default.aspx>.

To better ensure image quality, the technical parameter charts should be distributed to the individual modalities to guarantee protocol compliance. These charts are available at: <http://www.acrin.org/PROTOCOLSUMMARYTABLE/PROTOCOL6671/6671ImagingMaterials/tabid/417/Default.aspx>.

12.1.6 Image Quality Review (11/16/09)

A review of all imaging procedures will be performed to ascertain image processing at the contributing institutions for adequate quality. The first three (3) cases from each institution along with a continual random sampling of cases will be examined. (11/16/09) In order to assure PET/CT image quality, the instructions for **PET/CT IMAGING QUALITY CONTROL STANDARDS** (Appendix X) must be followed for the duration of the study. (11/16/09) The Quality Control Review of the PET/CT images for the initial three (3) cases, along with the continual random sampling, will be performed at ACRIN Headquarters. ACRIN will be monitoring all images that come in for the duration of the study.

12.1.7 PET/CT Review at Imaging Institutions (11/16/09)

PET/CT images will be assessed by trained PET/CT readers blinded to the results of other imaging examinations and clinical data. Images will be evaluated qualitatively for focal areas of abnormally increased FDG uptake in the nodal region and other organs, and data forms will be completed.

12.2 Central Reader Study (11/16/09)

The analyses for evaluation of study objectives 3.1.1, 3.1.2, 3.2.1, 3.2.2, 3.2.3, 3.2.4, and 3.2.7 will be based on data obtained from one central reader study. (11/16/09)(06/27/11)

In one reader study, seven (7) readers will all interpret PET scans alone and then fused PET/CT scans obtained on each of 132 scans; 132 scans consists of:(11/16/09)

- 30 scans in participants with cervical cancer and pathology-proven metastases to abdominal lymph nodes;
- 36 with endometrial cancer and pathology-proven metastases to abdominal and/or pelvic lymph nodes;
- 30 with cervical cancer without abdominal lymph nodes;
- 36 with endometrial cancer without abdominal or pelvic lymph node involvement.

Scans will be presented to the participating readers in a randomized order. Readers will be aware of the inclusion criteria for participants in the protocol but will be blinded to all other clinical information about each case, any results of other tests and to information about the reference standard interpretation data for PET alone and PET/CT images will be recorded on separate data forms.(11/16/09) In addition to addressing the primary question of presence of abdominal node metastasis, readers will use the CT images to assess the presence and size of primary cervical cancer, nodal, and extra-nodal metastases, and will record on a separate data form. (11/16/09)

A second centralized reader study will be conducted on the Combidex MR component of the trial as described in Amendments 1 through 7 of the protocol.(06/27/11)

The central reader review could be conducted at the ACRIN HQ or the expert reviewer's institution. The central readers will be provided the training as electronic training aids.

12.3 PET/CT Review at Imaging Institutions (11/16/09)

PET/CT images will be assessed by trained PET/CT readers blinded to the results of other imaging examinations and clinical data. Images will be evaluated qualitatively for focal areas of abnormally increased FDG uptake in the nodal region and other organs, and data forms will be completed.

13.0 DRUG INFORMATION

13.1 Fluorodeoxyglucose (FDG)

13.1.1 Chemical Name: 2-[¹⁸F]fluoro-2-deoxy-D-glucose

13.1.2 Molecular Formula: C₆H₁₁¹⁸FO₅

13.1.3 Description: FDG is a positron-emitting radiopharmaceutical containing no-carrier added, radioactive fluoride F¹⁸ that is used for diagnostic purposes in conjunction with positron emission tomography (PET) imaging. FDG is an analog of glucose with a hydroxyl group substituted by F¹⁸. FDG maps the distribution of glucose metabolism in the body. The half-life of FDG is 110 minutes.

13.1.4 *Supplier/How Supplied:* Commercially available, although sites have the option of making their own. FDG is provided as a ready to use isotonic, sterile, pyrogen-free, clear and colorless solution.

13.1.5 *Solution Preparation:* FDG is typically packaged in a multiple-dose glass vial and does not contain any preservatives. FDG is typically provided in an isotonic, sterile, pyrogen free, clear and colorless solution.

13.1.6 *Dosage and Route of Administration:* 10-20 mCi of FDG will be administered intravenously as a bolus.

13.1.7 *Storage:* FDG should be stored upright in an appropriate lead or tungsten alloy shielded container at room temperature.

13.1.8 *Stability:* Refer to the guidelines from the provider, but typically FDG should be used within 10 hours of the end of synthesis.

13.1.9 *Precaution:* Caution related to the use of FDG is limited to blood glucose level; tumor FDG uptake is affected by high blood glucose level. FDG should be administered by nuclear medicine personnel trained to handle radioactive material.

13.1.10 *Synthesis, Apyrogenicity, and Purity:* FDG will be synthesized using the method in place at each performance site. The apyrogenicity of the product will be established with the bacterial endotoxin test. The radiochemical purity of the product will be evaluated by high-performance liquid chromatography and/or thin-layer chromatography (TLC) and should be greater than 90%.

(11/16/09)

14.0 CLINICAL STAGING AND LYMPHATIC EVALUATION (11/16/09)

Participants with cervical carcinoma will undergo clinical staging as permitted by FIGO rules, including examination under anesthesia, cystoscopy, and proctoscopy. Those with endometrial carcinoma will undergo surgical staging at the time of lymphadenectomy.

Participants will then undergo pelvic and abdominal lymph node sampling by an extra-peritoneal, laparoscopic, or trans-peritoneal (only for endometrial carcinoma) approach. For **cervical and endometrial cancers**, eight (8) lymph node “regions” will be sampled independent of one another: left obturator, right obturator, left external iliac, right external iliac, left common iliac, right common iliac, right para-caval, and left para-aortic. In **endometrial cancer cases only**, all additional regions of lymph node sampling (i.e., abdominal lymph node regions above the inferior mesenteric artery) will be collected, identified per region, and analyzed. The degree of sampling will be dictated by a combination of both the amount of lymphadenopathy and the investigator’s discretion. Non-suspicious lymph node regions must be removed completely in order to document them as negative. Overtly positive lymph node regions must be biopsy proven with intra-operative frozen section confirming metastatic disease unless a complete lymphadenectomy is to be performed. Each lymph node “region” is to be considered independently of one another. Therefore, even if a biopsy is positive in another region, a complete lymph node dissection is required in all other regions unless intra-operative

confirmation of metastatic disease outside lymph nodes obviates the need for any other given region.

14.1 Lymph Node Procedures

14.1.1 Cervical cancer only—Extra-peritoneal Pelvic and Abdominal Lymph Node

Sampling: Pelvic and abdominal lymph node sampling must be completed through an adequate incision as outlined in Appendix VI and the GOG Surgical Manual. Choice of incision may include, but is not limited to, midline, paramedian, double-“J” incision, and Pfannensteihl.

14.1.2 Cervical or endometrial carcinomas—Laparoscopic Pelvic and Abdominal

Lymph Node Sampling: Pelvic and abdominal lymph node sampling may also be performed through a laparoscopic approach as outlined in Appendix VI.

If the lymph node sampling cannot be completed successfully via a laparoscopic approach due to technical difficulties (i.e., inadequate exposure), an extra-peritoneal lymph node sampling must be attempted. If unresectable lymph nodes are encountered during the laparoscopic lymph node sampling, extra-peritoneal lymph node dissection is not required as long as tissue confirmation of each region has been obtained.

If the lymph node sampling cannot be accomplished due to retroperitoneal fibrosis/adhesions, which in the investigator’s opinion would alter an extra-peritoneal lymph node dissection, every reasonable attempt should be made to perform a biopsy of any available lymph nodes. An extra-peritoneal attempt at lymph node sampling is unnecessary and trans-peritoneal lymph node sampling will not be performed.

14.1.3 Endometrial cancer only—Trans-peritoneal Pelvic and Abdominal Lymph Node

Sampling: Pelvic and abdominal lymph node sampling must be completed through an adequate incision as outlined in Appendix VII and the GOG Surgical Manual. Choice of incision may include, but is not limited to, midline incision and Pfannensteihl.

15.0 PATHOLOGY INFORMATION

15.1 Lymph node dissection will be performed in accordance with strict anatomic boundaries for the eight (8) regions of interest for both cervical and endometrial carcinomas. Note that this differs from the standard GOG definitions. For details of the specific boundaries of dissection, see Section 8.2. Additional regions sampled in participants with endometrial cancer only will be performed at the surgeon’s discretion. H and E stained slides documenting tumor type and grade (and cervical stromal invasion if histologically documented) should be submitted along with complete surgical pathology reports. (11/16/09)

15.2 Pathologic Evaluation of Lymph Nodes

- 15.2.1** Most lymph nodes are small enough (1.0 cm maximum long axis dimension) to permit bisection into two halves approximately 5 mm thick. The node should be cut from hilum to periphery if possible. A slide should be made from each section. If the lymph node is divided into smaller sections, one slide from each should be evaluated.
- 15.2.2** If a lymph node is larger than 1.0 cm in long axis, then the node should be sectioned in at least 5-mm intervals in a “bread loaf” fashion parallel to the short axis. Again, if more sections are made, then one slide from each should be evaluated.
- 15.2.3** Size of positive submitted lymph nodes and size of metastatic focus will be recorded by the local institutional pathologist.
- 15.2.4** Slides (or recuts) of all lymph node specimens and copies of all surgical pathology reports will be submitted to GOG for review at semi-annual meetings by the pathology committee. The review will consist of two pathologists who will confirm size of the largest positive submitted lymph nodes and size of largest metastatic focus.

16.0 ADVERSE EVENTS REPORTING

16.1 Definition of Adverse Event (06/09/08)(06/27/11)

An **Adverse Event (AE)** is any untoward medical occurrence in a participant that does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory or physiological finding), symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). Abnormal results of diagnostic procedures are considered to be adverse events (AEs) if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

16.2 Definition of Serious Adverse Event

A **Serious Adverse Event (SAE)** is defined as any untoward medical occurrence that:

- results in death, or
- is life-threatening (at the time of the event), or

- requires inpatient hospitalization or prolongation of an existing hospitalization, or
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect.

16.3 Adverse Event Grading

Grade denotes the severity of the adverse event. An AE is graded using the following categories:

- 1 – Mild
- 2 – Moderate
- 3 – Severe
- 4 – Life-threatening or disabling
- 5 – Fatal

16.4 Adverse Event Attribution

Attribution determines whether an adverse event is related to a study treatment or procedure. Attribution categories are:

- Definite – AE *is clearly related* to the study treatment or procedure.
- Probable – AE *is likely related* to the study treatment or procedure.
- Possible – AE *may be related* to the study treatment or procedure.
- Unlikely – AE *is doubtfully related* to the study treatment or procedure.
- Unrelated – AE *is clearly NOT related* to the study treatment or procedure.

16.5 Potential Expected and Unexpected Adverse Events

Adverse events may be **expected** or **unexpected**:

- An **expected AE** is one that is described in the protocol, the consent form, or the investigator's clinical brochure.
- An **unexpected AE** is one that has not been described in the protocol, the consent form, or the investigator's clinical brochure.

