UTILITY OF PREOPERATIVE FDG-PET/CT AND FERUMOXTRAN-10 MRI SCANNING PRIOR TO PRIMARY CHEMORADIATION THERAPY TO DETECT RETROPERITONEAL LYMPH NODE METASTASIS IN PATIENTS WITH LOCOREGIONALLY ADVANCED (IB2, IIA ≥4 CM, IIB-IVA) CARCINOMA OF THE CERVIX

Agent Name: Ferumoxtran-10
Agent NSC Number: NSC 731411
IND number of the NCI-supplied agent: IND 70,900
Percapita Points: 15 Points
Membership Points: 3 Points

PARTIAL PROTOCOL—CONTACT ACRIN PROTOCOL DEVELOPMENT AND REGULATORY COMPLIANCE FOR A COMPLETE PROTOCOL

GOG-0233/ACRIN 6671

ACRIN Study Chair
Mostafa Atri, M.D., Dip., Epid
NCSB 1C569 Toronto General Hospital
Department of Medical Imaging
University Health Network
585 University Avenue
Toronto, ON Canada M5G 2N2
Tel: (416) 340-4800 x3255
Fax: (416) 480-5855
E-mail: mostafa.atri@uhn.on.ca

ACRIN Co-Chair
Farrokh Dehdashti, M.D.
Division of Nuclear Medicine
Mallinckrodt Institute of Radiology
510 S. Kingshighway Blvd.
St. Louis, MO 63110
Tel: 314-362-1474
Fax: (314) 362-5428
E-mail: dehdashtif@mir.wustl.edu

ACRIN Statistician
Suddhasatta Acharyya, Ph.D.
Center for Statistical Sciences
Brown University, Box G-S121
121 South Main Street, 7th Floor
Providence, RI 02912
Tel: (401) 863-9873
Fax: (401) 863-9182
E-mail: acharyya@stat.brown.edu

GOG Study Chair
Michael Gold, M.D.
Univ. of Oklahoma Health Sciences Center
OB/GYN, P.O. Box 26901, Oncology
Williams Pavilion-Room WP-2470
Oklahoma City, OK 73190
Tel: (405) 271-8707
Fax: (405) 271-2976
E-mail: michael-gold@ouhsc.edu

ACRIN Pathologist
Shahla Masood, M.D.
University of Florida
Department of Pathology
655 West 8th Street
Jacksonville, FL 32209
Tel: (904) 244-3487
Fax: (716) 845-8393
E-mail: shahla.masood@jax.ufl.edu

GOG Co-Chair
Wui-Jin Koh, M.D.
Fred Hutchinson Cancer Research Center
Puget Sound Oncology, Consortium, E-613
1100 Fairview Ave. N., P.O. Box 19024
22 S. Greene Street
Seattle, WA 98109
Tel: (206) 598-4115
Fax: (206) 667-4695
E-mail: wkoh@u.washington.edu

GOG Pathologist
William H. Rodgers, M.D., Ph.D.
University of Maryland Medical System
Professor and Director of Anatomic Pathology
Department of Pathology
Baltimore, MD 21201
Tel: (410) 328-5555
Fax: (410) 328-5508
E-mail: WRodgers@som.umaryland.edu

GOG Statistician
Shamshad Ali, M.S.
GOG Statistical & Data Center
Roswell Park Cancer Inst.
Elm & Carlton Streets
Buffalo, NY 14263-0001
Tel: (716) 845-5702
Fax: (716) 845-8393
E-mail: ali@gogstats.org
This protocol was designed and developed by the American College of Radiology Imaging Network (ACRIN) and Gynecologic Oncology Group (GOG). It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by ACRIN and GOG, nor does ACRIN and GOG assume any responsibility for unauthorized use of this protocol.
# Table of Contents

1.0 Abstract .................................................................................................................................7
2.0 Background and Significance .................................................................................................7
3.0 Specific Aims/Objectives .........................................................................................................12
4.0 Study Overview .......................................................................................................................13
5.0 Participant Selection ...............................................................................................................13
6.0 Site Selection ..........................................................................................................................16
7.0 Online Registration System ..................................................................................................17
8.0 Surgical Treatment and PET/CT Scan Evaluation .................................................................17
9.0 Study Procedures ....................................................................................................................23
10.0 Data Collection and Management .......................................................................................28
11.0 Data Collection Forms .........................................................................................................31
12.0 Image Procedures ..................................................................................................................32
13.0 Drug Information ...................................................................................................................39
14.0 Clinical Staging and Lymphatic Evaluation .........................................................................45
15.0 Pathology Information .........................................................................................................46
16.0 Adverse Events Reporting ....................................................................................................46
17.0 Ethical Considerations ..........................................................................................................59
18.0 Conflict of Interest ...............................................................................................................59
19.0 Publication Policy .................................................................................................................60
20.0 Institutional Audits ...............................................................................................................60
21.0 Statistical Considerations REMOVED FROM WEB VERSION ........................................62

References .....................................................................................................................................68

Appendix I: FIGO Guidelines ....................................................................................................74
Appendix II: Sample Informed Consent Form ................................................................. 76
Appendix III: Participating Institutions ........................................................................ 88
Appendix IV: Extraperitoneal Lymphadenectomy ............................................................. 89
Appendix V: Laparoscopic Pelvic and Abdominal Lymphadenectomy ............................... 91
Appendix VI: Guidelines for Laparoscopic Surgery .......................................................... 93
Appendix VII: Credentialing Procedures for PET/CT Imaging for this Study .................... 95
Appendix VIII: Ferumoxtran-10 Dosing Chart (Dose 2.6 mg Fe/kg) ................................ 96
Appendix IX: Sample Data Collection Sheets .................................................................. 97
Appendix X: PET/CT Imaging Quality Control Standards ................................................. 103
Appendix XI: MRI Technique Chart .................................................................................. 105
Appendix XII: Database Archiving ................................................................................... 107
Appendix XIII: Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA) ................................................................. 109
Appendix XIV: Responsibilities and Roles for Reporting of Adverse Events .................... 110
Locoregionally advanced, histologically confirmed invasive cervical cancer (Stages IB2, IIA ≥4 cm, IIB-IVA)

Pre-operative ferumoxtran-10 MRI\(^1\) (One MRI will be performed 24 - 36 hours after injection of ferumoxtran-10) and PET/CT Scan of the abdomen and pelvis and chest

No evidence of disease outside of the pelvis or abdominal nodal region amenable to biopsy or sampling (i.e. intrahepatic, pulmonary, or thoracic or supraclavicular lymphadenopathy on PET/CT)

Evidence of disease outside of the pelvis or abdominal nodal region amenable to biopsy or sampling (i.e. intrahepatic, pulmonary, or thoracic or supraclavicular lymphadenopathy on PET/CT)

Extra-peritoneal or laparoscopic abdominal & pelvic lymph node sampling

Biopsy of metastatic disease outside of the pelvis or abdominal nodal region by FNA, core biopsy, or surgical biopsy

Chemoradiation Therapy protocol to start within four weeks of enrollment into the study

Chemotherapy Protocol for Advanced / Recurrent Disease

\(^1\)On day 1, just prior to receiving ferumoxtran-10, a subgroup of 40 consenting patients will have the option to undergo a pre-ferumoxtran-10 MRI in addition to the post-ferumoxtran-10 protocol. Please refer to section 2.3 for more details.
CONFIDENTIAL

SPECIFIC AIMS/OBJECTIVES
The primary aim of this study is to define the utility of preoperative FDG-PET/CT and ferumoxtran-10 MRI scanning prior to primary chemoradiation therapy to detect retroperitoneal lymph node metastasis in patients with locoregionally advanced carcinoma of the cervix. The optional arm to the study will explore the use of a pre-ferumoxtran-10 MRI with parameters similar to post ferumoxtran-10 MRI to validate that Combidex does not change the size of lymph nodes on Combidex insensitive sequences.

METHODS/METHODOLOGY
In this study, 325 women will be enrolled. Enrollment will take place in at least 10 sites and is expected to be completed within 36 months from protocol activation. About 30-38 positive cases will have been enrolled by the end of the 20th month of the study. This will be the timing for the performance of the interim analysis. In the optional arm of the study, forty of the 325 patients who consent to undergo 2 MRI (one pre-ferumoxtran-10, and one post-ferumoxtran-10) will provide a cohort of MRI examinations in order to validate the similarity of nodal size in pre and post-ferumoxtran-10 MR images. The analysis for the optional arm is mainly exploratory.

ELIGIBILITY (see Section 5.0 for details)
1. Patients must have primary, previously untreated, histologically confirmed, locoregionally advanced invasive carcinoma of the cervix or 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. Normal organ function is required within specified parameters (see section 5.1.4 for details).
4. Patients of child-bearing potential must have a negative urine or serum pregnancy test result within 7 days prior to undergoing PET/CT and ferumoxtran-10 MRI. In addition, they would undergo a urine pregnancy test on the day of PET/CT examination. Combidex is injected 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 to be of child-bearing potential.
5. Patients must sign an 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. There can be no 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 a pelvic or abdominal lymphadenectomy performed.
10. There can be no evidence of prior pelvic radiation therapy for any reason.
11. Any outside circumstances that interfere with the completion of the imaging studies or required follow-up are not permitted.

REQUIRED SAMPLE SIZE
A total of 325 participants will be enrolled into the study. For the optional arm of the study, 40 of these participants will be enrolled in the study.

GOG-0233/ACRIN 6671 6 August 16, 2007
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.

In the United States, cervix cancer is the third most common gynecologic malignancy, with approximately 15,000 new cases and 5,000 deaths annually. Primary radiotherapy (RT) fails to control locoregional disease in 20-85% of patients with locally advanced carcinoma. 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.

More recently, FDG-PET imaging has demonstrated its utility in detecting nodal involvement in a few small series in cervical cancer. The sensitivity and specificity of MRI for detection of malignant lymphadenopathy has shown to improve by using superparamagnetic iron oxide nanoparticles. Ferumoxtran-10 (also know as Combidx®, Sinerem®, AMI_227), an ultra-small particle iron oxide (USPIO) agent, is the most widely investigated contrast medium in clinical trials. It has been used in a number of malignancies, including breast, lung, head, neck, abdominal, and pelvic malignancies. Results are favorable when compared to MRI without an iron oxide agent. However, there has been no published trial on the use of ferumoxtran-10 in cervical cancer. There have been no significant adverse reactions reported in the literature in a number of Phase II-III clinical trials on ferumoxtran-10 and other iron oxide agents, but some serious allergic events have been recorded and are shown in the drug brochure. The safety profile for ferumoxtran-10 is similar to iodine contrast agents.

The diagnostic sensitivity and specificity of the currently performed imaging modalities has been less than optimal in the evaluation of lymph node metastasis from cervical cancer. The preliminary results of FDG-PET and ferumoxtran-10 MRI for detection of lymph node metastasis in this cohort have been encouraging. The primary objective of this study is to evaluate the diagnostic sensitivity and specificity of FDG-PET/CT and ferumoxtran-10 (Combidx) MRI imaging in identifying metastases to abdominal (common iliac, para-aortic, and para-caval) lymph nodes in patients with cervical carcinoma who are to undergo chemoradiation therapy (stages IB2, IIA ≥4 CM, IIB-IVA). Three-hundred twenty-five patients 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 by laparoscopic or retroperitoneal lymphadenectomy. The diagnostic sensitivity and specificity of these two modalities will be evaluated in a central reader study including seven (7) expert readers. Moreover, the inter-observer agreement between the readers will be assessed. Accrual for this protocol is expected to be reached within 36 months. The optional arm to this study will validate the similarity of nodal size in pre and post-ferumoxtran-10 MR images. A subset of patients will have the option of participating in this optional arm and will undergo a pre-ferumoxtran-10 MRI. For more information on this optional arm, please refer to section 2.3 of the protocol.