16.6 Expected Adverse Events

16.6.1 Adverse Events Associated with Lymph Node Sampling and Lymphadectomy

Multiple series of patients undergoing pretreatment surgical staging for cervical and endometrial cancer have been reported. Adverse events may be due to surgery alone or due to the combination of surgery followed by radiation or chemoradiation (56, 58, 59, 62).(11/16/09)

Vascular Injury	2.3-3.5%
Wound Infection	2.3-10.1%
Lymphocyst	3.5-19.9%
Lymphocyst requiring intervention (drainage of laparotomy)	6.7%
Lymphedema	18.4%
Treatment Related Death (PE or post radiation bowel perforation)	1.1%

16.6.2 Adverse Events Associated with the Injection of Fluorodeoxyglucose (FDG)

FDG can cause allergic reactions when injected, such as mild itching or hives (small bumps on the skin). The injection can also cause bruising and infection at the site of the injection. Symptoms of a more serious allergic reaction include shortness of breath and swelling of the throat or other parts of the body.

16.6.3 Adverse Events Associated to the Oral and Intravenous Iodine Contrast

A history of contrast allergy or asthma excludes potential participants from this study. The injection may cause discomfort and irritation. The iodine-containing contrast used for PET/CT scanning may cause significant contrast reactions in about one in a thousand participants. Severe reaction is seen in as low as 4/10000 to as high as 2/1000 depending on the type of contrast used. Fatal reactions are exceedingly rare and have been reported in 1:170,000 irrespective of the type of contrast used. The most common reactions are nausea, vomiting, hives, or rash. The risk of death is less than 1 in 10,000.

16.6.4 Adverse Events Associated with Radiation Risks(11/16/09)

While the radiation dosage for PET/CT scanning varies with the part of the body being scanned, the exposure for this examination is approximately 2000-2800 millirems (*about 40% to 50% of recommended annual maximum exposure*). The radiation dose from the PET/CT has not been shown to have any adverse effects.(11/16/09)

(11/16/09)

16.6.5 Adverse Events Associated with PET/CT(11/16/09)

Participants may experience discomfort or claustrophobia during the PET scan. CT requires the injection of contrast material, which may cause an allergic reaction (see Section 16.6.3).(11/16/09)

16.7 Reporting of Adverse Events

Prompt reporting of adverse events is the responsibility of each investigator, clinical research associate, and/or nurse engaged in clinical research. Anyone uncertain about whether a particular adverse event should be reported should contact GOG headquarters at 215-854-0770 or ACRIN headquarters at 215-574-3150 for assistance. Please refer to Appendix XII for detailed reporting instructions. (06/09/08)(11/16/09)

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An adverse event should be reported if there is a reasonable suspicion that the AE is reasonably related to the protocol-specific medical treatment, investigational imaging contrast agent, and/or imaging procedures.

GOG will report all serious adverse events to NCI via electronic AdEERS. The ACRIN research associate will provide very detailed information on any imaging adverse event(s) and/or the investigative contrast agent AE(s) on the paper AdEERS to the GOG Data Manager (DM) for electronic AdEERS reporting.

All unresolved adverse events should be followed by the investigator or investigator-designee until the events are resolved, the participant is lost to follow-up, or the adverse events are otherwise explained. Any death or adverse event (e.g. development of cancer, congenital anomaly in conceived offspring) occurring at any time after a participant has discontinued or terminated study participation that may be reasonably related to the protocol-specific medical treatment, investigational imaging contrast agent, and/or imaging procedures should be reported by the GOG Data Manager.

Assignment of grades and attribution for each AE/SAE must be completed by the site principal investigator or investigator-designee. All AEs/SAEs should be documented in the study participant's chart, AE form, and/or AdEERS expedited report. The ACRIN research associate (RA) will capture all imaging AEs and/or the investigative contrast agent AEs on the AE form and paper AdEERS expedited report and provide them to the GOG Data Manager. The expedited AdEERS reports must be submitted by the GOG Data Manager to NCI and GOG must keep a copy of the report on file at the site. Significant new info on the on-going SAE should be promptly reported to NCI/CIP and ACRIN by GOG.

At each contact (site visit and/or telephone) with the study participant, the investigator or investigator-designee must seek information on adverse events through discussion and, as appropriate, by examination. Information on all serious and non-serious, expected and unexpected adverse events considered unrelated, unlikely, possibly, probably, or definitely related to the GOG-0233/ACRIN 6671 trial with the severity level of grades 1, 2, 3, 4, and 5 should be recorded immediately into the source document, e.g. adverse event log and/or progress notes of the study participant's chart, and retained at the site. These adverse events will also be recorded in the AE form and reviewed by the principal site investigator in real time to determine grade and attribution of the event and submitted to ACRIN/GOG.

All adverse events occurring during the study period must be recorded on the AE form. Each adverse event should be followed until resolution, stabilization, or until it has been determined that the study procedures or study participation is not the cause. All serious adverse events that are still ongoing at the end of the study must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be **possibly related** to the study procedures or study participation should be recorded and reported immediately.

(11/16/09)

- **Expedited AE reporting timelines:**
 - **24 Hours; 3 calendar days** – The GOG investigator or investigator-designee must initially report the AE via AdEERS within 24 hours of first knowledge of the event followed by a complete AdEERS report within 3 calendar days of the initial 24-hour report.
 - **7 calendar days** – A complete AdEERS report on the AE must be submitted within 7 calendar days of the GOG investigator or investigator-designee first knowledge 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 expedited adverse event reporting exclusions.
 - Any event that results in **persistent or significant disability/incapacity, congenital anomaly, or birth defect** must be reported via AdEERS by GOG if the event occurs following treatment with an agent under a CIP IND.
 - Expedited reporting is defined as immediate notification of NCI/CTEP by the GOG Data Manager within the specified timeframe outlined in the protocol. CTEP and GOG will then notify CIP and ACRIN of the expedited reporting. Routine reporting requirements also apply.
 - Use the NCI protocol number and the protocol-specific participant ID provided during trial registration on all reports.

* Hospitalizations are defined as lasting 24 hours or longer and these events must be reported via AdEERS.

(11/16/09)

16.8 Adverse Event Reporting for Any Surgical and Imaging Procedures (11/16/09)

Table 5: Expedited Reporting of Adverse Events occurring 30 Days of the Surgical Procedure. The following table summarizes the regulatory requirements for expedited reporting of AEs that occur within 30 days of the surgical procedure.(11/16/09)

From the period of protocol activation through June 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 AdEERS system. (6/27/11)

Beginning July 1, 2011, the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 will be utilized for AE reporting through the AdEERS 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 (<https://gogmember.gog.org> under MANUALS). (06/27/11)

	Grade 1	Grade 2			Grade 3				Grades 4 & 5	
	Unexpected and Expected	Unexpected		Expected	Unexpected		Expected		Unexpected	Expected
		with Hospitalization	without Hospitalization		with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization		
Unrelated Unlikely	Not Required	Not Required	Not Required	Not Required	7 Calendar Days	Not Required	Not Required	Not Required	7 Calendar Days	7 Calendar Days
Possible Probable Definite	Not Required	7 Calendar Days	Not Required	Not Required	7 Calendar Days	7 Calendar Days	7 Calendar Days	Not Required	24-Hour; 3 Calendar Days	7 Calendar Days

Hospitalization is defined as initial hospitalization or prolongation of hospitalization for ≥ 24 hours, **due to adverse event**.

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

1 Adverse events that occur more than 30 day(s) after the last dose of investigational agent and have an attribution of possible, probable, or definite require reporting as follows:

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

- Grade 4 and Grade 5 Unexpected Events

AdeERS 7 calendar day report:

- Grade 3 Unexpected Events with Hospitalization
- Grade 5 Expected Events

All CTCAE v 4.0 expedited AEs must be reported by the GOG Data Manager. All expedited AE reports must be submitted by using the CTEP automated system for expedited reporting (AdeERS). Submitting a report through AdeERS serves as a notification to GOG, and satisfies the GOG requirements for expedited AE reporting. GOG may contact site PI for imaging or surgery depending on the nature of SAE.

GOG CRF Forms:

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 (<http://www.gog.org> under MANUALS) and can be mailed to the institution registering a patient to this study if requested. (6/27/10)

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to the surgical 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 AdEERS within 24 hours of learning of the event, followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.(11/16/09)

“7 calendar days”- A complete AdEERS report on the AE must be submitted within 7 calendar days of the investigator or investigator-designee first knowledge of the event.

- Any medical event equivalent to CTCAE grades 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 expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities and/or incapacities must be reported via AdEERS by the GOG Data Manager if the event occurs following a protocol procedure.
- Use the NCI protocol number and the protocol-specific participant ID provided during trial registration on all reports.
- CTEP and GOG will then notify CIP and ACRIN of the expedited reporting.

16.8.1 Additional instructions or exceptions to AdEERS expedited reporting requirements for this protocol:(11/16/09)

16.8.1.1 Adverse events associated with any primary study procedures: Lymph Node Sampling, any protocol-specific surgical procedures, and PET/CT will be reported.(11/16/09)

16.8.2 AdEERS reporting of all relevant SAEs will be entered into the electronic AdEERS by the GOG Data Manager. The reporting of surgical, commercial contrast agent, and imaging AEs for this protocol will conform to the following:(11/16/09)

1. Grades 1 and 2 unexpected and expected adverse events that are unrelated (surgical **only**, not necessary for imaging), unlikely (surgical **only**, not necessary for imaging), possible, probable, or definite will be reported by **routine reporting procedures only**.
2. Grade 3 unexpected and expected adverse events with hospitalization that are unrelated (surgical **only**, not necessary for imaging), unlikely (surgical **only**, not necessary for imaging), possible, probable, or definite require a complete AdEERS report on the AE to be submitted within **7 calendar days** of the investigator or investigator-designee first knowledge of the event. **Routine reporting procedures also apply**.

3. Grade 3 unexpected and expected adverse events without hospitalization that are unrelated (surgical **only**, not necessary for imaging), unlikely (surgical **only**, not necessary for imaging), possible, probable, or definite will be reported by **routine reporting procedures only**.
4. Grades 4 and 5 unexpected and expected adverse events that are unrelated (surgical **only**, not necessary for imaging), unlikely (surgical **only**, not necessary for imaging), possible, probable, and definite require a complete AdEERS report on the AE to be submitted within **7 calendar days** of the investigator or investigator-designee first knowledge of the event. **Routine reporting procedures also apply**.
5. Expedited adverse event reporting must be completed within 7 calendar days of first knowledge of all unexpected and expected Grade 5 events, regardless of attribution. Routine reporting procedures also apply.
6. All fatal/Grade 5 adverse events (Imaging procedures: only deaths with attributions of possible, probable, or definite) should also be reported by telephone to NCI by the GOG Data Manager within 24 hours of first knowledge of the event. Routine reporting procedures also apply.

The ACRIN research associate (RA) will complete an AE form and paper AdEERS expedited report, if appropriate, for imaging adverse events and forward it to the GOG Data Manager for submission to NCI and GOG.(11/16/09) The GOG Data Manager will be responsible for reporting all adverse events that occur at the site level.

16.8.3 Procedures for Expedited Adverse Event Reporting (11/16/09)

Expedited reports are to be submitted using AdEERS, available at <http://ctep.cancer.gov>. The NCI guidelines for expedited event reporting requirements are also available at this site.

Up until June 30, 2011, AML/MDS events must be reported via AdEERS (in addition to your routine AE reporting mechanisms). In CTCAE v3.0, the event can be reported as: “Secondary malignancy-Other (specify)”. (06/27/11)

Starting July 1, 2011 when use of CTCAE v4.0 begins: AML/MDS events must be reported via AdEERS (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. (06/27/11)

16.9 How to Report (11/16/09)

- 16.9.1** Some adverse events require 24-hour notification (refer to Table 5 in Section 16.8) via AdEERS.(11/16/09) When Internet connectivity is disrupted, a 24-hour notification is to be made to GOG by telephone at: 215-854-0770. An

electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper AdEERS forms have been removed from the CTEP website and will NO LONGER be accepted. **(06/27/11)**

When the adverse event requires expedited reporting, submit the report within the number of calendar days of first knowledge of the event specified in Table 5 in Section 16.8.**(11/16/09)** An expedited adverse event report requires submission to NCI/CTEP by the GOG Data Manager via the AdEERS system. CTEP and GOG will then notify CIP and ACRIN of the expedited reporting.

16.9.2 AdEERS Reports Recipients: AdEERS Reports to the Following

To GOG:

Attention: Manager of Regulatory Affairs

Shawn Griffin: sgriffin@gog.org

RE: Adverse Event Report

GOG-0233/ACRIN 6671

4 Penn Center, 1600 JFK Blvd.

Suite 1020

Philadelphia, PA 19103

To NCI/CIP: (06/27/11)

Medical Monitors at CIP: NCICIPMD@mail.nih.gov

RE: Adverse Event Report

Cancer Imaging Program

6130 Executive Blvd., MSC 7412

Room 6050

Bethesda, MD 20892-7412

(11/16/09)

To ACRIN: (06/09/08)(11/16/09)(06/27/11)

Maria Oh: moh@acr.org

Attention: ACRIN AE Coordinator

Cornelia Worley: cworley@acr.org

RE: Adverse Event Report

ACRIN Protocol 6671

1818 Market Street

Suite 1600

Philadelphia, PA 19103

To make a telephone report, contact NCI at (301) 496-0737, available 24 hours a day (recorder after hours from 4:30 PM to 8:00 AM Eastern Time).

- 16.9.3** A copy of all expedited adverse event reports will be forwarded by GOG to NCI/CTEP. CTEP and GOG will then notify CIP and ACRIN of the expedited reporting at the email addresses provided above.
- 16.9.4** All fatal adverse events identified in the imaging component of the study must be reported by telephone within 24-hours of the event. To make a telephone report call GOG at (215) 854-0770, available 24 hours a day (recorder after hours from 4:30 PM to 8:00 AM Eastern Time). All fatal adverse events must also be reported to CIP by telephone at (301) 496-0737 and to GOG within 24-hours of the event and via AdEERS. All fatal adverse events identified to the surgical component of the study must be reported to GOG through AdEERS, per GOG AE/SAE reporting policies.
- 16.9.5** All expedited adverse event reports should be sent to the local Institutional Review Board (IRB). Refer to the IRB policies and procedures for adverse event reporting.
- 16.9.6** For automated CDUS reporting for studies using investigational agents, the GOG Statistical and Data Center (SDC) routinely reports adverse events electronically to the CTEP Clinical Data Update System (CDUS Version 3.0). The SDC submits this data quarterly. The AEs reported through AdEERS will also be included with the quarterly CDUS data submissions.

As of 7/1/2011, this study will cease using CTCAE v3 and switch to CTCAE v4 for the purposes of reporting through AdEERS and/or CDUS. The GOG Statistical and Data Center will internally convert the adverse event terms and grades reported through AdEERS for this study from April 1, 2011 onward from version 4 to version 3. Additionally, the Statistical and Data Center will map all CTCAE v3 data reported for this study on GOG case report forms to CTCAE v4 defined terms and grades for CDUS reporting purposes. This will allow use of a consistently defined set of criteria for reporting adverse events throughout the study with minimal impact on the participating sites. **(06/27/11)**

17.0 ETHICAL CONSIDERATIONS

This study is to be conducted according to US and international standards of Good Clinical Practice [International Conference of Harmonization (ICH) guidelines], applicable government regulations, and ACRIN research policies and procedures.**(11/16/09)**

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB) for a formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to ACRIN before implementation of the study. The investigator will provide ACRIN with the institution's assurance number, along with the IRB approval letter.

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All study participants in this study will be provided a consent form describing the study and providing sufficient information for participants to make informed decisions about their participation in this study (see Appendix III for the sample informed consent forms).**(11/16/09)** This consent form will be submitted along with the protocol for review and approval by the EC/IRB. The study participant **MUST** be consented with the EC/IRB approved consent form before the participant is subjected to any study procedures. The approved consent form **MUST** be signed and dated by the study participant or legally acceptable representative and the investigator-designated research staff obtaining the consent.

18.0 CONFLICT OF INTEREST

Any investigator and/or research staff member who has a conflict of interest with this study (such as patent ownership, royalties, or financial gain greater than the minimum allowable by their institution) must fully disclose the nature of the conflict of interest in accordance with ACRIN policies and applicable federal, state, and local laws and regulations.

19.0 PUBLICATION POLICY

Neither complete nor partial study results will be published or passed on to any third party without the formal consent of the ACRIN Publication Committee and GOG Publication Committee. Investigators will follow both the ACRIN Publication Policy (ACRIN website at <http://www.acrin.org/ADMINISTRATION/ADMINISTRATIVEPOLICIES/tabid/292/Default.aspx>) and GOG Publication Policy (<http://gogmember.gog.org/>). **(06/09/08)**

20.0 INSTITUTIONAL AUDITS

The investigator will permit study-related auditing and inspections of all study-related documents by the EC/IRB, government regulatory agencies, and ACRIN/GOG.(11/16/09) The investigator will ensure the capability for inspection of all participating site's study-related facilities (e.g. imaging center, satellite sites). The investigator will allocate adequate time for these activities, allow access to all study-related documents and facilities, and provide adequate space to conduct these visits. ACRIN will conduct audits for the imaging component of the trial per standard regulatory guidelines indicated in the ACRIN Audit Manual. This manual is available online at www.acrin.org. GOG will conduct audits for the surgical component of the trial. The guidelines can be found in the GOG Data Management Manual.

All participating institutions that enroll participants will be audited. The timing of the initial on-site audit will depend upon several factors, including the rate of accrual (both study-wide and site-specific), the number of evaluable participants enrolled at an individual site, the status of the protocol and pending amendments, and monitoring status. Generally, audits will be conducted after the number of evaluable participants reaches 20% of targeted accrual, either study-wide and/or site-specific. Audits are typically scheduled to occur at least 3 months after an institution has been monitored, providing that monitoring did not identify issues that mandate immediate auditing. This schedule may be altered in the event of pending protocol amendments. Closure of the study to accrual will trigger auditing of all participating institutions not yet audited. Additionally, site-specific circumstances may prompt an audit at any time.(11/16/09) Subsequent audits will be scheduled per the outcome of the initial audit.(11/16/09) The audits will be conducted per procedures established by the Cancer Imaging Program (CIP) of the NCI or CTEP. Instructions for preparation for the audit visit will be sent to the site prior to the scheduled audit visit. These instructions will specify which participant case records will be reviewed during the audit. On-site records will be verified against the submitted form, and the findings will be recorded on specially prepared audit reports. Major discrepancies will be forwarded to the appropriate oversight body within ACRIN/GOG. IRB procedures, approvals, and consent forms will also be reviewed at the time of the audit visit.

To help sites prepare for audits and assure that the investigator and the research staff maintain records appropriately, the ACRIN data management and auditing departments will offer training to sites. This training will cover all aspects of data collection, including special instructions to obtain and file the various source documents needed to verify the accuracy of submitted data for this trial.

20.1 Source Documents

Source data are found in all information, original records of findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents represent the first recording of any observations made or data generated about a study participant while he or she is enrolled in a clinical trial. Source documents must verify the eligibility criteria and data submitted on all case report forms (CRFs).

Research records for each case should contain source documents for the data reported to ACRIN/GOG. If data are abstracted from medical charts that are not filed at the

investigative sites (e.g. hospital charts), copies of these records should be filed in the research chart. However, every attempt must be made to obtain all records/charts that were used to abstract any study data for this protocol at the time of the audit visit. This will prevent any discrepancies and the inability to verify the document and the data reported.(11/12/08)

20.2 Case Report Forms

Case report forms (CRFs) are the primary data collection instruments for the study. All data requested on the CRFs must be recorded, and any missing data must be explained. If a space is left blank because the procedure was not done or the question was not asked, “N/D” must be noted. If the item is not applicable to the individual case “N/A” must be noted. All entries must be printed legibly in black ink on the paper case report forms. In the event of any entry errors, corrections must be made by drawing a single straight line through the incorrect entry, writing the initials of the person making the correction, recording the date when the correction is being made, and entering the correct data above the strike through. Do not use white out or an eraser.

Data elements that are extracted from the medical record (such as participant history or official clinical interpretations of images, pathology, or surgery results) and recorded on the CRFs will be audited against the appropriate component of the medical record.(11/16/09) Data elements gathered from signed participant questionnaires may be documented on the CRF. The image interpretation data required by the study that is a more detailed extraction of information from the image and is not typically documented in the standard radiology report may be recorded on the CRF and is accepted as source documentation if signed by the Investigator. At the time of audit, the auditor will verify the occurrence of the imaging examination, the reader, and the date on which the exam took place from the medical record. Any use of an approved CRF as source documentation requires that the CRF be signed and dated and refer to the source of the information (participant questionnaire, CT, etc.).(11/16/09)

Any use of CRFs as source documentation when the protocol has designated the source data will be medical record documentation will be considered a deficiency.

20.3 Institutional Review Board

Sites must obtain local IRB initial approval. Prior to participant registration, a copy of the IRB approval letter for the protocol and the informed consent form must be sent to ACRIN (see Section 6.2), along with a copy of the IRB approved informed consent form.(11/16/09) ACRIN/GOG investigator will provide a copy(s) of IRB approval letter(s) for any amendment(s), and copy(s) of annual renewal(s). Copies of IRB documentation will also be forwarded to the GOG Regulatory Affairs department for their files.

21.0 STATISTICAL CONSIDERATIONS

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APPENDIX I
CLINICAL STAGING - CARCINOMA OF THE CERVIX UTERI
FIGO CLASSIFICATION (6/27/11)
(2010)

Stage I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)
IA	Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤ 5 mm and largest extension ≥ 7 mm
IA1	Measured stromal invasion of ≤ 3.0 mm in depth and extension of ≤ 7.0 mm
IA2	Measured stromal invasion of > 3.0 mm and not > 5.0 mm with an extension of not > 7.0 mm
IB	Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA*
IB1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
IB2	Clinically visible lesion > 4.0 cm in greatest dimension
Stage II	Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina
IIA	Without parametrial invasion
IIA1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
IIA2	Clinically visible lesion > 4 cm in greatest dimension
IIB	With obvious parametrial invasion
Stage III	The tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney**
IIIA	Tumor involves lower third of the vagina, with no extension to the pelvic wall
IIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to Stage IV
IVA	Spread of the growth to adjacent organs
IVB	Spread to distant organs

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- * All macroscopically visible lesions—even with superficial invasion—are allotted to stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.00 mm and a horizontal extension of not >7.00 mm. Depth of invasion should not be >5.00 mm taken from the base of the epithelium of the original tissue—superficial or glandular. The depth of invasion should always be reported in mm, even in those cases with “early (minimal) stromal invasion” (-1 mm). The involvement of vascular/lymphatic spaces should not change the stage allotment.
- ** On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. All cases with hydronephrosis or non-functioning kidney are included, unless they are known to be due to another cause.