2.0 BACKGROUND AND SIGNIFICANCE
Cancer of the uterine cervix is the second most common cancer in females, representing 15% of all female cancers, 80% of which is diagnosed in underdeveloped countries (1). In the United States, cervical cancer is the third most common gynecologic malignancy, with approximately 11,000 new
cases and 3,700 deaths annually (2). Though incidence and mortality in the United States dropped steadily from 1940 through 1990, there has recently been a plateau, arresting the decline (1, 3). The vast majority of cases are diagnosed with early-stage disease, but some with locally advanced disease require radiation therapy (60). Unfortunately, primary radiotherapy (RT) fails to control locoregional disease in 20–85% of patients with locally advanced carcinoma, depending on stage, tumor bulk, and nodal status (30, 39, 48, 59, 65).

One reason for the high failure rate may be that cervical cancer remains the only major gynecologic malignancy that is clinically staged (44). When compared with surgical findings, clinical staging is accurate in only 60% of cases (9, 10). A recent study by ACRIN/GOG cooperative group (31) 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 (5, 31). In many instances, errors in staging are related to undiagnosed lymph node metastases (9, 10). It is commonly accepted that patients with lymph node metastases have lower overall survival, disease-free survival, and survival after recurrence (5, 31, 38). Although not permitted to alter FIGO staging (12), 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 (14). 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 (55).

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 patients were evaluated with PET, CT, and US prior to undergoing complete lymphadenectomy (15). 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%, 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 (24). 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” (4).

Several reports have also demonstrated the utility of FDG-PET imaging in the diagnosis of lymph node metastases from cervical carcinoma. Rose et al. (52) pre-operatively evaluated 32 patients with IIB–IVA cervical cancer with no evidence of extra-pelvic disease. Fluorodeoxyglucose was taken up by 91% of the cervical tumors and accurately diagnosed six of eight patients 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. (62) correctly identified six of seven (86%) patients with known lymph node metastases using PET, compared to only four with CT. Reinhardt et al. (50) compared the diagnostic accuracy of MRI with that of PET in a group of 35 patients with stage IB and II cervical cancer. Eleven patients 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 MR imaging were
73%, 83%, 67%, 87%, and 80%. A recent analysis of 15 published PET studies in cervical cancer by Havrilesky et al. 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) (28). In this review, the pooled sensitivity of FDG-PET for para-aortic lymph nodes are 84% (95% CI 68%-94%) and 95% (89%-98%), respectively (the pooled sensitivity and specificity for CT or MRI are not available).

There is limited data available on the utility of PET/CT on the evaluation of lymph node metastases in cervical cancer. Sironi et al. studied 47 patients with cervical cancer. Fifteen patients had metastatic lymph nodes at histopathologic examination, and 32 had no histopathologically confirmed nodal metastasis (58). 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 compared PET with PET/CT. However, in various types of cancers, this comparison has been made and demonstrated improvement of PET performance when fused PET/CT images were used (68). For example in a study of 260 patients with various types of cancer, 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 (6). Thus, an improvement of approximately 10% in the performance of PET is expected when PET/CT is used.

While to date, no study is available in cervical cancer that compared PET/CT with MRI in the detection of metastatic lymph nodes, limited comparison studies are available for these two modalities in other types of cancers. For example, in a study of 98 patients with various types of cancers, Antoch et al. compared whole-body PET/CT to whole-body MRI and demonstrated that for detection of lymph node metastasis, FDG-PET/CT had sensitivity and specificity of 95% and 92%, respectively and whole-body MRI had sensitivity and specificity of 79% and 78%, respectively (7). To date, there are no comparison studies for FDG-PET/CT and MRI using USPIO.

### 2.1 Ferumoxtran-10 MRI

The sensitivity and specificity of MRI for detection of malignant lymphadenopathy can be improved by using ferumoxtran-10 nanoparticles (61, 70). These nanoparticles have a monocrystalline, inverse spinel, and superparamagnetic iron oxide core. Furthermore, they contain a dense packing of dextran to prolong their time in circulation and are avidly taken up by lymph nodes in animals (43). Ferumoxtran-10, an ultra-small particle iron oxide (USPIO) agent, is the most widely investigated contrast medium in clinical trials. It has been used in a number of malignancies, including breast (43, 47), lung (47), head and neck (42, 57), and abdominal and pelvic malignancies (26). Results are favorable when compared to MRI without ferumoxtran-10. In a recent study by Harisinghani et al. (25) correlating lymph nodes removed at surgery with ferumoxtran-10 MRI in 80 patients with prostate cancer, MRI showed a per patient sensitivity of 100% and specificity of 96%. Per node sensitivity was 90.5% and specificity was 97.8%. Literature review of efficacy of ferumoxtran-10 in abdominal and pelvic malignancies is summarized in Table 1.

In a recent study, Rockall et al. (51) evaluated 44 women with endometrial (n=15) and cervical (n=29) cancer with ferumoxtran-10 prior to lymphadenectomy. Ferumoxtran-10 MRIs were
reviewed by two radiologists. The per patient sensitivity and specificity of pre-USPIO MRI based on size criteria (short axis/long axis > 0.8) were 27% and 94%. This is compared to sensitivity and specificity of ferumoxtran-10 criteria of 100%/91% and 94%/87% respectively for Reviewers #1 and #2. The sensitivity values of ferumoxtran-10 MRI was significantly higher than size criteria for one reviewer (p = 0.031) and showed a trend in the other reviewer (p = 0.06) without compromise of specificity.

There have been no significant adverse reactions reported in a number of Phase II-III clinical trials on ferumoxtran-10 and other iron oxide agents (8, 40, 41, 56, 64), but some serious allergic events have been recorded and are shown in the drug brochure. The safety profile for ferumoxtran-10 is similar to iodine contrast agents.

Table 1: Efficacy of Ferumoxtran-10 in Abdominal and Pelvic Malignancy

<table>
<thead>
<tr>
<th>Number of patients (nodes)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>80* (334)</td>
<td>100</td>
<td>96</td>
<td>25</td>
</tr>
<tr>
<td>50 (64*)</td>
<td>82</td>
<td>94</td>
<td>8</td>
</tr>
<tr>
<td>63 (34*)</td>
<td>86</td>
<td>80</td>
<td>63</td>
</tr>
<tr>
<td>30 (60*)</td>
<td>100</td>
<td>80</td>
<td>11</td>
</tr>
<tr>
<td>58 (172*)</td>
<td>95</td>
<td>96</td>
<td>18</td>
</tr>
<tr>
<td>AVERAGE</td>
<td>92.6</td>
<td>89.2</td>
<td></td>
</tr>
</tbody>
</table>

* indicates node vs. patient analysis

2.2 Surgical Staging

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 (22, 26). Recent evidence suggests a survival advantage both in patients with para-aortic lymph node metastases who receive radiation (14, 49) and in patients who receive prophylactic para-aortic radiation, despite having negative or unevaluated para-aortic lymph nodes (53). 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 (21, 71).

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 (34, 35). 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 (36, 37). 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) (20, 69, 71).

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) (19). 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 (17). In addition to surgical debulking, Goff et al. (23) 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 (20, 37, 45, 67).

PET/CT and ferumoxtran-10 MRI are thought to have a higher sensitivity and specificity to detect retroperitoneal lymph node metastasis as compared to the current cross-sectional imaging modalities.

The study will primarily focus on two critical areas. It is important 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 patients with locoregionally advanced cervical carcinoma. Furthermore, emphasis will also be placed on evaluating the diagnostic sensitivity and specificity of preoperative ferumoxtran-10 MRI scan in identifying metastases to abdominal (common iliac, para-aortic and para-caval) lymph nodes in patients with locoregionally advanced cervical carcinoma.

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 comparison of sensitivity and specificity of the two modalities (not addressed in the primary aims), the analysis of the original scan interpretations performed at the participating sites, and the analysis of data on complications from surgery and imaging.

2.3 Validation of the Similarity of Nodal Size in Pre and Post-Ferumoxtran-10 T2-Weighted MR Images

The optional arm to ACRIN 6671 will explore the use of a pre-ferumoxtran-10 MRI with parameters similar to post ferumoxtran-10 MRI to validate that Combidex does not change the size of lymph nodes. In 40 consenting subjects at willing and IRB approved sites, we will perform both examinations and compare the number and size of lymph nodes visualized on similar MRI sequences. On day 1, just prior to receiving ferumoxtran-10, the subject will undergo the same MR imaging as planned for all subjects in the post-ferumoxtran-10 protocol. Subsequently, 3 blinded readers will compare the same MRI sets collected before and after ferumoxtran-10 independently and at two different times. This will be performed in a central reader study. One of the readers marks the nodes to be measured. After each review, the measurement will be locked. The reviewers will not be aware of the first measurement at the time of the second measurement. For all nodes > 5mm identified on both sets, the reader will determine the smallest axis diameter. Statistical analysis will be performed on the resulting “same node” sets, estimated to number about 400 pairs of nodes, to determine if there is a significant difference greater than 0.5 mm between the pre and post-ferumoxtran-10 nodal measurement.
3.0 SPECIFIC AIMS/OBJECTIVES

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 patients with locoregionally advanced cervical carcinoma.

3.1.2 To evaluate the diagnostic sensitivity and specificity of preoperative ferumoxtran-10 (Combidex) MRI scanning in identifying metastases to abdominal (common iliac, para-aortic, and para-caval) lymph nodes in patients with locoregionally advanced cervical carcinoma.

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 patients with locoregionally advanced cervical carcinoma.

3.2.2 To compare the diagnostic sensitivity and specificity of preoperative ferumoxtran-10 MRI scanning in identifying metastases to pelvic lymph nodes (obturator, external iliac) and pelvic and abdominal lymph nodes combined in patients with locoregionally advanced cervical carcinoma.

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 locoregionally advanced cervical carcinoma.

3.2.4 To compare the diagnostic sensitivity and specificity of PET/CT scanning to preoperative ferumoxtran-10 MRI scanning 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 locoregionally advanced cervical carcinoma.

3.2.5 To compare the diagnostic sensitivity and specificity of Combidex MRI with MRI based on size criteria in the abdomen and pelvis.

3.2.6 To determine the percentage of patients with locoregionally advanced cervical cancer that have biopsy proven disease outside abdominal or pelvic lymph nodes detected by PET/CT.

3.2.7 To determine the complications associated with extra-peritoneal or laparoscopic abdominal and pelvic lymphadenectomy including delay in the initiation of radiation therapy or interruption in radiation therapy in patients with cervical carcinoma.
**3.2.8** To collect data on the adverse effects of the ferumoxtran-10 agent.

**3.2.9** Compare the size of lymph nodes on pre and post Combidex MRIs in a subset of 40 patients.

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, and 3.2.4 will be evaluated primarily through central reader studies that also address inter-observer variability in diagnostic sensitivity and specificity. In addition, evaluations will be made of objectives 3.1.1, 3.1.2, 3.2.1, and 3.2.2 by blinded independent reading of PET/CT and ferumoxtran-10 MRI of patients accrued in each center by two different institutional PI radiologists at the same center.

**4.0 STUDY OVERVIEW**

A total of 325 women will be enrolled in this study from at least 10 sites. Eligible participants are women who have met the pre-entry requirements specified in the Eligibility Criteria section of the protocol. Participants must be accrued at GOG member institutions or affiliates who are also accredited by ACRIN. Enrollment is expected to be completed within 36 months from protocol activation. Forty of the 325 patients who consent to undergo 2 MRIs (one pre-ferumoxtran-10, and one post-ferumoxtran-10) will provide a cohort of MRI examinations in order to validate the similarity of nodal size in pre and post-ferumoxtranumoxran-10 MR images.

Assuming that approximately 20-25% of the enrolled women will actually have positive abdominal nodes, the expected number of women with positive nodes in the abdomen in the study sample is between 60 and 75. After a study initiation period of 6 months, a uniform rate of accrual over the duration of the study is expected, with steady rates of positive and negative cases. Thus, about 30-38 positive cases will have been enrolled by the end of the 20th month of the study. This will be the timing for the performance of the interim analysis.

**5.0 PARTICIPANT SELECTION**

**5.1 Inclusion Criteria**

**5.1.1** Patients must have primary, previously untreated, histologically confirmed, locoregionally advanced (IB2, IIA ≥4cm, IIB-IVA) invasive carcinoma of the cervix (any cell type).