APPENDIX II
CLINICAL STAGING - CARCINOMA OF THE CORPUS UTERI
FIGO CLASSIFICATION (11/16/09)(06/27/11)
(2010)

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 ^π
IIIB*	Vaginal and/or parametrial involvement ^π
IIIC*	Metastases to pelvic and/or para-aortic lymph nodes ^π
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 Stage II.

π Positive cytology has to be reported separately without changing the stage.

APPENDIX III

GOG-0233/ACRIN 6671

SAMPLE CONSENTS FOR RESEARCH STUDY

TEMPLATE #1: CERVICAL CANCER

(11/16/09)(6/27/11)

Protocol Title:

UTILITY OF PREOPERATIVE FDG-PET/CT SCANNING TO DETECT RETROPERITONEAL LYMPH NODE METASTASIS IN PATIENTS WITH LOCOREGIONALLY ADVANCED CARCINOMA OF THE CERVIX AND HIGH RISK ENDOMETRIAL CANCER (11/16/09)

[Note: ACRIN does not monitor compliance with the Health Insurance Portability and Accountability Act (HIPAA); that is the responsibility of local IRBs].

You are being asked to be in this trial because you have cervical cancer. This is a clinical trial (a type of research study) run by the American College of Radiology Imaging Network (ACRIN), the Gynecologic Oncology Group (GOG), and funded by the National Cancer Institute (NCI). Clinical trials include only participants who choose to take part. Please take your time to make your decision.

You may discuss this research study with your family and friends. You are being asked to volunteer because you meet the study requirements. Your participation is voluntary, which means you can choose whether or not you want to be in this study.

This study will evaluate a type of test, often called a “scan.” The scan for this trial is a PET/CT scan using an agent called “FDG” (Fluorodeoxyglucose). Researchers hope to learn:

- if the scan can find cancer that may have spread to your lymph nodes.(11/16/09)

Answering this question is important because treatment of patients with cervical cancer that has spread to lymph nodes is different than cancer that has not spread.(11/16/09)

Before you make a decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will be asked to do in this study. The research team is going to talk to you about the study and you will be given this consent form to read. You can discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the study doctor and/or research staff about this form or if you have any questions. If you decide to do this study, you will be asked to sign and date this form.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to learn if the FDG-PET/CT can find cancer that may have spread to your lymph nodes.(11/16/09)

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HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 380 people with cancer—165 women with cervical cancer and 215 women with endometrial cancer—will take part in this study at a number of cancer centers in the United States and Canada. (11/16/09)

WHAT AM I BEING ASKED TO DO IN THE STUDY?

Before you begin the study...

You will need to have the following exams, tests, or procedures to find out if you can be in the study. These exams, tests, or procedures may be part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Physical examination,
- Medical history, including pregnancy test,
- Tumor measurement (part of qualifying for trial),
- Blood tests, including checking your kidney health before imaging, (06/27/11)
- Chest X-ray (previous chest imaging may mean you do not have to have a chest X-ray),
- ECG,
- Obtain signed consent,
- Gather Fast Fact Sheet.

During the study...

If the exams, tests, and procedures show that you can be in the study, and you choose to take part, then you will have the following as part of the research study:

- FDG-PET/CT,(11/16/09)
- If PET/CT suggests disease outside your lymph glands, you may undergo biopsy with imaging guided by imaging (CT or ultrasound) prior to surgery. This biopsy may be able to diagnose disease outside your lymph glands that would influence your treatment,(06/27/11)
- Surgery.

DESCRIPTION OF THE FDG-PET/CT SCAN (11/16/09)

Positron emission tomography scan (PET) is a diagnostic procedure in which a small amount of radioactive glucose (sugar) called FDG (Fluorodeoxyglucose) is injected into a vein. You will have the injection 50 minutes before the scan. Then a scanner is used to make detailed, computerized pictures of areas inside the body where the glucose is used. Because cancer cells often use more glucose than normal cells, the pictures can be used to find cancer cells in the body. Computed tomography (CT) is a diagnostic procedure that uses special x-ray equipment to obtain cross-sectional pictures of the body. Combined PET/CT scanning joins these tests into one procedure. (11/16/09)

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AFTER YOU HAVE THE SCAN THAT IS PART OF THE RESEARCH STUDY (11/16/09)

Results of the scan will be explained to you prior to surgery/biopsies since the results determine the procedure. After reviewing the scan results and the results of other tests, certain lymph nodes will be removed and biopsied. Biopsies are the removal of a sample of tissue for examination. Other biopsies may be necessary if your scan shows that cancer may have spread to areas other than your abdominal and pelvic lymph nodes. Once your lymph nodes have been checked for cancer cells, you will receive appropriate treatment with chemotherapy and radiation therapy (chemoradiation) for your cancer. Your treatment will be determined by the results of the biopsy.(11/16/09)

OVERVIEW OF TIMELINE AND PROCEDURES ASSOCIATED WITH STUDY FOR PATIENTS WITH CERVICAL CANCER:

Day	Exams, tests, procedures. and scans	What happens in standard care
You are diagnosed with cervical cancer, stages IB2, IIA ≥4cm, IIB-IVA		
Prior to starting study	<ul style="list-style-type: none"> • Tumor measurement (part of qualifying for trial), • Medical history including pregnancy test, • Blood tests, including checking your kidney health, (06/27/11) • Chest X-ray, • ECG. 	<ul style="list-style-type: none"> • Medical history, • Blood tests, • Chest X-ray, • ECG.
Day 1	<ul style="list-style-type: none"> • Fast (no food or drink) for 4 hours prior to the FDG-PET/CT imaging, • Injection of FDG 50 minutes prior to scan, • Drink oral contrast drug prior to CT, • Urine pregnancy test, • PET/CT scan of abdomen, pelvis and chest. 	The CT and combined PET/CT scans are part of standard of care.
Prior to surgery (06/27/11)	<ul style="list-style-type: none"> • Biopsy of any disease identified by the PET scan outside the abdomen, if feasible. 	This procedure is standard of care; an imaging-guided biopsy may be needed to make sure there is no more disease, only if previous results are negative.
Day 3-15	<ul style="list-style-type: none"> • Lymph node examination, by surgery, laparoscopy, or appropriate biopsy of lesions outside lymph glands. 	The procedure is part of standard care at some centers.
Within 28 days	<ul style="list-style-type: none"> • Begin appropriate treatment with chemoradiation, as defined by standard treatment guidelines for your diagnosis, your physician and you. 	This is standard care.
Within 6 weeks post-op	<ul style="list-style-type: none"> • Physical examination. 	This is standard care.
6 months after enrolling (06/27/11)	<ul style="list-style-type: none"> • Medical history, • CT scan or PET/CT if a finding is visible on PET/CT and was not able to be biopsied or was negative on imaging-guided biopsy. 	Medical history is standard care. The CT or PET/CT scan is part of the standard of care at some centers.

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Every 3 months for 2 years	<ul style="list-style-type: none">● Routine blood tests and medical exams and x-rays at doctor's discretion.	These procedures are standard care.
Every 6 months for 3 additional years	<ul style="list-style-type: none">● Routine blood tests and medical exams and x-rays at doctor's discretion.	These procedures are standard care.

WHAT HAPPENS WHEN I HAVE A PET/CT SCAN?

You will have the CT scan first, and then a PET scan, in the same room and on the same table. You will be told not to eat or drink for 4 hours before the PET/CT scan. When you arrive to have the PET/CT scan, you will have an intravenous (IV) line inserted into a vein and a blood sample taken. Then, a small amount of radioactive tracer, a type of glucose (sugar) called FDG (Fluorodeoxyglucose) will be injected into the IV line. Approximately 50 minutes after the injection of FDG, you will be asked to drink about 2 cups of an oral contrast drug.

You will then be asked to change into a hospital gown and will have a chance to go to the bathroom (urinate). You will be brought to the scanning room, and you will lie on your back on a scanning table. Your arms will be placed above your head, and pillows may be placed under your knees and back to make you more comfortable. The scans will take approximately 45-60 minutes. A second contrast drug will be injected into your IV line. The injection does not hurt. The contrast drug may cause you to feel warm, and may create a pressure in your pelvic area. This will go away.

During the CT scan you lie very still. The table slowly passes through the center of a large x-ray machine. You might hear whirring sounds during the procedure, and you may be asked to hold your breath. After the CT scan is complete, the table will automatically pass into the PET scan system. You will continue to lie still and you may be asked to hold your breath again.

PET/CT scans do not cause any pain. However, lying in one position during the procedure may be slightly uncomfortable.

ARE THERE RISKS ASSOCIATED WITH A PET/CT SCAN?

The radiation exposure from a PET/CT scan is no higher than what you would experience with a normal CT scan. This can be higher than the radiation exposure from a regular x-ray. Approximately 1 person in 1000 may have an allergic reaction from the contrast drugs. These reactions are temporary and treatable. Allergic reactions may include:

- mild itching or hives (small bumps on the skin), and
- shortness of breath and swelling of the throat or other parts of the body.

You should tell the technologist immediately if you experience any of these symptoms so you can be treated promptly.

(11/16/09)

WHAT IS AN IMAGING-GUIDED BIOPSY? (06/27/11)

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When you undergo the PET/CT, the scan may show disease that your doctors did not know about yet. Your surgeon may decide to take a sample (biopsy) of the area seen on PET/CT. Standard of care may be to take some tissue using a needle to test the cells. If the result from this test is negative (no cancer), then another test will be needed as part of this trial, called an imaging-guided biopsy. Ultrasound or CT scan would guide the doctor to biopsy the suspicious spot. If the result is positive (for newly found cancer), you will not continue on the study. Your treating doctor will know about this new information to guide your treatment. If it is negative, then you will stay on the study and have a follow-up CT scan after 6 months.

ARE THERE RISKS ASSOCIATED WITH AN IMAGING-GUIDED BIOPSY? (06/27/11)

Most people who join the study will not have to have an imaging-guided biopsy. If you do, then the removal of cells will involve a needle. The biopsy may cause minor discomfort and involves a low risk of bleeding or bruising and a very low risk of infection. If an ultrasound guides the biopsy, then no risks are associated with this technology. If a CT scan is used, there is low risk of anxiety or stress, discomfort, or claustrophobia during the scan.

WHAT IS A LYMPH NODE DISSECTION? WHAT IS THE PROCEDURE?

Lymph nodes are areas in the body that help to fight the spread of infection and cancer. If your cancer has spread to your lymph nodes, the treatment for your cancer may be modified. In this study, certain lymph nodes will be removed and examined to see if cancer has spread. Lymph node dissection is part of standard treatment at some but not all medical centers, so you may have lymph nodes dissected whether or not you participate in this study.

Lymph nodes lie along the blood vessels deep in your abdomen or pelvis. They can be removed surgically (using either one large incision) or laparoscopically (using multiple small incisions).

Once the incision (or incisions) reach the lymph nodes, a portion of the group of the nodes will be cut away and sent to a pathologist who will help to determine whether or not your cancer may have spread to them.

For this study, the lymph nodes to be removed and checked are the left and right pelvic lymph nodes (called external iliac, obturator, and common iliac lymph nodes) and the lower abdominal lymph nodes (called para-aortic and para-caval lymph nodes).

Following surgery, you will remain in the hospital until you have recovered from your surgery, usually about 1 to 3 days. Although it is not anticipated that you will have any long-term complications, the following is a list of the possible side effects.

WHAT ARE THE RISKS ASSOCIATED WITH THIS TYPE OF SURGERY?

As with all operations, the lymph node sampling has risks and discomforts that include the following:

Hematologic: injury to arteries and veins with potentially heavy bleeding could occur. Blood transfusions may be necessary. Shock with damage to other organs may develop. Death is possible.

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Urinary: injury to the urinary bladder or ureter (the tube carrying urine from the kidney to the bladder) may occur and require surgical repair.

Gastrointestinal: injury to the intestines may occur and require surgical repair.

Neurological: injuries to nerves in the operative areas may occur resulting in loss of sensation or function. Usually these are temporary but could be permanent.

Skin: a hernia (protrusion of an organ or body part) can form in the areas of incision and may need further surgery to repair them. Cancer cells may be deposited in the incision and begin to grow there.

Pulmonary: blood clots can form in large veins and pass into the lungs, causing breathing failure and possibly death.

Infection: infection may occur and will require further treatment.

Lymphedema: swelling in the leg(s) because fluid in your lymph nodes is not draining properly and builds up. This can lead to trouble moving your limb(s), infection, and/or hardening of the skin around the limb(s). Lymphedema cannot be cured, but it can be treated. **(11/12/08)**

Other unknown side effects can occur but are rare and will be monitored.

You will sign a separate consent form for your surgery. Your doctor has discussed with you possible risks of the surgery you will be undergoing, and will be able to answer questions you may have.

WHAT ARE THE POSSIBLE RISKS OR DISCOMFORTS OF THE STUDY?

Risks and discomforts that may occur during the FDG-PET/CT scan or surgery have been discussed above. You may have side effects while on the study and receiving treatment for your cancer. There are risks associated with surgery, lymph node sampling, and chemoradiation used to diagnose and treat cervical cancer.

Everyone taking part in the study will be watched carefully for any side effects. However, doctors do not know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the drugs. In some cases, side effects can be serious, long lasting, or may never go away. There is also a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

ARE THERE REPRODUCTIVE RISKS?

If you are pregnant or nursing you cannot take part in this research study. The effects on the fetus are unknown. If you are breast-feeding a baby, or are a mother-to-be, this study may cause harm because the

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FDG chemical used for the PET/CT scan in this study can affect a baby.(11/16/09) Also, you should not nurse your baby while on this study.

Ask about counseling and more information about preventing pregnancy. For more information about risks and side effects, ask your study doctor. During the study, you need to take safety measures to avoid pregnancy.

HOW LONG WILL I BE IN THE STUDY?

After you are finished with the scans and treatment for your cancer, the study doctor will ask you to visit the office for follow-up exams for 5 years. This is the same follow-up that you would receive if you were not in the trial.

This study is expected to end after all study participants have completed the visits and all the information has been collected. This study may be stopped at any time by your study doctor, GOG, ACRIN, Food and Drug Administration (FDA), or National Cancer Institute (NCI) without your consent in the following situations:

- For your health or safety
- For not following study instructions
- For study administrative decision by ACRIN, GOG, the study doctor, FDA, or NCI

These actions do not require your consent, but you will be informed of any of these decisions if such a decision is made.

CAN I STOP BEING IN THE STUDY?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely. It is important to tell the study doctor if you are thinking about stopping to discuss what follow-up care and testing could be most helpful for you.

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

WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART IN THIS STUDY?

Taking part in this study may or may not make your health better. The information from this study will help study doctors learn whether PET/CT scans will help identify cancer that has spread to lymph nodes.(11/16/09) This knowledge will help doctors decide on the best treatment for patients with cervical cancer, which will benefit women with cervical cancer in the future. In some participants, a change in treatment that will better treat their cancer is predicted.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT WANT TO PARTICIPATE?

You may choose not to participate in this study. If you choose not to participate, there will be no penalty or loss of benefits to which you are otherwise entitled. Your doctor can tell you the different available treatments for your cervical cancer.

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WHAT ABOUT CONFIDENTIALITY?

You understand that every attempt will be made by the investigators to keep all the information collected in this study strictly confidential, including your personal information. Absolute confidentiality can not be guaranteed. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the American College of Radiology Imaging Network (ACRIN) and Gynecologic Oncology Group (GOG). All data sent to ACRIN/GOG over the Internet will be coded so that other people cannot read it. Your personal information may be disclosed if required by law.

You further understand that authorized representatives of ACRIN/GOG, the Food and Drug Administration (FDA), the National Cancer Institute (NCI), the Institutional Review Board (IRB) of <<Institution>> and other groups or organizations that have a role in this study will have access to and may copy both your medical and research records due to your participation in this study.(11/16/09) This access is necessary to ensure the accuracy of the findings and your safety and welfare. If any publication or presentations result from this study, you will not be identified by name. Results will be reported in a summarized manner in which you cannot be identified.

Your images will be kept permanently on file at ACRIN/GOG and may be used for future research. All personal identifiers are removed and replaced with a unique identifying number.

WILL I HAVE TO PAY FOR ANYTHING?

During the study, you will undergo an imaging examination.(11/16/09) You will not be responsible for the costs of any study-related examinations and treatments. ACRIN and the individual insurance carriers will assume responsibility for the financial burden of the study. In regards to co-pays, you and/or your health plan/insurance company may need to pay for some or all of the costs of treating your cancer in this study.(11/16/09)

Every effort to prevent injury as a result of your participation will be taken. It is possible, however, that you could develop complications or injuries as a result of participating in this research study. In the event of injury resulting from this research, emergency medical treatment is available but will be provided at the usual charge. You and/or your insurance will be responsible for the cost of the medical care of that illness or injury. There is no financial compensation that has been set aside to compensate you in the event of injury.

WILL I BE PAID FOR BEING IN THIS STUDY?

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

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Taking part in this study is voluntary. You may choose not to take part in the study. If you decide to participate, you are free to leave the study at any time.(11/16/09) Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your decision to participate in this study will not interfere with your future care.

During the study, more information that could be important to you may be discovered. A Data Safety and Monitoring Board, an independent group of experts, will review the data from this research throughout the study. This includes information that might cause you to change your mind about being in the study. If information becomes available from this or other studies that may affect your health, welfare, or willingness to stay in this study, you will be contacted about it as soon as possible.

At any time, the study doctor may discontinue your participation in this study. The study doctor may decide to take you off this study if it is determined that the treatment is further intensifying the disease and endangers the participant.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

This document explains your rights as a study participant. If you have any questions regarding your participation in this research study or you have any questions regarding your rights as a research participant, do not hesitate to speak with your study doctor or anyone listed below.

For additional information about your health or medical emergency, you may contact: *Usually the name of the local hospital information is provided with instructions to study participants to inform the ER doctor of their participation in a clinical trial.*

Name

Telephone Number

For information about this study, you may contact:

Name

Telephone Number

For information about your rights as a research subject, you may contact <<*Institution Name*>> Institutional Review Board (a group of people who review the research to protect your rights): *(Provide the name of local IRB contact person)*

Name

Telephone Number

WHERE CAN I GET MORE INFORMATION?

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You may call the NCI's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI's Web sites for comprehensive clinical trials information, <http://cancertrials.nci.nih.gov>, or the American College of Radiology Imaging Network Web site, www.acrin.org or www.gog.org. You can find additional information about imaging tests, including PET/CT, on the ACRIN web site:
<http://www.acrin.org/PATIENTS/ABOUTXRAYSANDSCANS/tabid/135/Default.aspx>.
(06/09/08)(11/16/09)

ACKNOWLEDGEMENT

When you sign this document, you are agreeing to take part in this study. This means you have read all the above information, asked questions regarding your participation, and received answers that you understand to all your questions. You have also had the opportunity to take this consent form home for review or discussion if you want to.

You willingly give your consent to participate in this study. A copy of this signed consent form will be given to you.

Printed Name of Study Participant/
Legal Representative

Signature Date

Printed Name of Person Obtaining Consent

Signature Date

APPENDIX III Con't

GOG-0233/ACRIN 6671

SAMPLE CONSENTS FOR RESEARCH STUDY

TEMPLATE #2: ENDOMETRIAL CANCER

(11/16/09)

Protocol Title:

UTILITY OF PREOPERATIVE FDG-PET/CT SCANNING TO DETECT RETROPERITONEAL LYMPH NODE METASTASIS IN PATIENTS WITH LOCOREGIONALLY ADVANCED CARCINOMA OF THE CERVIX AND HIGH RISK ENDOMETRIAL CANCER (11/16/09)

[Note: ACRIN does not monitor compliance with the Health Insurance Portability and Accountability Act (HIPAA); that is the responsibility of local IRBs].

You are being asked to be in this trial because you have endometrial cancer. This is a clinical trial (a type of research study) run by the American College of Radiology Imaging Network (ACRIN), the Gynecologic Oncology Group (GOG), and funded by the National Cancer Institute (NCI). Clinical trials include only participants who choose to take part. Please take your time to make your decision.

You may discuss this research study with your family and friends. You are being asked to volunteer because you meet the study requirements. Your participation is voluntary, which means you can choose whether or not you want to be in this study.

This study will evaluate a types of test, often called a “scan.” The scan is an PET/CT scan using an agent called “FDG” (Fluorodeoxyglucose). Researchers hope to learn:

- if the scans can find cancer that may have spread to your lymph nodes.(11/16/09)

Answering this question is important because treatment of patients with endometrial cancer that has spread to lymph nodes is different than cancer that has not spread.(11/16/09)

Before you make a decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will be asked to do in this study. The research team is going to talk to you about the study and you will be given this consent form to read. You can discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the study doctor and/or research staff about this form or if you have any questions. If you decide to do this study, you will be asked to sign and date this form.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to learn if the FDG-PET/CT can find cancer that may have spread to your lymph nodes.(11/16/09)

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

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About 380 people with cancer—165 women with cervical cancer and 215 women with endometrial cancer—will take part in this study at a number of cancer centers in the United States and Canada. (11/16/09)

WHAT AM I BEING ASKED TO DO IN THE STUDY?

Before you begin the study...

You will need to have the following exams, tests, or procedures to find out if you can be in the study. These exams, tests, or procedures may be part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Physical examination,
- Medical history, including pregnancy test,
- Tumor measurement (part of qualifying for trial),
- Blood tests, including checking your kidney health before imaging, (06/27/11)
- Chest X-ray (previous chest imaging may mean you do not have to have a chest X-ray),
- ECG,
- Obtain signed consent,
- Gather Fast Fact Sheet.

During the study...

If the exams, tests, and procedures show that you can be in the study, and you choose to take part, then you will have the following as part of the research study:

- FDG-PET/CT,(11/16/09)
- If PET/CT suggests disease outside your lymph glands, you may undergo biopsy with imaging guided by imaging (CT or ultrasound) prior to surgery. This biopsy may be able to diagnose disease outside your lymph glands that would influence your treatment,(06/27/11)
- Surgery.