**5.1.2** Patients must be appropriate surgical candidates to undergo extra-peritoneal or laparoscopic lymph node sampling.

**5.1.3** GOG performance status of 0, 1, or 2.

**5.1.4** Patients must have normal organ and marrow function as defined below:

- Leukocytes ≥3,000/μL
- Absolute neutrophil count ≥1,500/μL
- Platelets ≥100,000/μL
- Total bilirubin within normal institutional limits
The text is too long to be displayed in full. It contains details about medical conditions and criteria for patient inclusion and exclusion. The text is primarily in English and includes bullet points outlining various medical conditions and criteria. The document appears to be a medical report or guideline, possibly related to patient care or medical research. The page is marked as 'CONFIDENTIAL' at the top.
5.2.13 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.

5.2.14 Any contraindication to the performance of MRI (i.e., severe claustrophobia, pacemaker, aneurysm clips, defibrillators, or other institutional contraindication to MRI).

5.2.15 Patients having a history of allergic reactions attributed to compounds of chemical or biologic composition similar to ferumoxtran-10 (i.e., iron preparations, parenteral iron, parenteral dextran, parenteral iron-dextran, or parenteral iron-polysaccharide preparations).

5.2.16 Patients with immunodeficiencies that predispose a participant to specific or nonspecific mediator release.

5.2.17 Patients who have received ferumoxides within 2 weeks of enrollment.

5.2.18 Patients with pre-study ferritin levels greater than 600 ng/ml and percent saturation of transferrin level greater than 50%. However, patients with laboratory values above these limits may be included in the study if documented hematology consultation rules out iron overload. Patients with increased iron-levels in their blood are not included in the protocol. This is done to avoid adding to their iron overload.

5.2.19 Patients with a history of cirrhosis.

5.2.20 Patients receiving any other investigational agents within a 30-day period.

5.2.21 Patients with poorly controlled, insulin-dependent diabetes (fasting blood glucose level >200 mg/dL).

5.3 Recruitment and Screening

Potential study participants will be seen by a GOG investigator as part of their standard care for their cervical 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. A subset of patients (40 total) can elect to participate in the optional arm of the protocol. Detailed information on this optional arm is found in section 2.3 of the protocol. More information about study participant enrollment is available on the GOG and ACRIN websites.

Investigators who wish to participate in the trial are required to complete an ACRIN Protocol Specific Application (PSA) found on the ACRIN web site (www.acrin.org/6671_protocol.html). 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.
5.4 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 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

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Sex</th>
<th>Females</th>
<th>Males</th>
<th>Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic or Latino</td>
<td></td>
<td>40</td>
<td>N/A</td>
<td>N/A</td>
<td>40</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td></td>
<td>285</td>
<td>N/A</td>
<td>N/A</td>
<td>285</td>
</tr>
<tr>
<td>Ethnic Category: Total of all patients</td>
<td></td>
<td>325</td>
<td>N/A</td>
<td>N/A</td>
<td>325</td>
</tr>
<tr>
<td>Racial Category</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
<td></td>
<td>3</td>
<td>N/A</td>
<td>N/A</td>
<td>3</td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td>15</td>
<td>N/A</td>
<td>N/A</td>
<td>15</td>
</tr>
<tr>
<td>Black or African American</td>
<td></td>
<td>90</td>
<td>N/A</td>
<td>N/A</td>
<td>89</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td></td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td></td>
<td>217</td>
<td>N/A</td>
<td>N/A</td>
<td>215</td>
</tr>
<tr>
<td>Racial Category: Total of all patients</td>
<td></td>
<td>325</td>
<td>N/A</td>
<td>N/A</td>
<td>325</td>
</tr>
</tbody>
</table>

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 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.

**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. The informed consent form is included in this
protocol as Appendix II. 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 form
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.

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 form to the GOG Regulatory Office (ATTN: Shawn Griffin,
email: sgriffin@gog.org; fax: 215-854-0716). 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 or by phone (800-523-2917). 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.

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. Participant’s will be registered at GOG only. ACRIN will be notified of
each registration after GOG completes the registration process.

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, pulmonary, or thoracic or supraclavicular
lymphadenopathy) on PET/CT needs to be pathologically evaluated prior to
performance of the pelvic and abdominal lymph node sampling. If surgical approach
is required, this may be performed at 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.

- 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.

- The participant will remain in the study 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 that this differs from the standard GOG definitions.**

- **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

8.3.1 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.
- It is inappropriate to convert to a trans-peritoneal approach for the sake of removing lymph nodes.

8.3.2 Laparoscopic Lymphadenectomy

8.3.2.1 Technical Difficulty

- 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.

8.3.2.2 Unresectable Lymph Nodes

- 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.
- Finally, if an overtly suspect lymph node is encountered during a laparoscopic approach, conversion to an extra-peritoneal lymphadenectomy in order to completely remove the lymph node may be performed at the surgeon’s discretion.
8.3.2.3 Retroperitoneal Fibrosis

- In the event of an inability to develop the retroperitoneal spaces (i.e., retroperitoneal fibrosis or adhesions), the procedure should be terminated.
- If, 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.
- Every reasonable attempt should be made to perform a biopsy of any available lymph nodes. Trans-peritoneal lymph node sampling will not be performed.

8.3.3 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, 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.

- This will also be documented on the Pelvic and Abdominal Lymphadenectomy form.
- 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 cancer (i.e. axillary lymph nodes) should not be considered as requiring biopsy as per the protocol. 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.
8.4.2 Once metastatic disease is biopsy proven, the lymphadenectomy is to be abandoned and clearly documented on the Pelvic and Abdominal Lymphadenectomy form.

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.

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 the schema for surgical evaluation and for pathologic evaluation.

8.5.2 All PET/CT and ferumoxtran-10 MRI scans will be required to undergo centralized/decentralized review to be organized by ACRIN (See Section 12.2.5 for instructions on submitting images to ACRIN). The central reading for PET/CT will be conducted at the ACRIN headquarters (Philadelphia, PA). The central reading for MRI will be conducted either at ACRIN or at the expert readers’ institutions. There are a limited number of ferumoxtran-10 MRI readers and these readers are located mainly in Europe since the agent is not yet approved in North America. The central readers will be chosen from Europe or North America. The expert readers for ferumoxtran-10 MRI could be from the accruing institutions as long as they are not involved in the institutional reviews. All readers will be provided with the same interactive tool to review the cases.

8.5.2.1 Suspicious lymphadenopathy on PET/CT and ferumoxtran-10 MRI scanning 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. MRI review will start with evaluation of iron insensitive T1W sequences to determine normality/abnormality of LNs based on size criteria. After this information is entered in a locked box, iron sensitive sequences will be evaluated in conjunction with iron insensitive sequences. It has been shown in a phase II study that
Combidx does not affect the signal intensity of LNs on T1W sequence but drops the signal on T2W and T2* sequences (31). The same study shows that the effect of iron on the size of LN on T2W and T2* is negligible. Overall, lymph node size changed only minimally (mean, ≤0.3 mm) from before the dose to after the dose (31). In the absence of signal intensity change in the LNs on T1W sequence, there is no reason for the size of LNs to be different on T1W sequence on the post Combidx MRI.

8.5.2.2 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 characterized lymph node based on size). 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 (µCi/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 cancer, nodal and distant metastasis, and recorded on the data form. 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.

8.5.2.3 On MRI with ferumoxtran-10, lymph nodes are considered abnormal on T2*-weighted sequences if there are one or more discrete focal defects representing as foci of high signal intensity centrally or peripherally (excluding a fatty hilum), or if the node has diffuse high signal intensity. Lymph nodes are considered benign if their signal intensity relative to muscle low on T2*-weighted images and moderate or high on PD FSE images. Three-dimensional reconstructions of the relationship of the malignant or enlarged benign LNs to the adjacent vessels will be
prepared to help surgical identification of the LNs. The radiologists will provide a diagram to the surgeons identifying where there are positive lymph nodes since the MRI will be read before surgery.

8.5.3 All participants are expected to initiate chemoradiation therapy within 4 weeks of their enrollment in the study as outlined in Section 9.5. 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.

8.5.4 The result of the ferumoxtran-10 MRI will not affect the treatment plan because all participants will undergo standard lymphadenectomy unless PET/CT shows disease outside lymph nodes.

9.0 STUDY PROCEDURES

9.1 Patient Entry & Registration Visit
- Obtain prior medical history, including allergy history;
- Perform a physical examination;
- Perform a urine or serum pregnancy test;
- Obtain labs;
- Perform a chest X-ray;
- Conduct an echocardiogram (ECG);
- Determine if patient meets all eligibility requirements according to section 5.0;
- Obtain 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 such as MRI scans;
- 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: PET/CT and Ferumoxtran-10 Administration²-Within 7 days from Registration Visit
Visit 1 will occur within seven (7) days of the registration visit. Participants will undergo PET/CT scan as described in section 12.0;
- Conduct a urine pregnancy test;
- Perform the PET/CT with SUV calculation;

² On day 1, just prior to receiving ferumoxtran-10, subjects will have the option to undergo the same MR imaging as planned for all subjects in the post-ferumoxtran-10 protocol. Please refer to section 2.3 for more details.
• Administer the ferumoxtran-10 after the completion of PET/CT, but only if the MRI can be scheduled on the next day.

NOTE: If not scheduled on two consecutive days, participants may undergo ferumoxtran-10 MRI scans within one week of their PET/CT scan. Participants will return to receive ferumoxtran-10 later within one week of PET/CT. Ferumoxtan-10 must be administered within 24-36 hours before the MRI. In extreme circumstances, the MRI may be performed up to 48 hours after the completion of the intravenous administration of ferumoxtran-10. The institutions should provide explanation on why MRI was performed after 36 hours.

9.3 Visit 2: Ferumoxtran-10 MRI: 24-36 Hours after injection of Ferumoxtran-10
• Participants will return 24 – 36 hours after completion of receiving ferumoxtran-10 for an MRI examination as described in section 12.0.
• Perform an MRI scan;
• Assess for any study-related adverse event since Visit 1, especially in regards to ferumoxtran-10.

9.4 Visit 3: Within 2 Weeks after Visit 1
• 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.
• Assess for any study-related adverse event since Visit 2;
• Perform the lymph node sampling surgical procedure.

9.5 Visit 4: Within 4 Weeks from PET/CT Scan
• All participants are expected to initiate chemoradiation therapy within 4 weeks from PET/CT.
• Initiate the administration of the chemotherapy regimen.
• Assess for any study-related adverse events since Visit 3.

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.

9.6 Visit 5: Within 6 Weeks after Pelvic and Abdominal Lymph Node Sampling
• Perform a physical examination to monitor the effects of ferumoxtran-10 and all surgical procedures performed up to this time-point.
• Assess for any study-related adverse events since Visit 4.
9.7 **Visit 6: 6 Months after PET/CT Scan**
- 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.
- Assess for any study-related adverse events since Visit 5.

9.8 **Visit 7 - 14: Every 3 Months for 2 Years after PET/CT Scan-Per Standard of Care**
- Obtain routine blood tests;
- Perform physical examinations;
- Perform x-rays, per discretion of the investigator.
- Assess for any study related adverse events.