DESCRIPTION OF THE FDG-PET/CT SCAN(11/16/09)

Positron emission tomography scan (PET) is a diagnostic procedure in which a small amount of radioactive glucose (sugar) called FDG (Fluorodeoxyglucose) is injected into a vein. You will have the injection 50 minutes before the scan. Then a scanner is used to make detailed, computerized pictures of areas inside the body where the glucose is used. Because cancer cells often use more glucose than normal cells, the pictures can be used to find cancer cells in the body. Computed tomography (CT) is a diagnostic procedure that uses special x-ray equipment to obtain cross-sectional pictures of the body. Combined PET/CT scanning joins these tests into one procedure. (11/16/09)

AFTER YOU HAVE THE SCAN THAT IS PART OF THE RESEARCH STUDY (11/16/09)

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Results of the scan will be explained to you prior to surgery/biopsies since the results determine the procedure. After reviewing the scan results and the results of other tests, certain lymph nodes will be removed and biopsied. Biopsies are the removal of a sample of tissue for examination. Other biopsies may be necessary if your scan shows that cancer may have spread to areas other than your abdominal and pelvic lymph nodes. Your study doctor will want to collect samples from lymph nodes in any area that is biopsied to better understand how well the imaging works. Once your nodes have been checked for cancer cells, you may or may not need further treatment. This will be determined by the results of the biopsy. **(11/16/09)**

OVERVIEW OF TIMELINE AND PROCEDURES ASSOCIATED WITH STUDY FOR PATIENTS WITH ENDOMETRIAL CANCER:

Day	Exams, tests, procedures, and scans	What happens in standard care
You are diagnosed with endometrial carcinoma (Grade 3 endometrioid, serous papillary, clear cell, or carcinosarcoma, or any grade with cervical involvement)		
Prior to starting study	<ul style="list-style-type: none"> • Tumor measurement (part of qualifying for trial), • Medical history including pregnancy test, • Blood tests, including checking your kidney health, (06/27/11) • Chest X-ray, • ECG. 	<ul style="list-style-type: none"> • Medical history, • Blood tests, • Chest X-ray, • ECG.
Day 1	<ul style="list-style-type: none"> • Fast (no food or drink) for 4 hours prior to the FDG-PET/CT imaging, • Injection of FDG 50 minutes prior to scan, • Drink oral contrast drug prior to CT, • Urine pregnancy test, • PET/CT scan of abdomen, pelvis and chest. 	The CT and combined PET/CT scans are part of standard of care.
Prior to surgery (06/27/11)	<ul style="list-style-type: none"> • Biopsy of any disease identified by the PET scan outside the abdomen, if feasible. 	This procedure is standard of care; an imaging-guided biopsy may be needed to make sure there is no more disease, only if previous results are negative.
Day 3-15	<ul style="list-style-type: none"> • Lymph node examination, by surgery, laparoscopy, or appropriate biopsy of lesions outside lymph glands. 	The procedure is part of standard care at some centers.
Within 6 weeks post-op	<ul style="list-style-type: none"> • Physical examination. 	This is standard care.
6 months after enrolling (06/27/11)	<ul style="list-style-type: none"> • Medical history, • CT scan or PET/CT if a finding is visible on PET/CT and was not able to be biopsied or was negative on imaging-guided biopsy. 	Medical history is standard care. The CT or PET/CT scan is part of the standard of care at some centers.
Every 3 months for 2 years	<ul style="list-style-type: none"> • Routine blood tests and medical exams and x-rays at doctor's discretion. 	These procedures are standard care.

(06/27/11)

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WHAT HAPPENS WHEN I HAVE A PET/CT SCAN?

You will have the CT scan first, and then a PET scan, in the same room and on the same table. You will be told not to eat or drink for 4 hours before the PET/CT scan. When you arrive to have the PET/CT scan, you will have an intravenous (IV) line inserted into a vein and a blood sample taken. Then, a small amount of radioactive tracer, a type of glucose (sugar) called FDG (Fluorodeoxyglucose) will be injected into the IV line. Approximately 50 minutes after the injection of FDG, you will be asked to drink about 2 cups of an oral contrast drug.

You will then be asked to change into a hospital gown and will have a chance to go to the bathroom (urinate). You will be brought to the scanning room, and you will lie on your back on a scanning table. Your arms will be placed above your head, and pillows may be placed under your knees and back to make you more comfortable. The scans will take approximately 45 to 60 minutes. A second contrast drug will be injected into your IV line. The injection does not hurt. The contrast drug may cause you to feel warm, and may create a pressure in your pelvic area. This will go away.

During the CT scan you lie very still. The table slowly passes through the center of a large x-ray machine. You might hear whirring sounds during the procedure, and you may be asked to hold your breath. After the CT scan is complete, the table will automatically pass into the PET scan system. You will continue to lie still and you may be asked to hold your breath again.

PET/CT scans do not cause any pain. However, lying in one position during the procedure may be slightly uncomfortable.

ARE THERE RISKS ASSOCIATED WITH A PET/CT SCAN?

The radiation exposure from a PET/CT scan is no higher than what you would experience with a normal CT scan. This can be higher than the radiation exposure from a regular x-ray. Approximately 1 person in 1000 may have an allergic reaction from the contrast drugs. These reactions are temporary and treatable. Allergic reactions may include:

- mild itching or hives (small bumps on the skin), and
- shortness of breath and swelling of the throat or other parts of the body.

You should tell the technologist immediately if you experience any of these symptoms so you can be treated promptly.

(11/16/09)

WHAT IS AN IMAGING-GUIDED BIOPSY? (06/27/11)

When you undergo the PET/CT, the scan may show disease that your doctors did not know about yet. Your surgeon may decide to take a sample (biopsy) of the area seen on PET/CT. Standard of care may be to take some tissue using a needle to test the cells. If the result from this test is negative (no cancer), then another test will be needed as part of this trial, called an imaging-guided biopsy. Ultrasound or CT scan would guide the doctor to biopsy the suspicious spot. If the result is positive (for newly found cancer), you will not continue on the study. Your treating doctor will know about this new information

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to guide your treatment. If it is negative, then you will stay on the study and have a follow-up CT scan after 6 months.

ARE THERE RISKS ASSOCIATED WITH AN IMAGING-GUIDED BIOPSY? (06/27/11)

Most people who join the study will not have to have an imaging-guided biopsy. If you do, then the removal of cells will involve a needle. The biopsy may cause minor discomfort and involves a low risk of bleeding or bruising and a very low risk of infection. If an ultrasound guides the biopsy, then no risks are associated with this technology. If a CT scan is used, there is low risk of anxiety or stress, discomfort, or claustrophobia during the scan.

WHAT IS A LYMPH NODE DISSECTION? WHAT IS THE PROCEDURE?

Lymph nodes are areas in the body that help to fight the spread of infection and cancer. If your cancer has spread to your lymph nodes, the treatment for your cancer may be modified. In this study, certain lymph nodes will be removed and examined to see if cancer has spread. Lymph node dissection is part of standard treatment for endometrial cancer, so you will have lymph nodes dissected whether or not you participate in this study.

Lymph nodes lie along the blood vessels deep in your abdomen or pelvis. They can be removed surgically (using either one large incision) or laparoscopically (using multiple small incisions).

Once the incision (or incisions) reach the lymph nodes, a portion of the group of the nodes will be cut away and sent to a pathologist who will help to determine whether or not your cancer may have spread to them.

For this study, the lymph nodes to be removed and checked are the left and right pelvic lymph nodes (called external iliac, obturator, and common iliac lymph nodes) and the lower abdominal lymph nodes (called para-aortic and para-caval lymph nodes).

Following surgery, you will remain in the hospital until you have recovered from your surgery, usually about 1 to 5 days. Although it is not anticipated that you will have any long-term complications, the following is a list of the possible side effects.

WHAT ARE THE RISKS ASSOCIATED WITH THIS TYPE OF SURGERY?

As with all operations, the lymph node sampling has risks and discomforts that include the following:

Hematologic: injury to arteries and veins with potentially heavy bleeding could occur. Blood transfusions may be necessary. Shock with damage to other organs may develop. Death is possible.

Urinary: injury to the urinary bladder or ureter (the tube carrying urine from the kidney to the bladder) may occur and require surgical repair.

Gastrointestinal: injury to the intestines may occur and require surgical repair.

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Neurological: injuries to nerves in the operative areas may occur resulting in loss of sensation or function. Usually these are temporary but could be permanent.

Skin: a hernia (protrusion of an organ or body part) can form in the areas of incision and may need further surgery to repair them. Cancer cells may be deposited in the incision and begin to grow there.

Pulmonary: blood clots can form in large veins and pass into the lungs, causing breathing failure and possibly death.

Infection: infection may occur and will require further treatment.

Lymphedema: swelling in the leg(s) because fluid in your lymph nodes is not draining properly and builds up. This can lead to trouble moving your limb(s), infection, and/or hardening of the skin around the limb(s). Lymphedema cannot be cured, but it can be treated.

Other unknown side effects can occur but are rare and will be monitored.

You will sign a separate consent form for your surgery. Your doctor has discussed with you possible risks of the surgery you will be undergoing, and will be able to answer questions you may have.

WHAT ARE THE POSSIBLE RISKS OR DISCOMFORTS OF THE STUDY?

Risks and discomforts that may occur during the scans or surgery have been discussed above. You may have side effects while on the study and receiving treatment for your cancer. There are risks associated with surgery, lymph node sampling, and chemoradiation used to diagnose and treat endometrial cancer.

Everyone taking part in the study will be watched carefully for any side effects. However, doctors do not know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the drugs. In some cases, side effects can be serious, long lasting, or may never go away. There is also a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

ARE THERE REPRODUCTIVE RISKS?

If you are pregnant or nursing you cannot take part in this research study. The effects on the fetus are unknown. If you are breast-feeding a baby, or are a mother-to-be, this study may cause harm because the FDG chemical used for the PET/CT scan in this study can affect a baby. **(11/16/09)** Also, you should not nurse your baby while on this study.

Ask about counseling and more information about preventing pregnancy. For more information about risks and side effects, ask your study doctor. During the study, you need to take safety measures to avoid pregnancy.

HOW LONG WILL I BE IN THE STUDY?

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After you are finished with the scans and treatment for your cancer, the study doctor will ask you to visit the office for follow-up exams for 5 years. This is the same follow-up that you would receive if you were not in the trial.

This study is expected to end after all study participants have completed the visits and all the information has been collected. This study may be stopped at any time by your study doctor, GOG, ACRIN, Food and Drug Administration (FDA), or National Cancer Institute (NCI) without your consent in the following situations:

- For your health or safety
- For not following study instructions
- For study administrative decision by ACRIN, GOG, the study doctor, FDA, or NCI

These actions do not require your consent, but you will be informed of any of these decisions if such a decision is made.

CAN I STOP BEING IN THE STUDY?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely. It is important to tell the study doctor if you are thinking about stopping to discuss what follow-up care and testing could be most helpful for you.

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

WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART IN THIS STUDY?

Taking part in this study may or may not make your health better. The information from this study will help study doctors learn whether PET/CT scans will help identify cancer that has spread to lymph nodes.(11/16/09) This knowledge will help doctors decide on the best treatment for patients with endometrial cancer, which will benefit women with these cancers in the future. In some participants, a change in treatment that will better treat their cancer is predicted.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT WANT TO PARTICIPATE?

You may choose not to participate in this study. If you choose not to participate, there will be no penalty or loss of benefits to which you are otherwise entitled. Your doctor can tell you the different available treatments for your endometrial cancer.