9.9 **Visit 15 - 20: Every 6 Months for 3 Additional Years after Visit 14 – Per Standard of Care**
- Obtain routine blood tests;
- Perform physical examinations;
- Perform x-rays, per discretion of the investigator.
- 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.
### 9.10 Study Procedures Timetable

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Registration Visit</th>
<th>Visit 1: Day of PET/CT-7 Days from Registration</th>
<th>Visit 2: Day of MRI (Within 24-36 Hours after Ferumoxtran-10 administration)</th>
<th>Visit 3: Within 2 weeks after Visit 1</th>
<th>Visit 4: Within 4 weeks from PET/CT Scan</th>
<th>Visit 5: Within 6 weeks after PET/CT Scan</th>
<th>Visit 6: 6 months after PET/CT Scan</th>
<th>Visit 7-14: Every 3 months for 2 Years after PET/CT scan</th>
<th>Visit 15-20: Every 6 months for 3 additional years after visit 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed Consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eligibility/Registration</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fast Fact Sheet</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History (including allergy history)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Examination</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test (urine or serum): 7 days prior to PET/CT and ferumoxtran-10 MRI</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC/Diff/platelets, Basic Metabolic Panel, Creatinine, Bilirubin, SGOT, SGPT, LDH, PT, PTT, Alk phos, Albumin, Calcium, Phosphorus, Serum Iron, Ferritin, % Saturation Transferrin, TIBC</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest X-ray (per investigator’s discretion)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET/CT examination</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferumoxtran-10 injection (after PET/CT scan)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferumoxtran-10 MRI Scan</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic and Abdominal Lymph Node Sampling</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemoradiation Therapy</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT of the area with initial positive PET/CT outside abdomen and no biopsy proof of disease</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Event Assessment</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

GOG-0233/ACRIN 6671 26 August 16, 2007
If it is not possible to perform ferumoxtran-10 MRI scan the day after PET/CT, participants will return to receive ferumoxtran-10 later within one week prior to PET/CT. Ferumoxtran-10 must be administered within 24-36 hours before the MRI.

In extreme circumstances, the MRI may be performed up to 48 hours after the completion of the intravenous administration of ferumoxtran-10. The institutions should provide explanation on why MRI was performed after 36 hours.

On day 1, just prior to receiving ferumoxtran-10, the subjects will have the option to undergo the same MR imaging as planned for all subjects in the post-ferumoxtran-10 protocol. Please refer to section 2.3 for more details.
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 by the Biostatistics and Data Management Center (BDMC) of ACRIN under the direction of Dr. Constantine Gatsonis. The Biostatistics Center (BC) is located at Center for Statistical Sciences at Brown University in Providence, RI, and the Data Management Center (DMC) is located at the American College of Radiology’s Data Management Department in Philadelphia.

10.1.3 Participant enrollment and data collection occurs through a series of programmed screens accessed through the ACRIN web site to register/randomize 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 is 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.

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 is 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 is 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.

10.4.2 If checks at DMC or BC detect missing or problematic data, the DMC RA sends a Request for Information (ZI 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 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**

The following forms must be completed for all participants and must be received in the GOG Statistical and Data Center in accordance with the schedule below. All forms except: F-form, Pathology report, and Operative report must be submitted via the SDC Electronic Data Entry System (SEDES), which is available through the GOG website (www.gogstats.org). Pathology material (F-form, pathology report and slides) should be submitted together via postal mail.

<table>
<thead>
<tr>
<th>Form*</th>
<th>Due Within</th>
<th>Copies*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form R (Registration Form)</td>
<td>2</td>
<td>Registration</td>
<td>1</td>
</tr>
<tr>
<td>Form OSC (Primary Cervical Cancer - On Study Form)</td>
<td>2</td>
<td>Registration</td>
<td>1</td>
</tr>
<tr>
<td>Form DR(Pre-treatment Summary Form)</td>
<td>4</td>
<td>Registration</td>
<td>1</td>
</tr>
<tr>
<td>Form C (Surgical Reporting Form)</td>
<td>6</td>
<td>Surgery</td>
<td>2</td>
</tr>
<tr>
<td>Operative report</td>
<td>6</td>
<td>Surgery</td>
<td>2</td>
</tr>
<tr>
<td>Primary disease: Form F (Pathology Form)</td>
<td>6</td>
<td>Surgery</td>
<td>1</td>
</tr>
<tr>
<td>Pathology Report</td>
<td>6</td>
<td>Surgery</td>
<td>2</td>
</tr>
<tr>
<td>Slides</td>
<td>6</td>
<td>Surgery</td>
<td>6</td>
</tr>
<tr>
<td>Form PAL (Pelvic and Abdominal Lymphadenectomy)</td>
<td>6</td>
<td>Surgery</td>
<td>2</td>
</tr>
<tr>
<td>Form PRLN (Pathology Review of Lymph Nodes)</td>
<td>12</td>
<td>Surgery</td>
<td>1</td>
</tr>
<tr>
<td>Form PSF (Post Surgery Follow-up)</td>
<td>4</td>
<td>6 week post operative follow-up visit</td>
<td>1</td>
</tr>
<tr>
<td>Form D2R (Cycle Dose Drug Form)</td>
<td>4</td>
<td>PET/CT</td>
<td>1</td>
</tr>
<tr>
<td>Form T (Common Toxicity Reporting Form)</td>
<td>4</td>
<td>PET/CT</td>
<td>1</td>
</tr>
<tr>
<td>Form T (Common Toxicity Reporting Form)</td>
<td>4</td>
<td>Discharge after pelvic and abdominal lymph node sampling</td>
<td>1</td>
</tr>
<tr>
<td>Form T (Common Toxicity Reporting Form)</td>
<td>4</td>
<td>6 week post operative follow-up visit</td>
<td>1</td>
</tr>
</tbody>
</table>
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.

* 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. For recurrent or persistent disease submit Form F, Pathology Report, and slides only if histologically documented.

** IMAGE PROCEDURES **

12.1 Combidex MRI

12.1.1 MRI Technique

MRIs will be performed at 1.5 T with pelvic phased-array coils. Images of the pelvis and abdomen, extending from completion of the pubic symphysis to the level of the IMA will be obtained 24-36 hours after completion of the intravenous administration of ferumoxtran-10. In extreme circumstances, the MRI may be performed up to 48 hours after the completion of the intravenous administration of ferumoxtran-10. The institutions should provide explanation on why the MRI was performed after 36 hours. Furthermore, a subset of patients will have the choice of participating in an optional arm to the protocol and will receive a pre-ferumoxtran-10 MRI. For more information on this optional arm, please refer to section 2.3 of the protocol.

The MR pulse sequences will consist of T1 GRE, FSE, and T2* GRE obtained in axial and obturator planes depending on the sequence. To better ensure image quality, the technical parameter charts will be distributed to the individual modalities to guarantee protocol compliance. The MRI scanning parameters can be found in Appendix XI.

12.1.2 Ferumoxtran-10 MRI Review at Imaging Institutions

We will obtain only a post Combidex MRI since it has been validated that trained reviewers would perform equally well reviewing post Combidex MRI and combined pre and post Combidex MRI (27).

Anatomical criteria will be used to identify metastatic lymph nodes. A single or multiple discrete focal defects representing as focus (foci) of high signal intensity centrally or peripherally (excluding a fatty hilum) on T2* GRE sequences is considered evidence of metastatic disease. The below figure shows a drawing of examples of positive and negative lymph nodes.
The presence, size, and involvement of lymph nodes in para-aortic, paracaval, common
and external iliac, and obturator lymph nodes corresponding to surgical dissections will
be determined and data forms will be completed. In addition, data will be collected on
the size of primary tumor and presence of extra-uterine involvement.

12.1.3 MRI Institutional Reviewers Training
Institutional reviewers will be trained at a central location at the outset of the study. The
institutional MRI PIs will receive a tutorial lecture first followed by review of 10-15
proven known cases. At the end they will go through a quiz of 10-15 complete set of
images of proven cases. All training cases will not be from this study.

12.2 PET/CT Imaging
Participants must undergo whole-body PET and CT imaging with a PET/CT unit. 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 approved by ACRIN before
participating in this protocol. Detailed information can be found on the ACRIN website
at http://www.acrin.org/6671_protocol.html under ACRIN Credentialing Procedures
for PET Imaging. PET Technical Assessment Form will be used to ensure protocol
compliance. The PET Technical Assessment Form can be found on the ACRIN Web site
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 cancer, 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. The most common reasons that result in a suboptimal study can be found in Form C2.

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:

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, 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 a minimum of 4 cups of water, if intravenous hydration is not possible (e.g., if it is difficult to establish intravenous access).

4. 3/4 of the oral contrast agent is given to the participant.

5. Approximately 1 hour (+/- 10 minutes) after FDG injection, diagnostic CT scan with contrast agents (oral and intravenous) will be performed. Patients must void prior to imaging. The remaining 1/4 of the oral contrast agent is given while the participant is on the scanner table immediately before administration of intravenous contrast agent for diagnostic CT imaging. Diagnostic CT of the chest, abdomen, and pelvis should be completed not later than 60 minutes after FDG injection. See below (section 12.2.1) for detailed information about CT acquisition.

6. PET emission scan will be performed.

Some centers may perform a second CT scan only for attenuation correction of the PET images. 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. 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.

### 12.2.1 CT Imaging

CT imaging will be done approximately 1 hour (+/- 10 minutes) after the FDG injection (see section 12.2.4) beginning in a craniocaudal direction with the participant’s upper neck. The CT scanning parameter can be found on the
ACRIN Web site under Current Protocols 6671: CT Technique chart (http://www.acrin.org/6671_protocol.html). 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.

**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 pounds, 175 mL Optiray 350 will be given at the rate of 3 mL/sec with an 85-sec delay in imaging.

**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; 450 mL (3/4 of the dose) will be ingested approximately 30 minutes prior to FDG injection (in order to reduce the risk of oropharyngeal muscle uptake) and the remaining 150 mL (the remaining 1/4 of the dose) will be ingested immediately before imaging.

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 1 L of tap water. A 600 mL dose is equal to 22.9 g of iodine.

### 12.2.2 PET Imaging

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.

12.2.3 Optional Diuretic Treatment:

**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.

12.2.4 PET Technique

Imaging will begin approximately 1 hour (+/- 10 minutes) after FDG injection (see above in the beginning of this section for the order of CT and PET imaging). 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.

After acquisition of CT data (see 12.2.1 for CT technique), 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. CT data will be used for attenuation correction of the PET data. 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.

12.2.5 Image Submission to ACRIN

All images collected from PET/CT, CT, and MRI are to be in digital format. All CT and MR images must be in the DICOM format. ACRIN has developed
software that allows for electronic transmission of images to the IMC that have been scrubbed of all participant identifiers. ACRIN will contact each site individually to determine their readiness and ability to utilize this system. For preliminary questions, contact Fraser Wilton at 613-692-2620 and/or fwilton@phila.acr.org. Once technical capabilities have been established, imaging personnel from ACRIN will coordinate the image transmission process and options and train all operating research staff.

All PET images shall be submitted in the specific modality manufacturer’s native format in order to provide for secondary SUV analysis at the IMC. This may be accomplished via direct FTP or via submission of images on media. If FTP is the desired method, contact Tim Welsh at 215-717-2754 for instructions. For submission on media, the media type must be limited to MOD, CD, DVD-RW or DVD-RAM. Media will not be returned unless specifically requested and return instructions and packaging is provided. Each site will be required to be credentialed by ACRIN prior to participant accrual. For detailed information regarding site PET credentialing and PET/CT requirements, visit the ACRIN Web site (http://www.acrin.org/petcorelab.html).

- When images are not available utilizing direct transfer to the ACRIN Software as outlined above, contact the ACRIN Imaging Core Laboratory for further instructions.
- If required and part of the protocol, images maintained at ACRIN Headquarters Image Archive may be distributed to other participating sites using either FTP or CD-ROM where appropriate, for purposes of secondary review.
- The header recorded on DICOM-formatted image data often contains information identifying the participant by name. These identifiers must be scrubbed before the images are transferred. If using ACRIN software, header scrubbing is accomplished automatically. For further information on the scrubbing of pertinent participant information contact Fraser Wilton at 613-692-2620 and/or fwilton@phila.acr.org.
- In the event that the site is unable to transfer images with scrubbed headers, the images may be sent on a CD or other electronic medium to ACRIN IMC for digitization/transfer to the Image Archive. Contact the ACRIN IMC prior to sending the media to confirm compatibility.
- To better ensure image quality, the technical parameter charts should be distributed to the individual modalities to guarantee protocol compliance. These charts can be found at http://www.acrin.org/6671 protocol.html#imaging.

12.2.6 Image Quality Review
A review of all imaging procedures will be performed to ascertain the quality of 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. The first three (3) MRI ferumoxtran-10 cases will be
examined by Dr Mukesh Harisinghani from Massachusetts General Hospital to assure optimal quality. Continual random sample of remaining ferumoxtran-10 cases will be monitored by Drs. Mostafa Atri and Jelle Barentsz. The MRI images will be monitored for the compliance with the protocol parameters and interpretability of sequences especially T2* sequence with respect to the presence of artifacts, motion, and resolution. All sequences including repeat sequences will be included for the review both at the institution and for central reader study. 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. 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.

**12.2.7 PET/CT Review at Imaging Institutions**

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.

**12.3 Central Reader Study**

The primary analyses for evaluation of study objectives 3.1.1, 3.1.2, 3.2.1, 3.2.2 will be based on data obtained from two central reader studies.

In one reader study, seven (7) readers will all interpret PET scans alone and then fused PET/CT scans obtained on each of 120 women, 60 with pathology-proven metastases to abdominal lymph nodes and 60 without abdominal 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. 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.

In the other reader study, seven (7) readers will all interpret ferumoxtran-10 MRI scans for each of the same 120 women. The procedures for scan presentation and the available information to the readers will be as described in the previous paragraph. The entire scan including suboptimal and repeat sequences will be included in the review session. All data, even data from original scans that are repeated, will be kept and evaluated by the on-site and central readers. The PET/CT and ferumoxtran-10 MRI will be read by different readers.

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.
12.4 **PET/CT Review at Imaging Institutions**
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:* $2-[^{18}\text{F}]$fluoro-2-deoxy-D-glucose

13.1.2 *Molecular Formula:* $\text{C}_6\text{H}_{11}^{18}\text{FO}_5$

13.1.3 *Description:* FDG is a positron-emitting radiopharmaceutical containing no-carrier added, radioactive fluoride $^{18}\text{F}$ 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 $^{18}\text{F}$. 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%.
13.2 Ferumoxtran-10 (NSC #731411; IND #70,900)

Investigator Brochure for Ferumoxtran-10 will be available to ACRIN/GOG approved sites. The brochure will provide detailed information regarding the investigational agent. For adverse events related to this agent, see section 16.0.

13.2.1 Chemistry and Mechanism of Action: Combidex ® (ferumoxtran-10), a superparamagnetic iron oxide colloid, is being developed by AMAG Pharmaceuticals, Inc. The injection powder, lyophilized for solution, is a superparamagnetic iron oxide covered with low-molecular-weight dextran for intravenous administration as an MRI contrast media. The average particle size is less than 50 nm. Each vial of ferumoxtran-10 contains 210 mg of iron. Ferumoxtran-10 is administered after dilution in 100 ml of saline. Blood half-life of ferumoxtran-10 is approximately 25 to 30 hours, independent of dose.

In the late phase of distribution (24 to 36 hours after administration), the contrast agent accumulates in the lymph nodes and causes darkening of normal lymph nodes on T2-weighted and T2* sequences. In metastatic disease, the macrophages in the lymph nodes are slowly replaced by tumor. In this situation, ferumoxtran-10 is not taken up by the nodes without macrophages and the nodes have high signal (appear light grayish with no blackening) on T2-weighted or T2* MR images. Because cancer is a progressive disease, the uptake of ferumoxtran-10 can vary producing various nodal patterns on MRI due to the decreased phagocytic activity within the lymph node.

13.2.2 Pharmacologic Data: Toxicology studies that have been performed to date include and are described in detail in the Investigator Brochure for Combidex (dated April 4, 2005). The brochure includes acute studies, repeat-dose studies, special toxicology studies, reproductive studies, and mutagenicity studies.

Three Phase I, nine Phase II, and three Phase III studies with intravenous administration of ferumoxtran-10 have been completed in the United States. Two Phase II and six Phase III studies have been completed in Europe. Additional studies are ongoing in the United States and the European Union.

Overall, the incidence of adverse events is 15.8% in participants when the contrast agent was administered by infusion following dilution in 100 ml of saline. Table 2 shows the current safety profile in 1,236 participants who have received ferumoxtran-10 using dilution in 100 ml of saline and infusion only (Table 2). For adverse events related to this agent, see section 16.0.

**Table 2: Adverse Events >0.5% with 100 ml dilute administration**
Ferumoxtran-10 iron and iron metabolism determinations are consistent with normal metabolism of an iron injection. Serum iron and TIBC measurements may not be meaningful for 3 to 7 days following administration because of assay interference. Serum ferritin levels remain within normal range, peak at 3 days after administration, and slowly return to baseline levels. Small transient decreases in transferrin were noted with no dose-response effect.

Ferumoxtran-10 produced no consistent, clinically significant effects on blood chemistry, hepatic function, electrolytes, or ancillary tests. The changes that occurred were attributed to the participants’ primary diseases, underlying conditions such as diabetes, concomitant medications, or pre-existing laboratory abnormalities.

Ferumoxtran-10 may interfere with laboratory tests that employ colorimetric methods for determination due to the dark color of the drug. In evaluations of serum samples spiked with varying concentrations of ferumoxtran-10 made to approximate levels circulating in the blood after drug administration, ferumoxtran-10 was found to interfere with bilirubin (increases), uric acid (decreases), and triglycerides (increases).

The effect of ferumoxtran-10 (at doses of 1.1 and 2.6 mg Fe/kg) on immune function was evaluated in a placebo-controlled clinical trial in 23 healthy participants. Nineteen participants received ferumoxtran-10 (9 male, 10 female) and four participants received placebo. No effects on total white blood cells, lymphocytes, lymphocyte subtypes, natural killer cells, and suppressor/cytotoxic T-cell activity were observed up to 6 months after administration of ferumoxtran-10 or placebo. There were no dose-or time-dose-related effects on any
immunologic parameter studied. Ferumoxtran-10 had no immediate or delayed effect on immune function.

In one study of the 389 participants who received ferumoxtran-10, 2% had their injections temporarily stopped due to adverse events. In each case, dose administration was later resumed, the adverse event(s) did not recur, and the participant was able to complete the study. Detailed adverse event information can be found in the Investigator Brochure.

Additionally, the serious adverse events monitored by the administration of ferumoxtran-10 were reduced using dilution and infusion. There were 3/131 (2.3%) participants with serious adverse events who received the drug undiluted as compared with 5/1930 (0.3%) which were classified as serious by the investigator when ferumoxtran-10 was administered diluted and infused.

The rate of serious adverse events when ferumoxtran-10 is administered by dilution and infusion is significantly lower (0.3%) than with the direct injection (2.3%). The rate of serious adverse events with diluted administration of ferumoxtran-10 is lower than that in the current labeling for iodinated contrast agents with CT such as Iohexol® (1.1% serious adverse reactions) and Oxilan® (1.5% serious adverse reactions) which are currently used in anatomic imaging for evaluation of lymph node disease.

The total dose of ferumoxtran-10 will remain constant. In the event of suspected agent-related adverse effects, the infusion may be discontinued and restarted at the discretion of the supervising physician unless there is serious adverse event or evidence of hypersensitivity to Ferumoxtran-10 as indicated by generalized rash, urticaria, or pruritus. Any such delay/modification of the agent infusion will be recorded.

13.2.3 **How Supplied:** Ferumoxtran-10 is supplied by the Pharmaceutical Management Branch/NCI as a lyophilized product in a sterile, single use vial containing 210.4 mg of iron, 631 mg of dextran and 27 mg of sodium citrate.

13.2.4 **Agent Ordering:** NCI-supplied agents may be requested by the Principal Investigator (or their authorized designees) at each participating institution. The agent will be shipped directly to various trial sites, where the participant is to be studied. Pharmaceutical Management Branch (PMB) policy requires that the agent be shipped directly to the institution where the participant is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). Completed Clinical Drug Requests (NIH-986) should be submitted to the PMB by fax (301) 480-4612 or mailed to:

Pharmaceutical Management Branch  
CTEP, DCTD, NCI  
9000 Rockville Pike
13.2.5 Solution Preparation: Reconstitute the 210.4 mg vial with 10 mL of 0.9% Sodium Chloride Injection, USP to yield 10.5 mL of a reddish-brown aqueous solution containing 20 milligrams iron/mL (mg Fe/mL). The osmolality of the resulting solution is 365 mOs/kg water, the viscosity is 1.6 cps at 25°C and the specific gravity is 1.052 g/mL. The dose of ferumoxtran-10 should be added to a 100 mL bag of 0.9% Sodium Chloride injection, USP. The infusion should be completed within 4 hours of mixing.

13.2.6 Dosage and Administration: The injection dose is 2.6 mg of iron per kilogram of body weight (see Appendix VIII).

Prior to ferumoxtran-10 administration, a documented history and physical examination must be noted in the medical record. Ferumoxtran-10 should be administered at least two hours after administration of iodinated contrast.

In the MRI suite under physician supervision, the imaging technologist or nurse will administer ferumoxtran-10 at 2.6 mg Fe/kg diluted in 100 mL of normal saline through the supplied filter by slow infusion (over at least 30 minutes), with an initial flow rate of 2 mL/min for the first 10 minutes increased to 4 mL/min as tolerated, followed by a saline flush. If ferumoxtran-10 is not administered in the MRI suite due to logistical problems it may also be administered in a GCRC or any other venue in which appropriate personnel, crash cart, and monitoring equipment are available. A fully equipped emergency cart and ACLS certified personnel will be available. The infusion will be terminated in any participant who exhibits anaphylaxis, significant hypotension (systolic blood pressure <80 mmHg on two measurements obtained within 1-2 minutes of each other), or an O₂ saturation lower than 80%, or evidence of hypersensitivity defined as generalized rash, urticaria, or pruritus. Any participant who has a serious adverse event during the procedure should have his/her infusion permanently discontinued (Refer to section 16.0 for Adverse Event Reporting Regulations). Any participant who has a serious adverse event during the procedure should have his/her infusion permanently discontinued (Refer to section 16.0 for Adverse Event Reporting Regulations).

Participants will undergo one MRI examination 24-36 hours after injection of ferumoxtran-10 (ferumoxtran-10, AMAG Pharmaceuticals, Inc, USA).

13.2.7 Caution: The single-use lyophilized dosage form contains no antibacterial preservatives. Therefore, it is advised that the reconstituted product be discarded 6 hours after initial entry.
13.2.8 **Storage and Stability:** Ferumoxtran-10 should be stored at room temperature (19-25°C) away from direct sunlight. The intact vials remain clinically acceptable until the expiration date indicated on the vial.

13.2.9 **Accountability:** ACRIN will identify an investigational pharmacist (through the ACRIN site PI) who will be the responsible party designated by the investigator. This pharmacist will maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form. The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form. Storage is per the manufacturer’s recommendation at room temperature ([http://ctep.cancer.gov/requisition/storage.html](http://ctep.cancer.gov/requisition/storage.html)).

13.3 **Monitoring for physiological effects of Ferumoxtran-10 injection**

13.3.1 **Vital signs:**
Vital signs, including oral temperature, blood pressure (BP), heart rate (HR), peripheral pulse oxygenation (pulse ox), and respiratory rate (RR) will be measured prior to injection. All vital signs except the oral temperature will be repeated at 5-minute intervals throughout the infusion, at 15-minute intervals for the first hour post-infusion as permitted by the MRI protocol, and at 30-minute intervals for the remaining 2 hours post-infusion. Oral temperature will be monitored hourly during the 3-hour post-infusion monitoring period. Values of any of these parameters outside the normal clinical ranges will be tabulated.

13.3.2 **Laboratory studies:**
The laboratory studies indicated below will be performed prior to ferumoxtran-10 infusion and on the last imaging day. Values of any of these parameters outside the normal clinical ranges will be tabulated.

13.3.2.1 **Serum Chemistry Levels to be Monitored:** total bilirubin, urea nitrogen, alkaline phosphatase, calcium, creatinine, phosphorus, albumin, sodium, AST (SGPT), sodium, ALT (SGOT), potassium, lactic dehydrogenase, and glucose.

13.3.2.2 **Other Laboratory Testing:** complete blood count with differential and platelets, serum iron, ferritin, % saturation, transferrin, and TIBC, prothrombin and activated partial thromboplastin times (PT, PTT), and electrocardiogram (ECG).