WHAT ABOUT CONFIDENTIALITY?

You understand that every attempt will be made by the investigators to keep all the information collected in this study strictly confidential, including your personal information. Absolute confidentiality can not be guaranteed. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the American College of Radiology Imaging Network (ACRIN) and Gynecologic Oncology Group (GOG). All data sent to ACRIN/GOG over the

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Internet will be coded so that other people cannot read it. Your personal information may be disclosed if required by law.

You further understand that authorized representatives of ACRIN/GOG, the Food and Drug Administration (FDA), the National Cancer Institute (NCI), the Institutional Review Board (IRB) of <<Institution>> and other groups or organizations that have a role in this study will have access to and may copy both your medical and research records due to your participation in this study.(11/16/09) This access is necessary to ensure the accuracy of the findings and your safety and welfare. If any publication or presentations result from this study, you will not be identified by name. Results will be reported in a summarized manner in which you cannot be identified.

Your images will be kept permanently on file at ACRIN/GOG and may be used for future research. All personal identifiers are removed and replaced with a unique identifying number.

WILL I HAVE TO PAY FOR ANYTHING?

During the study, you will undergo an imaging examination.(11/16/09) You will not be responsible for the costs of any study-related examinations and treatments. ACRIN and the individual insurance carriers will assume responsibility for the financial burden of the study. In regards to co-pays, you and/or your health plan/insurance company may need to pay for some or all of the costs of treating your cancer in this study.(11/16/09)

Every effort to prevent injury as a result of your participation will be taken. It is possible, however, that you could develop complications or injuries as a result of participating in this research study. In the event of injury resulting from this research, emergency medical treatment is available but will be provided at the usual charge. You and/or your insurance will be responsible for the cost of the medical care of that illness or injury. There is no financial compensation that has been set aside to compensate you in the event of injury.

WILL I BE PAID FOR BEING IN THIS STUDY?

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part in the study. If you decide to participate, you are free to leave the study at any time.(11/16/09) Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your decision to participate in this study will not interfere with your future care.

During the study, more information that could be important to you may be discovered. A Data Safety and Monitoring Board, an independent group of experts, will review the data from this research throughout the study. This includes information that might cause you to change your mind about being in the study. If information becomes available from this or other studies that may affect your health, welfare, or willingness to stay in this study, you will be contacted about it as soon as possible.

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At any time, the study doctor may discontinue your participation in this study. The study doctor may decide to take you off this study if it is determined that the treatment is further intensifying the disease and endangers the participant.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

This document explains your rights as a study participant. If you have any questions regarding your participation in this research study or you have any questions regarding your rights as a research participant, do not hesitate to speak with your study doctor or anyone listed below.

For additional information about your health or medical emergency, you may contact: *Usually the name of the local hospital information is provided with instructions to study participants to inform the ER doctor of their participation in a clinical trial.*

Name

Telephone Number

For information about this study, you may contact:

Name

Telephone Number

For information about your rights as a research subject, you may contact *<<Institution Name>>* Institutional Review Board (a group of people who review the research to protect your rights): *(Provide the name of local IRB contact person)*

Name

Telephone Number

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI's Web sites for comprehensive clinical trials information, <http://cancertrials.nci.nih.gov>, or the American College of Radiology Imaging Network Website, www.acrin.org or www.gog.org. You can find additional information about imaging tests, including PET/CT, on the ACRIN web site: <http://www.acrin.org/PATIENTS/ABOUTXRAYSCANANDSCANS/tabid/135/Default.aspx>. **(06/09/08)(11/16/09)**

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ACKNOWLEDGEMENT

When you sign this document, you are agreeing to take part in this study. This means you have read all the above information, asked questions regarding your participation, and received answers that you understand to all your questions. You have also had the opportunity to take this consent form home for review or discussion if you want to.

You willingly give your consent to participate in this study. A copy of this signed consent form will be given to you.

Printed Name of Study Participant/
Legal Representative

Signature

Date

Printed Name of Person Obtaining Consent

Signature

Date

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APPENDIX IV
PARTICIPATING INSTITUTIONS

At a minimum of ten (10) participating institutions, Site Principal Investigators will be identified upon review and approval of completed ACRIN Protocol Specific Application (PSA).**(11/16/09)**

APPENDIX V
EXTRAPERITONEAL LYMPHADENECTOMY

PURPOSE

- 1) Histologic evaluation of pelvic and periaortic nodes.

INDICATION

- 1) Surgical staging of gynecologic malignancy.

CONTRAINDICATION

- 1) Evidence of extra-abdominal and extra-nodal METASTASES by cytology, radiographic, or histologic parameters.
- 2) Poor surgical risk.

CONTENT OF PROCEDURE

- 1) The skin incision may be of the surgeon's choosing including midline vertical, transverse, and lateral vertical.
- 2) The peritoneum is exposed and may be opened before or after retroperitoneal exploration if biopsies and cytologic washings are indicated.
- 3) The retroperitoneum is exposed by rolling the peritoneum medially until psoas muscle and iliac vessels are visualized.
- 4) The aorta, vena cava and iliac vessels on the side of entry are exposed.

NOTE: The ureter should be left attached to the peritoneum on the side of entry.

- 5) Proceed with abdominal lymphadenectomy:
 - a) The bifurcation of the aorta, the inferior vena cava, the ovarian vessels, the inferior mesenteric artery, the ureters and duodenum should be identified.
 - b) Any enlarged or suspicious nodes will be excised or biopsied if unresectable.
 - c) The nodal tissue around the distal vena cava from the level of the inferior mesenteric artery to the bifurcation of the aorta is removed.(11/16/09)
 - d) The nodal tissue between the aorta and the left ureter from the inferior mesenteric artery to the left mid common iliac artery is removed.
 - e) Ligation of the proximal and distal nodal tissue is recommended.(11/16/09)

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- f) Dissection cephalad to the inferior mesenteric artery is restricted to those cases with palpably suspicious nodes above that level.

6. Proceed with pelvic lymphadenectomy.

- a) Identify the bifurcation of the common iliac, external iliac, hypogastric arteries and veins and the ureters, bilaterally.
- b) Any enlarged or suspicious nodes will be excised or biopsied if unresectable.
- c) The nodal tissue from the bifurcation of the aorta along each common iliac artery to the bifurcation of the common iliac artery should be removed and the iliac vessels skeletonized; laterally from the mid portion of the psoas to the ureter medially. This will be sent as Common Iliac Lymph Nodes. **(11/16/09)**
- d) The nodal tissue along the external iliac vessels should be removed and the iliac vessels skeletonized; laterally from the mid portion of the psoas medially to the ureter including the hypogastric artery and vein, distally to the circumflex iliac vein. This will be sent as External Iliac Lymph Nodes.
- e) The nodal tissue anterior to the obturator nerve and deep to the external iliac vessels should be removed from the obturator fossa and sent as Obturator Lymph Nodes.
- f) Ligation of the proximal and distal attachments of the nodal tissue is recommended. Unresectable nodes should be outlined with clips.

APPENDIX VI
LAPAROSCOPIC PELVIC AND ABDOMINAL LYMPHADENECTOMY

PURPOSE

- 1) Histologic evaluation of pelvic and periaortic nodes.
- 2) Reduction of nodal tumor bulk.
- 3) Surgical-pathologic staging of gynecologic malignancy.
- 4) Provide guidelines for subsequent therapy.

INDICATION

- 1) Surgical staging of gynecologic malignancy.

CONTRAINDICATION

- 1) Evidence of extra-abdominal and extra-nodal METASTASES by cytology, radiographic, or histologic parameters.
- 2) Medical inoperability.

CONTENT OF PROCEDURE

A) **Pelvic Lymphadenectomy**

- 1) Identify the bifurcation of the common iliac, external iliac, hypogastric arteries and veins and the ureters, bilaterally.
- 2) Any enlarged or suspicious nodes will be excised or biopsied if unresectable.
- 3) The nodal tissue from the distal one-half of each common iliac artery should be removed and the iliac vessels skeletonized; laterally from the mid portion of the psoas to the ureter medially. This will be sent as Common Iliac Lymph Nodes.
- 4) The nodal tissue along the external iliac vessels should be removed and the iliac vessels skeletonized; laterally from the mid portion of the psoas medially to the ureter including the hypogastric artery and vein, distally to the circumflex iliac vein. This should be sent as External Iliac Lymph Nodes.
- 5) The nodal tissue anterior to the obturator nerve and deep to the external iliac vessels should be removed from the obturator fossa and sent as Obturator Lymph Nodes.
- 6) Ligation of the proximal and distal attachments of the nodal tissue is recommended.

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B) Abdominal

- 1) The bifurcation of the aorta, the inferior vena cava, the ovarian vessels, the inferior mesenteric artery, the ureters and duodenum should be identified.
- 2) Any enlarged or suspicious nodes will be excised or biopsied if unresectable.
- 3) The nodal tissue around the distal vena cava from the level of the inferior mesenteric artery to the mid right common iliac artery is removed.
- 4) The nodal tissue between the aorta and the left ureter from the inferior mesenteric artery to the left mid common iliac artery is removed.
- 5) Ligation of the proximal and distal nodal tissue is recommended.
- 6) Dissection cephalad to the inferior mesenteric artery is restricted to those cases with palpably suspicious nodes above that level.

APPENDIX VII
TRANSPERITONEAL LYMPHADENECTOMY (11/16/09)

PURPOSE

- 1) Histologic evaluation of pelvic and periaortic nodes.

INDICATION

- 1) Surgical staging of gynecologic malignancy.

CONTRAINDICATION

- 1) Evidence of extra-abdominal and extra-nodal METASTASES by cytology, radiographic, or histologic parameters.
- 2) Poor surgical risk.

CONTENT OF PROCEDURE

1) Proceed with abdominal lymphadenectomy:

- a) The bifurcation of the aorta, the inferior vena cava, the ovarian vessels, the inferior mesenteric artery, the ureters and duodenum should be identified.
- b) Any enlarged or suspicious nodes will be excised or biopsied if unresectable.
- c) The nodal tissue around the distal vena cava from the level of the inferior mesenteric artery to the bifurcation of the aorta is removed.
- d) The nodal tissue between the aorta and the left ureter from the inferior mesenteric artery to the left mid common iliac artery is removed.
- e) Ligation of the proximal and distal nodal tissue is recommended.
- f) Dissection cephalad to the inferior mesenteric artery is restricted to those cases with palpably suspicious nodes above that level.

2) Proceed with pelvic lymphadenectomy.

- a) Identify the bifurcation of the common iliac, external iliac, hypogastric arteries and veins and the ureters, bilaterally.
- b) Any enlarged or suspicious nodes will be excised or biopsied if unresectable.
- c) The nodal tissue from the bifurcation of the aorta along each common iliac artery to the bifurcation of the common iliac artery should be removed and the iliac vessels skeletonized; laterally from the mid portion of the psoas to the ureter medially. This will be sent as Common Iliac Lymph Nodes.

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- d) The nodal tissue along the external iliac vessels should be removed and the iliac vessels skeletonized; laterally from the mid portion of the psoas medially to the ureter including the hypogastric artery and vein, distally to the circumflex iliac vein. This will be sent as External Iliac Lymph Nodes.
- e) The nodal tissue anterior to the obturator nerve and deep to the external iliac vessels should be removed from the obturator fossa and sent as Obturator Lymph Nodes.
- f) Ligation of the proximal and distal attachments of the nodal tissue is recommended. Unresectable nodes should be outlined with clips.