13.4 **Monitoring for Adverse Events**
Adverse events will be evaluated at each imaging session. Adverse events are defined as any signs of illness or symptoms that have appeared or worsened since the infusion of ferumoxtran-10. Participants will be queried for potential adverse effects. The adverse events that will be specifically monitored during the infusion include localized discomfort at the IV injection site, pain, respiratory difficulties, blood pressure instability,
flushing, dizziness, pruritis/rash, and any other symptoms that could be secondary to an anaphylactoid-type reaction (See Section 16.0 for AE reporting requirements).

14.0 CLINICAL STAGING AND LYMPHATIC EVALUATION

Participants will undergo clinical staging as permitted by FIGO rules, including examination under anesthesia, cystoscopy, and proctoscopy.

Participants will then undergo pelvic and abdominal lymph node sampling by either an extra-peritoneal or laparoscopic approach. Eight 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. 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 Sampling

14.1.1 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 V and the GOG Surgical Manual. Choice of incision may include, but is not limited to, midline, para-median, double-“J” incision, and Pfannenstiehl.

14.1.2 Laparoscopic Pelvic and Abdominal Lymph Node Sampling (Appendix V): Pelvic and abdominal lymph node sampling may also be performed through a laparoscopic approach as outlined in Appendix V.

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.
15.0 PATHOLOGY INFORMATION

15.1 Lymph node dissection will be performed in accordance with strict anatomic boundaries. Note that this differs from the standard GOG definitions. For details of the specific boundaries of dissection, see Section 8.2

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

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 cancer have been reported. Adverse events may be due to surgery alone or due to
the combination of surgery followed by radiation or chemoradiation (13, 17, 23, 69).

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular Injury</td>
<td>2.3-3.5%</td>
</tr>
<tr>
<td>Wound Infection</td>
<td>2.3-10.1%</td>
</tr>
<tr>
<td>Lymphocyst</td>
<td>3.5-19.9%</td>
</tr>
<tr>
<td>Lymphocyst requiring intervention (drainage of laparotomy)</td>
<td>6.7%</td>
</tr>
<tr>
<td>Lymphedema</td>
<td>18.4%</td>
</tr>
<tr>
<td>Treatment Related Death (PE or post radiation bowel perforation)</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

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:
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 40-50% of recommended annual maximum exposure). The radiation dose from the PET/CT has not been shown to have any adverse effects.

16.6.5 Reported Adverse Events and Potential Risks Associated with Ferumoxtran-10 (NSC #731411; IND #70,900)

<table>
<thead>
<tr>
<th>Table 2: Adverse Events &gt;0.5% with 100 ml dilute administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body as a Whole:</strong></td>
</tr>
<tr>
<td>Pain Back</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Pain Chest/Breast</td>
</tr>
<tr>
<td>Pain</td>
</tr>
</tbody>
</table>
Cardiovascular System:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasodilation</td>
<td>42 (3.4%)</td>
</tr>
</tbody>
</table>

Digestive System:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>14 (1.2%)</td>
</tr>
</tbody>
</table>

Respiratory System:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>16 (1.3%)</td>
</tr>
</tbody>
</table>

Skin and Appendages:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>37 (3.0%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>27 (2.2%)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>27 (1.7%)</td>
</tr>
<tr>
<td>Sweating</td>
<td>12 (0.7%)</td>
</tr>
</tbody>
</table>

The following adverse reactions were reported in <0.5% of the participants receiving ferumoxtran-10:

**Body as a Whole:** asthenia, injection site edema/hematoma, injection site pain, neck pain, subcutaneous hematoma, hypothermia, malaise, breast pain, substernal chest pain, and scleroderma

**Cardiovascular:** arrhythmia, bradycardia, palpitations, and peripheral vascular disease

**Digestive:** dry mouth, flatulence, cardiospasms, abnormal stool, and tongue disorder

**Hematologic and Lymphatic:** coagulation disorder and cyanosis

**Metabolic and Nutritional:** peripheral edema

**Musculoskeletal:** leg cramps, arthralgia, joint disorder, hypotonia, and paresis

**Neurologic:** hypertonia, stupor, insomnia, nervousness, sleep disorder, somnolence, and vertigo

**Respiratory:** polypnea, rhinitis, voice alteration, asthma, increased cough, larynx edema, hyperventilation, hypoxia, laryngismus, pharyngitis, and respiratory disorder

**Dermatologic:** maculopapular rash, erythema multiforme, and skin discoloration

**Special Senses:** conjunctivitis, eye disorder, abnormal vision, mydriasis, and tinnitus

**Urologic:** urinary incontinence, urinary tract infection, and abnormal urine.

There have been 5/2013 (0.2%) adverse events which were classified as serious by the investigator when ferumoxtran-10 was administered diluted and infused. These events were cardiovascular or respiratory and occurred/lasted from 5 seconds to 2 hours after the start of infusion. The participant was either observed or was medically treated with no sequelae. All necessary, detailed adverse event
information regarding this issue is located in the IDB and is distributed to all the sites.

16.6.6 Adverse Events Associated with MRI
While there are no significant risks from MRI, the participant may be uncomfortable due to the loud noise and/or feelings of claustrophobia during the MRI. If the participant experiences a sensation of claustrophobia while in the magnet, the MRI will be immediately stopped. Having a pacemaker or other electromagnetic device or vascular clip in the head excludes potential participants from this study. No serious biological effects have been reported from the magnetic fields used in clinical MRI. The FDA approved substance gadolinium is sometimes used for contrast in MRI. Although approximately two percent of participants experience some side effects, these are mostly mild (nausea, headache, hives, temporary low blood pressure). Serious side effects are almost unheard of.

16.6.7 Adverse Events Associated with PET/CT
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).

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. 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.

### 16.8 AdEERS Expedited Reporting Requirements for Adverse Events that occur within 30 Days of the Last Dose of the Investigational Agent: Ferumoxtran-10

**Table D1:** Reporting Requirements for Adverse Events that occur within 30 Days of the Last Dose of the Investigational Agent (Ferumoxtran-10) on the Phase 2 and 3 Trials

<table>
<thead>
<tr>
<th>Attribution</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 3</th>
<th>Grades 4 &amp; 5</th>
<th>Grades 4 &amp; 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unexpected and Expected</td>
<td>Unexpected</td>
<td>Expected</td>
<td>Unexpected with Hospitalization</td>
<td>Expected with Hospitalization</td>
<td>Unrelated</td>
<td>Expected</td>
</tr>
<tr>
<td>Unrelated</td>
<td>Not Required</td>
<td>Not Required</td>
<td>Not Required</td>
<td>7 Calendar Days</td>
<td>7 Calendar Days</td>
<td>7 Calendar Days</td>
<td>7 Calendar Days</td>
</tr>
<tr>
<td>Unlikely</td>
<td>Not Required</td>
<td>Not Required</td>
<td>Not Required</td>
<td>7 Calendar Days</td>
<td>7 Calendar Days</td>
<td>7 Calendar Days</td>
<td>7 Calendar Days</td>
</tr>
<tr>
<td>Possible</td>
<td>Not Required</td>
<td>7 Calendar Days</td>
<td>Not Required</td>
<td>7 Calendar Days</td>
<td>7 Calendar Days</td>
<td>24-Hour; 3 Calendar Days</td>
<td>7 Calendar Days</td>
</tr>
<tr>
<td>Probable</td>
<td>Not Required</td>
<td>7 Calendar Days</td>
<td>Not Required</td>
<td>7 Calendar Days</td>
<td>7 Calendar Days</td>
<td>7 Calendar Days</td>
<td>7 Calendar Days</td>
</tr>
<tr>
<td>Definite</td>
<td>Not Required</td>
<td>7 Calendar Days</td>
<td>Not Required</td>
<td>7 Calendar Days</td>
<td>7 Calendar Days</td>
<td>7 Calendar Days</td>
<td>7 Calendar Days</td>
</tr>
</tbody>
</table>

1. Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CIP IND require reporting as follows: AdEERS 24-hour notification followed by complete report within 3 calendar days for:
   - Grade 4 and Grade 5 unexpected events with attribution of possible, probable, and definite

   AdEERS 7 calendar day report:
   - Grade 2 unexpected events with attribution of possible, probable, and definite
   - Grade 3 unexpected events with hospitalization or prolongation of hospitalization with attribution of unrelated and unlikely and

GOG-0233/ACRIN 6671

51

August 16, 2007
possible, probable, and definite

- Grade 3 unexpected events without hospitalization or prolongation of hospitalization with attribution of possible, probable, and definite
- Grade 3 expected events with hospitalization or prolongation of hospitalization with attribution of unrelated and unlikely and possible, probable, and definite
- Grade 4 and 5 unexpected events with attribution of unrelated and unlikely
- Grade 4 and 5 expected events with attribution of unrelated and unlikely and possible, probable, and definite

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

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

- **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.

**16.9 When to Report for Ferumoxtran-10 Related Adverse Events**

It is the responsibility of the GOG and ACRIN investigators or investigator-designees to document all Adverse Events (AEs), which occur during the course of the study. For each adverse event, the GOG and ACRIN investigator will evaluate and assign attribution and grade (see section 16.1 for definition). AEs not previously documented in the study will be recorded on the Adverse Event Log within the study participant’s chart to identify any potentially related to any study procedures. The nature of each event, date, and time
(when appropriate) of onset, outcome, frequency, maximum intensity, action taken, and attribution will be recorded.

AEs already documented in the CRF (i.e., at a previous assessment) and designated as ‘ongoing’ should be reviewed at subsequent visits as necessary. If these have been resolved, the documentation in the CRF should be completed including an end date for the event and not the date of the visit. If an adverse experience increases in frequency or severity during a study period, an up to date record of the experience will be documented. The ACRIN RA will complete the AE form for any ferumoxtran-10 and/or imaging adverse events for both serious and non-serious and forward it to the GOG Data Manager for submission to the data center. The GOG Data Manager is responsible for reporting all adverse events that occur at the site level.

Routine reporting is defined as documentation of adverse events on source documents and AE CRF, and submission to GOG for preparation of a report for Data and Safety Monitoring Committee (DMC) review, quarterly reports to CDUS, FDA annual reports, and the final study report.

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.

16.9.1 Any adverse events associated with any primary study procedures in this protocol are ferumoxtran-10 administration, study-related imaging procedures, and surgical procedures. For this protocol, all adverse events associated with the primary study procedures will be reported as adverse events to the data center and/or NCI, when appropriate, by the GOG Data Manager.

16.9.2 The reporting of AEs for the investigational contrast agent, ferumoxtran-10, in this protocol will conform to the following:

1. Grade 1 unexpected and expected adverse events that are unrelated, unlikely, possible, probable, or definite will be reported by routine reporting procedures only.

2. Grade 2 unexpected adverse events that are unrelated or unlikely will be reported by routine reporting procedures only.

3. Grade 2 unexpected adverse events that are 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.

4. Grade 2 expected adverse events that are unrelated, unlikely, possible, probable, or definite will be reported by routine reporting procedures only.
5. Grade 3 unexpected adverse events with hospitalization that are unrelated, unlikely, 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.**

6. Grade 3 unexpected adverse events without hospitalization that are unrelated or unlikely will be reported by **routine reporting procedures only.**

7. Grade 3 unexpected adverse events without hospitalization that are 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.**

8. Grade 3 expected adverse events with hospitalization that are unrelated, unlikely, 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.**

9. Grade 3 expected adverse events without hospitalization that are unrelated, unlikely, possible, probable, or definite will be reported by **routine reporting procedures only.**

10. Grade 4 and 5 unexpected adverse events that are unrelated or unlikely 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.**

11. Grade 4 and 5 unexpected adverse events that are possible, probable, and definite will be reported within a 24-hour time period via AdEERS by the investigator or investigator-designee. In addition, a complete AdEERS report is due within 3 calendar days of the initial 24-hour report. **Routine reporting procedures also apply.**

12. Grade 4 and 5 expected adverse events that are unrelated, unlikely, 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.**

13. Expedited adverse event reporting must be completed within 7 calendar days of first knowledge of the event for all unexpected and expected
Grade 4 and Grade 5 events, regardless of attribution. **Routine reporting procedures also apply.**

14. All fatal (Grade 5) adverse events 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.**

### 16.10 Adverse Event Reporting for Any Surgical and Imaging Procedures

Table D2: 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.

All CTCAE v 3.0 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.

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 3</th>
<th>Grades 4 &amp; 5</th>
<th>Grades 4 &amp; 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated</td>
<td>Expected</td>
<td>Expected</td>
<td>Unexpected</td>
<td>With Hospitalization</td>
<td>Expected</td>
<td>Without Hospitalization</td>
</tr>
<tr>
<td>Unlikely</td>
<td>Not Required</td>
<td>Not Required</td>
<td>Not Required</td>
<td>7 Calendar Days</td>
<td>Not Required</td>
<td>7 Calendar Days</td>
</tr>
<tr>
<td>Possible</td>
<td>Not Required</td>
<td>Not Required</td>
<td>Not Required</td>
<td>7 Calendar Days</td>
<td>Not Required</td>
<td>7 Calendar Days</td>
</tr>
<tr>
<td>Probable</td>
<td>Not Required</td>
<td>Not Required</td>
<td>Not Required</td>
<td>7 Calendar Days</td>
<td>Not Required</td>
<td>7 Calendar Days</td>
</tr>
<tr>
<td>Definite</td>
<td>Not Required</td>
<td>Not Required</td>
<td>Not Required</td>
<td>7 Calendar Days</td>
<td>Not Required</td>
<td>7 Calendar Days</td>
</tr>
</tbody>
</table>

*Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after surgery require reporting as follows:

AdEERS 7 calendar day report:
- Grade 3 unexpected events with hospitalization or prolongation of hospitalization with attribution of unrelated/unlikely and possible, probable, and definite
- Grade 3 expected events with hospitalization or prolongation of hospitalization with attribution of unrelated/unlikely and possible, probable, and definite
- Grade 4 and 5 unexpected and expected events with attribution of unrelated/unlikely and possible, probable, and definite
- **Grade 5:** All deaths within 30 days of the surgical procedure must be reported within 7 calendar days using expedited reporting regardless of causality

“See exceptions below under the section entitled, “Additional Instructions or Exceptions to Expedited Reporting Requirements for Surgical Trials.”

March 2005

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:**
“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.

16.10.1 Additional instructions or exceptions to AdEERS expedited reporting requirements for this protocol:

16.10.1.1 Adverse events associated with any primary study procedures:
Lymph Node Sampling, any protocol-specific surgical procedures, PET/CT, and MRI procedures will be reported.

16.10.2 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:

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 ferumoxtran-10 and imaging adverse events and forward it to the GOG Data Manager for submission to NCI and GOG. The GOG Data Manager will be responsible for reporting all adverse events that occur at the site level.

**16.10.3 Procedures for Expedited Adverse Event Reporting**

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

**16.11 How to Report**

**16.11.1** Some adverse events require 24-hour notification (refer to Tables D1 and D2 in sections 16.8 and 16.10) via AdEERS. When Internet connectivity is disrupted, a 24-hour notification is to be made to CIP by telephone at 301-496-0737 and CTEP by telephone at 301-897-1704. Once Internet connectivity is restored, a 24-hour notification that was phoned in must be entered electronically into AdEERS by the original GOG submitter at the site.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of first knowledge of the event specified in Tables D1 and D2 in sections 16.8 and 16.10. 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.

**16.11.2 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:  
Lalitha Shankar: shankarl@mail.nih.gov  
Barbara Galen: bgalen@mail.nih.gov  
Carl Jaffe: jaffec1@mail.nih.gov  
Paula Jacobs: jacobsp@mail.nih.gov  
James L. Tatum: tatumj@mail.nih.gov  
RE: Adverse Event Report  
Cancer Imaging Program  
6130 Executive Blvd., MSC 7412  
Room 6050  
Bethesda, MD 20892-741

To AMAG Pharmaceuticals:  
Gerard Wolf: gwolf@amagpharma.com  
Jana Subramaniam: jsubramaniam@amagpharma.com  
RE: Adverse Event Report  
AMAG Pharmaceuticals, Inc.  
125 Cambridge Park Drive  
6th Floor  
Cambridge, MA 02140

To ACRIN:  
Maria Oh: moh@phila.acr.org  
Pamela Harvey: pharvey@phila.acr.org  
Attention: ACRIN SAE Liaison  
Marcella Moore: mmoore@phila.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).

16.11.3 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.
16.11.4 All fatal adverse events identified in the imaging and ferumoxtran-10 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.

16.11.5 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.

16.11.6 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.

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.

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.

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 II for a copy of the sample informed consent form). 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/pubpolicy.html) and GOG Publication Policy (http://gogmember.gog.org/).

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, AMAG Pharmaceuticals, and ACRIN/GOG. 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.

Institutional on-site audits will be completed within 18-36 months after first participant enrollment of each site’s enrollment. Subsequent audits will be scheduled per the outcome of the initial audit. 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 is 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.

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 case report forms (CRFs) will be audited against the appropriate component of the medical record. 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, MR, etc.).

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. 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

This section has been intentionally left blank.
This section has been intentionally left blank.
This section has been intentionally left blank.
This section has been intentionally left blank.
This section has been intentionally left blank.
REFERENCES


24. Gupta NC, Graebner GM, Bishop HA. Comparative efficacy of positron emission tomography with fluorodeoxyglucose in evaluation of small (<1 cm), intermediate (1 to 3 cm), and large (>3 cm). *Chest* 2000; 117:773-8.


38. Kosary CL. FIGO stage, histology, histologic grade, age and race as prognostic factors in determining survival for cancers of the female gynecologic system: an analysis of 1973-87 SEER


APPENDIX I

CLINICAL STAGING - CARCINOMA OF THE CERVIX UTERI

FIGO CLASSIFICATION

PRE-INVASIVE CARCINOMA

STAGE 0: Carcinoma in situ, intraepithelial carcinoma.

(Cases of Stage 0 should not be included in any therapeutic statistics)

INVASIVE CARCINOMA

STAGE I: Carcinoma strictly confined to the cervix.

STAGE IA: Invasive cancer identified only microscopically. (All gross lesions, even with superficial staging, are stage IB cancers)

Invasion is limited to measured stromal invasion with maximum depth of 5.0 mm and no wider than 7.0 mm.\(^1\)

STAGE IA1: Measured invasion of stroma no greater than 3.0 mm in depth and no wider than 7.0 mm.

STAGE IA2: Measured invasion of stroma greater than 3 mm and no greater than 5 mm and no wider than 7 mm.

STAGE IB: Clinical lesions confined to the cervix or pre-clinical lesions greater than stage IA.

STAGE IB1: Clinical lesions no greater than 4.0 cm in size.

STAGE IB2: Clinical lesions greater than 4 cm in size.

STAGE II: The carcinoma extends beyond the cervix but has not extended on to the pelvic wall. The carcinoma involves the vagina, but not the lower third.

STAGE IIA: No obvious parametrial involvement.

STAGE IIB: Obvious parametrial involvement.

STAGE III: The carcinoma has extended on to the pelvic wall. On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. The tumor involves the lower third of the vagina. All cases with hydro-nephrosis or non-functioning kidney.

STAGE IIIA: No extension on to the pelvic wall.
STAGE IIIB: Extension on to the pelvic wall and/or hydro-nephrosis or non-functioning kidney.

STAGE IV: The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum. A bullous edema as such does not permit a case to be allotted to Stage IV.

STAGE IVA: Spread of the growth to adjacent organs.

STAGE IVB: Spread to distant organs.

Notes on Staging

Stage IA carcinoma should include minimal microscopically evident stromal invasion as well as small cancerous tumors of measurable size. Stage IA should be subdivided into those lesions with minute foci or invasion visible only microscopically as Stage IA1 and the macroscopically measurable microcarcinomas as Stage IA2 in order to gain further knowledge of the clinical behavior of these lesions. The term IB occult should be omitted.

The diagnosis of both Stage IA1 and IA2 should be based on microscopic examination of removed tissue, preferably a cone, which must include the entire lesion. As noted above, the lower limit of Stage IA2 should be that it can be measured macroscopically (even if dots need to be placed on the slide before measurement) and the upper limit of IA2 is given by measurement of the two largest dimensions in any given section. The depth of invasion should not be more than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. The second dimension, the horizontal spread, must not exceed 7 mm. Vascular space involvement, either venous or lymphatic, should not alter the staging but should be specifically recorded as it may affect treatment decisions in the future.

Lesions of greater size should be staged as IB.

As a rule, it is impossible to estimate clinically whether a cancer of the cervix has extended to the corpus. Extension to the corpus should therefore be disregarded.

A patient with a growth fixed to the pelvic wall by a short and indurated, but not nodular, parametrium should be allotted to Stage IIB. It is impossible at clinical examination to decide whether a smooth and indurated parametrium is truly cancerous or only inflammatory. Therefore, the case should be placed in Stage III even if according to the other findings the case should be allotted to Stage I or Stage II.

The presence of the bullous edema as such should not permit a case to be allotted to Stage IV. Ridges and furrows into the bladder wall should be interpreted as signs of submucous involvement of the bladder if they remain fixed to the growth at palpation (i.e., examination from the vagina or the rectum during cystoscopy). A cytological finding of malignant cells in washings from the urinary bladder requires further examination and a biopsy from the wall of the bladder.

1 The depth of invasion should be no more than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. Vascular space involvement, either venous or lymphatic, should not alter the staging.
SAMPLE CONSENT FOR RESEARCH STUDY

Protocol Title:

UTILITY OF PREOPERATIVE FDG-PET/CT AND FERUMOXTRAN-10 MRI SCANNING PRIOR TO PRIMARY CHEMORADIATION THERAPY TO DETECT RETROPERITONEAL LYMPH NODE METASTASIS IN PATIENTS WITH LOCOREGIONALLY ADVANCED (IB2, IIA ≥4 CM, IIB-IVA) CARCINOMA OF THE CERVIX

[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 two types of tests, often called “scans.” The scans are a PET/CT scan and an MRI scan using an investigative contrast drug. Both scans are described in detail below. Researchers hope to learn the following:

- if the scans can find cancer that may have spread to your lymph nodes and,
- if the investigative contrast drug, ferumoxtran-10, helps MRI scans locate cancer in lymph nodes.

These questions are important to answer for treatment of patients with cervical cancer. Cancer that has spread to lymph nodes is treated differently than cancer that has not spread. This study may help determine if these scans along with the investigative contrast drug can locate cancer that has spread, so that patients can receive appropriate treatment.

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 one or both of these two scans, PET/CT and MRI using an investigative contrast agent, can find cancer that may have spread to your lymph nodes.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 325 people will take part in this study at a number of cancer centers in the United States and Canada. Forty of these 325 participants will consent to participate in the optional arm of the study.

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,
- 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:

- PET/CT,
- MRI with a special contrast drug,
- Surgery.

DESCRIPTION OF THE PET/CT SCAN

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.
DESCRIPTION OF THE MRI SCAN

Magnetic resonance imaging (MRI) uses a powerful magnet to create radio frequency signals that a computer uses to make detailed pictures of areas inside the body without the use of radiation.

For the MRI scan you will receive an injection of an MRI contrast drug. Some participants (40 total) will have the choice to receive an MRI before receiving the special contrast drug. The contrast drug helps to make any abnormal lymph nodes easier to see on the MRI scan. You will have the injection between 24 and 36 hours before the MRI scan. In rare cases, this may be done up to 48 hours. The investigational agent that is being studied is called ferumoxtran-10.

AFTER YOU HAVE THE SCANS THAT ARE PART OF THE RESEARCH STUDY

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 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. Your treatment will not be determined by the MRI scans, which are part of the study.