APPENDIX VIII
GUIDELINES FOR LAPAROSCOPIC SURGERY

Preparation of the Patient

1. Liquid diet for 48 hours prior to the procedure.
2. Magnesium Citrate 8 oz, 36 hours and 12 hours prior to procedure.
3. Fleet enemas in the a.m. of the procedure.
4. General anesthesia.
5. Nasogastric tube.
6. Pulse oximeter.
7. Arms tucked to the side.
8. Low dorsal lithotomy position.
9. Vaginal prep and placement of a sponge stick in the vagina if appropriate.

Instrumentation

1. High flow electronic insufflator, high intensity light source, high resolution camera, 2 monitors, coagulation source, 4 forceps and dissecting scissors.
2. 10-11 mm operating laparoscope inserted at the umbilicus.
3. 10-11 mm trocar in the midline above the pubic symphysis.
4. 5 mm trocars in the right and left mid-abdomen.

Aortic Lymphadenectomy

1. Steep Trendelenburg's position.
2. Posterior peritoneum incised medial to the right ureter from the common iliac artery to the level of the inferior mesenteric artery.
3. Retract the ureter laterally.

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4. Retract the inferior mesenteric artery and its branches superiolaterally.
5. Remove the para-caval and para-aortic lymph nodes. Nodes judged to be unresectable by laparoscopy should be biopsied.

Pelvic Lymphadenectomy

1. The peritoneum between the round ligament and the ovarian pedicle is incised over the psoas muscle.
2. The ureter and ovarian vessels retracted medially.
3. The umbilical artery is identified and retracted medially.
4. Remove the pelvic lymph nodes.
5. Nodes judged to be unresectable by laparoscopy should be biopsied.

APPENDIX IX
CREDENTIALING PROCEDURES FOR PET/CT IMAGING FOR THIS STUDY

ACRIN's standard operating procedure (SOP) for credentialing PET/CT imaging can be found on the ACRIN web site at: <http://www.acrin.org/PROTOCOLSUMMARYTABLE/PROTOCOL6671/6671ImagingMaterials/tabid/417/Default.aspx>. (06/09/08)

APPENDIX X
(11/16/09)
PET/CT IMAGING QUALITY CONTROL STANDARDS

Detailed criteria/specifications for performance of PET and CT imaging are described in **Appendix IX**.

1. FDG-PET/CT imaging will be performed using “state-of-the-art” equipment. The PET/CT unit should have a multislice CT (> 1-slice) and BGO (Bismuth Germinate Oxide), LSO (Lutetium Oxyorthosilicate) and GSO, which will have the following:
 - A field of view appropriate for body imaging (> 10 cm)
 - High intrinsic spatial resolution at transaxial plane ($\text{FWHM} \leq 6.5$ mm at the center) and high sensitivity
 - Post-injection transmission capability using CT. (Please note that intrinsic resolution is usually better than the reconstructed resolution which is heavily dependent on the type of filter used. The intrinsic resolution at transverse plane typically is in the range of 4.2-6.3 mm at the center).
(09/09/08)

2. **PET Scanner Quality Assurance:** Daily and monthly steps will be taken to assure quantitative accuracy of PET/CT imaging studies and reliable imaging results at all performance sites. Daily quality assurance includes a simplified chi-square test to assure consistent sensitivity and uniformity of the PET component of the camera. The calculation provides a quantitative means of monitoring drift of the scanner electronics with time. A liquid-filled or standardized sealed-source cylinder phantom is used monthly to validate the quantitative accuracy of the images against a dose calibrator. The dose calibrator is itself calibrated daily against standards for constancy and annually for accuracy using NIST-traceable standards. Each month, fine gain calibration of all detectors in the PET system will be performed, followed by recalculation of the sensitivity normalization factors for the scanner. Quality assurance tests should also be performed on the CT component of the PET/CT camera. Such test may include daily scanning of a standardized phantom to validate the CT number calibration and the slice thickness.

CT scan will be used for attenuation correction of PET data with CT data from a combined PET/CT scanner, in accordance with manufacturer’s recommendations). An algorithm to correct for activity in the field of view should be used for processing of the post-injection transmission images, if provided by the vendor. Then the corresponding emission images, each at least 5 minutes per bed position for BGO, LSO and GSO systems operated in the 2-D mode; at least 3 minutes per bed position for BGO, LSO, and GSO systems operated in the 3-D mode; and at least 6 minutes per bed position for NaI systems. The PET images will be reconstructed by standard vendor-provided reconstruction algorithms. We recommend an iterative reconstruction using OSEM algorithm in a 128 x 128 matrix with a Zoom of 1 and with a 5 mm Gaussian filter. Scatter, decay and deadtime correction, as provided by the manufacturer. The emission images will be reconstructed both with and without attenuation correction.

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3. SUV Calculation: To enable accurate and meaningful SUVs to be calculated, the following information must be recorded for each scan:

- Injection time
- Tracer dosage
- Tracer dosage assay time
- Start-of-scan time
- Scan duration
- Patient height (to be measured on the day of scan)
- Patient weight (to be measured on the day of scan)
- Blood glucose level prior to scan

APPENDIX XI
(11/16/09)
DATABASE ARCHIVING

The Archived Images Database will be set up utilizing Microsoft SQL Server 7.0 running under Microsoft NT Server 2000 Enterprise Edition with clustering and full fault tolerance enabled. Image storage will be maintained on multiple servers connected to a distributed Level 5 RAID architecture, which will have sufficient capacity to handle the required number of diagnostic images anticipated for this trial. Backup will be performed on a DAT tape server with backup sets maintained both on and off site. Digitally acquired images will be received from the institutions where possible via the Web via a dedicated T3 link. The proprietary software utilized for acquisition and transmission has been developed by the ACR specifically for use in direct digital image acquisition for ACRIN trials. The digitally acquired images will be maintained in their original DICOM format and stored as individual files in the archive.

The archive environment will be set up utilizing a central SQL image database that will maintain the indexing of all the image series files sorted by study, case, exam, and image type. The software developed for management of the archive also includes a DICOM compliant viewer capable of retrieval and display of both digitally acquired and scanned film images. The viewing package includes the ability to pan and zoom as well as window/level the images for enhanced viewing and review purposes. There is a separate remote client image acquisition package that will be installed at the institution with connections to both the internal DICOM network as well as to the Web for purposes of image transmission. This software is Windows XP compatible and is set up on a PC that then becomes a node on the DICOM network. When images are “pushed” by the modality to this workstation the technician will be notified that there are received images ready for forwarding to the central archive in our Philadelphia office. Using the client software the technician will identify the study and case number whereupon the software will automatically scrub the DICOM image file headers of all identifying information and replace selected tags with study and case ID. The images are then encrypted and transmitted to the secure FTP site in Philadelphia. Once received the central management software will automatically import the images through the firewall into the permanent database and image archive. The images may then be made available for review either through web based retrieval or via media for review and other approved research activities.

The following includes detail on the Server and RAID configurations typically used throughout the ACR for all projects as exemplified here with our clinical server configuration.

Server Setup:

Reliable-Fault-Tolerant Configuration

Mirror Set

The boot and the system partition are mirrored to significantly reduce the amount of time needed to get the Windows NT Server back up if there is a problem with the hard disk containing the operating system. The mirrored disks are identical to the original disk in size, number of tracks, and cylinders.

RAID

The Database resides on a Redundant Array of Independent Disks (RAID) system. RAID is a method of combining several disk drives into a single logical storage unit. RAID provides real-time data recovery when a disk drive fails, increasing system uptime and network availability. RAID also increases system performance when multiple drives work together.

RAID level 5 distributes parity information among each drive in the array in such a way that the data can be reconstructed on the fly in the event of a drive failure without bringing the server down.

Clustering Server:

The Cluster Services in each node of a cluster are in constant communication with each other. Services in a Windows XP cluster are exposed as *virtual servers*. Client Workstations believe they are connecting with a physical system, but are in fact, connecting to a service, which is provided by either Clinical_Server (Production) or the Clinical_Backup. Clients create a TCP/IP session with a service in the cluster using a known IP address. This address appears to the cluster software as a resource in the same group as the application providing the service. In the event the Production Server fails the cluster service moves the entire group to another system. This provides higher availability of the service. Clinical Application uses transactions to guarantee that the client request has been committed to the server database to gain fault tolerant semantics.

APPENDIX XII

(11/16/09)

**GOG-0233/ACRIN 6671 RESPONSIBILITIES AND ROLES FOR REPORTING
OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS**

Adverse Event Reporting – Serious and Non-Serious Assessed at the Time of Study Procedure(s) or Reported by Study Participant to ACRIN RA and/or GOG Data Manager

ACRIN RA Responsibilities:

Non-Serious Imaging AE – Routine Reporting

1. Document the report of or the assessment of the AE in the participant's study chart/file;
2. Have the PI evaluate the AE to determine grade and attribution, as well as expected or unexpected;
3. Determine the regulatory reporting requirements for the imaging AE (see Sections 16.8 – Table 5 and 16.8.2);(11/16/09)
4. Complete the AE form with all the information reported or assessed;
5. Have the PI sign and date the AE form;
6. Submit the completed AE form to the GOG data manager for data entry and submission into the clinical database.

Serious Imaging AE – Routine and Expedited Reporting

1. Document the report of or the assessment of the AE in the participant's study chart/file;
2. Have the PI evaluate the AE to determine grade and attribution, as well as expected or unexpected;
3. Complete the AE form and paper template of AdEERS with all the information reported or assessed;
4. Have the PI sign and date the AE form and paper template of AdEERS;
5. Submit the completed AE form to the GOG data manager for data entry and submission into the clinical database and the electronic AdEERS.

GOG Data Manager Responsibilities:

Non-Serious Imaging AE – Routine Reporting

1. Review the documentation and completed AE form for the imaging AE forwarded by ACRIN RA to ensure forms are completed;
2. Data enter and submit the AE into the clinical database.

(11/16/09)

Serious Imaging AE – Routine and Expedited Reporting

1. Review the documentation and completed AE form and paper template of AdEERS (see Sections 16.8 – Table 5 and 16.8.2) for the imaging AE forwarded by the ACRIN RA to ensure forms are completed;(11/16/09)

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2. Data enter and submit the AE form into the clinical database and the AdEERS information into the electronic AdEERS within the specified regulatory reporting timeframe.

Non-Serious Surgical AE – Routine Reporting

1. Document the report of or the assessment of the AE in the participant's study chart/file;
2. Have the PI evaluate the AE to determine grade and attribution, as well as expected or unexpected;
3. Determine the regulatory reporting requirements for the surgical AE (see Sections **16.8** – Table 5 and **16.8.2**);(11/16/09)
4. Complete the AE form with all the information reported or assessed;
5. Have the PI sign and date the AE form and the paper template of AdEERS;
6. Data enter and submit the AE information into the clinical database.

Serious Surgical AE – Routine & Expedited Reporting

1. Document the report of or the assessment of the AE in the participant's study chart/file;
2. Have the PI evaluate the AE to determine grade and attribution, as well as expected or unexpected;
3. Complete the AE form and paper template of AdEERS with all the information reported or assessed;
4. Have the PI sign and date the AE form and paper template of AdEERS;
5. Data enter and submit the AE information into the clinical database and the electronic AdEERS.