OVERVIEW OF TIMELINE AND PROCEDURES ASSOCIATED WITH STUDY:

<table>
<thead>
<tr>
<th>Day</th>
<th>Exams, tests, procedures and scans</th>
</tr>
</thead>
<tbody>
<tr>
<td>You are diagnosed with cervical cancer, stages IB2, IIA ≥4cm, IIB-IVA</td>
<td></td>
</tr>
</tbody>
</table>
| Prior to starting study | ● Tumor measurement (part of qualifying for trial),  
● Medical history including pregnancy test,  
● Blood tests,  
● Chest X-Ray,  
● ECG.                                                                  |
| Day 1        | ● 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,  
● Inject contrast drug ferumoxtran-10 for the MRI scan. |
| Day 2        | ● MRI scan 24-36 hours after injection of MRI drug (This may be done up to 48 hours in rare cases).  
● MRI scan in some centers is standard, but not with the contrast drug ferumoxtran-10 |
| Prior to surgery | ● Biopsy of any disease identified by the PET scan outside the abdomen, if feasible |

The CT and combined PET/CT scans are part of standard of care.


**CONFIDENTIAL**

<table>
<thead>
<tr>
<th>Day 3-15</th>
<th>• Lymph node examination, by surgery, laparoscopy or appropriate biopsy of lesions outside lymph glands.</th>
<th>The procedure is part of standard care at some centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 28 days</td>
<td>• Begin appropriate treatment with chemoradiation, as defined by standard treatment guidelines for your diagnosis, your physician and you</td>
<td>This is standard care</td>
</tr>
<tr>
<td>Within 6 weeks post-op</td>
<td>• Physical examination,</td>
<td>This is standard care</td>
</tr>
<tr>
<td>6 months after enrolling</td>
<td>• Medical history, • CT scan or PET/CT if a finding is visible on PET/CT and was not able to be biopsied,</td>
<td>Medical history is standard care. The CT or PET/CT scan is part of the standard of care at some centers.</td>
</tr>
<tr>
<td>Every 3 months for 2 years</td>
<td>• Routine blood tests and medical exams and x-rays at doctor’s discretion,</td>
<td>These procedures are standard care</td>
</tr>
<tr>
<td>Every 6 months for 3 additional years</td>
<td>• Routine blood tests and medical exams and x-rays at doctor’s discretion,</td>
<td>These procedures are standard care</td>
</tr>
</tbody>
</table>

**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 glucose (sugar) called FDG (Fluorodeoxyglucose) will be injected into the IV line. The chemical is a “radioactive tracer” and is called FDG. 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. Approximate 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.

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

WHAT HAPPENS WHEN I HAVE A MRI SCAN?

The day before you arrive for the MRI scan you will be injected with an experimental contrast drug called ferumoxtran-10. (See next question for details regarding this drug.) When you arrive to have the MRI, you will change into a hospital gown and an MRI technologist will help you lie on your back on the scanning table. The technologist will insert an IV line into your vein so that a drug to help relax your bowel can be injected into the line. The drug will help obtain a better image.

The technologist will place a piece of equipment called a “coil” that is made of curved hard plastic bands over your pelvic area. The coil helps to increase the radio frequency signals sent to the computer to produce good MRI images.

The table will slide into a tube-like machine that contains the MRI magnet. The technologist will talk with you through a special sound system to make sure you are comfortable. You will hear loud “knocking” noises during the scan. These noises are normal. The entire MRI scan will take about 30-40 minutes.

You will have to lie very still during this time. MRI scans do not cause any pain. However, lying in one position during the procedure may be slightly uncomfortable. A padded table will be used to keep you from becoming too uncomfortable.

WHAT IS FERUMOXTRAN-10?

Ferumoxtran-10 is an experimental MRI contrast drug. It was developed so that lymph nodes with cancer could be more clearly seen on MRI scans. Other studies have shown that it may help to find cancer in lymph nodes, which helps determine the best treatment for patients. In a recent study, Rockall et al. (51) evaluated 44 women with cervical cancer with ferumoxtran-10 prior to removal of the lymph nodes.

ARE THERE RISKS ASSOCIATED WITH FERUMOXTRAN-10?

Ferumoxtran-10 has been used in approximately 2000 people in the United States and Europe. It is not approved for general use. Most participants who receive ferumoxtran-10 do not have side effects.
The side effects reported are usually mild and temporary. That means the side effects will stop once the drug is discontinued. Side effects in this category include:

**Likely:**
- flushing (3.3%),
- rash (3.0%)
- back pain (2.4%),

**Less Likely:**
- itching (2.2%),
- hives (1.7%),
- shortness of breath (1.3%).

**Rare:**
- nausea (1.2%)
- chest pain (1.1%)
- pain (0.8%)
- sweating (0.7%)
- headache (0.6%),

Ferumoxtran-10 has caused a rare, but serious allergic reaction. Your chance of having this type of reaction is less than 2 in 1000. 1 of the 2000 participants who have received ferumoxtran-10 worldwide had an allergic reaction that resulted in death. This death was due to a severe allergic reaction to the administrative method of the drug. This method of administration is no longer used. Participants with other known allergies and liver disease may be more likely to react to ferumoxtran-10.

You should tell the study doctor and/or technologist immediately if you experience any of these symptoms so they can be treated promptly.

**WHAT IS THE PROCEDURE FOR INJECTING FERUMOXTRAN-10?**

Ferumoxtran-10 will be injected slowly through an intravenous (IV) line (a small plastic tube) placed in a hand or arm vein over 30-45 minutes. You will be observed at the hospital for 2 to 3 hours after the ferumoxtran-10 is injected to see if you experience any side effects. If you do, you will be treated immediately. Secondly, a blood test will be done to look for any other possible effects of ferumoxtran-10. The next day (after 24 hours) you will return for a MRI scan. The time between injection and the MRI scan allows the ferumoxtran-10 to reach your lymph nodes.

**ARE THERE RISKS ASSOCIATED WITH THIS KIND OF MRI?**

MRI scans have been used worldwide for many years, and have no known harmful effects in participants without metal in their body. The MRI uses radio waves and strong magnets to make images of the body. Anything that can be affected by a magnet should not be taken into the MRI scanning area.
This includes credit cards with magnetic strips. In addition, if you have any metal implants in your body (e.g. aneurysm clips, metal plates) you should not be in this study. If you have any questions please notify your doctor.

During the MRI you will hear loud noises. The procedure may lead to some anxiety because of the noise of the MRI scanner and its enclosed space. Earplugs or headphones may help decrease the sound. These will be supplied to you.

Finally, you must lie still in a confined area, which may make you feel claustrophobic. If you find the procedure for the MRI intolerable the study will be stopped or you may be sedated. Being immobilized for 45 minutes for the scan may lead to mild stiffness and discomfort.

You may develop a bruise or have bleeding at the needle site where the IV is placed. Occasionally, an infection may develop which can be treated with antibiotics. In rare instances, a person feels faint when a needle is inserted into a vein.

**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 laparscopically (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.
**CONFIDENTIAL**

**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.

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 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; breast-feeding baby, or mother-to-be, and this study may cause harm. Because the MRI contrast drug and FDG chemical used for the PET/CT scan in this study can affect a baby. 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 and MRI scans using ferumoxtran-10 will help identify cancer that has spread to lymph nodes. 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.

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
CONFIDENTIAL

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), AMAG Pharmaceuticals (manufacturer of ferumoxtran-10), 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. 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 imaging examinations as well as ferumoxtran-10 administration. 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. The Division of Cancer Treatment and Diagnosis, NCI, will provide you with the ferumoxtran-10 free of charge for this study.

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 decided to participate, you are free to leave the study at any time. 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.

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>

For information about this study, you may contact:

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>

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)

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>

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 MRI and PET/CT on the ACRIN website: http://www.acrin.org/xrays_scan.html.

OPTIONAL MRI PORTION
I agree to participate in the optional MRI that is being done for research as part of this study.

☐ Yes Initials____  ☐ No Initials____

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/Signature Date
Legal Representative

__________________
Printed Name of Person Obtaining Consent/Signature Date
APPENDIX III
PARTICIPATING INSTITUTIONS

A minimum of ten (10) participating institutions, Site Principal Investigators will be identified upon review and approval of completed ACRIN Protocol Specific Application (PSA).
APPENDIX IV
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 mid right common iliac artery 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. It is also recommended that bilateral retroperitoneal drains should be placed in each of the lymph node beds upon completion of the lymphadenectomy.
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 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.

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 V
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.

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.

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 VI
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.
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 VII
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 [www.acrin.org/6671_protocol.html#application](http://www.acrin.org/6671_protocol.html#application).

**Credentialing Procedures for MRI Images:** It is a requirement for this study to submit one (1) test MRI case. Information on the technical parameters that should be utilized and how to submit these images can be found at: [www.acrin.org/6671_protocol.html#application](http://www.acrin.org/6671_protocol.html#application). Data from this case will be reviewed centrally and each site will receive feedback regarding the test case before finalizing the first study participant.
FERUMOXTRAN-10 MUST BE DILUTED IN 100 ML OF NORMAL SALINE AND INFUSED OVER 30 MINUTES

<table>
<thead>
<tr>
<th>Body wt</th>
<th>Volume (ml)</th>
<th>Body wt</th>
<th>Volume (ml)</th>
<th>Body wt</th>
<th>Volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>kg</td>
<td>lbs</td>
<td>2.6 mg Fe/kg</td>
<td>kg</td>
<td>lbs</td>
<td>2.6 mg Fe/kg</td>
</tr>
<tr>
<td>40</td>
<td>88</td>
<td>5.2</td>
<td>71</td>
<td>156</td>
<td>9.2</td>
</tr>
<tr>
<td>41</td>
<td>90</td>
<td>5.3</td>
<td>72</td>
<td>158</td>
<td>9.4</td>
</tr>
<tr>
<td>42</td>
<td>92</td>
<td>5.5</td>
<td>73</td>
<td>161</td>
<td>9.5</td>
</tr>
<tr>
<td>43</td>
<td>95</td>
<td>5.6</td>
<td>74</td>
<td>163</td>
<td>9.6</td>
</tr>
<tr>
<td>44</td>
<td>97</td>
<td>5.7</td>
<td>75</td>
<td>165</td>
<td>9.8</td>
</tr>
<tr>
<td>45</td>
<td>99</td>
<td>5.9</td>
<td>76</td>
<td>167</td>
<td>9.9</td>
</tr>
<tr>
<td>46</td>
<td>101</td>
<td>6.0</td>
<td>77</td>
<td>169</td>
<td>10.0</td>
</tr>
<tr>
<td>47</td>
<td>103</td>
<td>6.1</td>
<td>78</td>
<td>172</td>
<td>10.1</td>
</tr>
<tr>
<td>48</td>
<td>106</td>
<td>6.2</td>
<td>79</td>
<td>174</td>
<td>10.3</td>
</tr>
<tr>
<td>49</td>
<td>108</td>
<td>6.4</td>
<td>80</td>
<td>176</td>
<td>10.4</td>
</tr>
<tr>
<td>50</td>
<td>110</td>
<td>6.5</td>
<td>81</td>
<td>178</td>
<td>10.5</td>
</tr>
<tr>
<td>51</td>
<td>112</td>
<td>6.6</td>
<td>82</td>
<td>180</td>
<td>10.7</td>
</tr>
<tr>
<td>52</td>
<td>114</td>
<td>6.8</td>
<td>83</td>
<td>183</td>
<td>10.8</td>
</tr>
<tr>
<td>53</td>
<td>117</td>
<td>6.9</td>
<td>84</td>
<td>185</td>
<td>10.9</td>
</tr>
<tr>
<td>54</td>
<td>119</td>
<td>7.0</td>
<td>85</td>
<td>187</td>
<td>11.1</td>
</tr>
<tr>
<td>55</td>
<td>121</td>
<td>7.2</td>
<td>86</td>
<td>189</td>
<td>11.2</td>
</tr>
<tr>
<td>56</td>
<td>123</td>
<td>7.3</td>
<td>87</td>
<td>191</td>
<td>11.3</td>
</tr>
<tr>
<td>57</td>
<td>125</td>
<td>7.4</td>
<td>88</td>
<td>194</td>
<td>11.4</td>
</tr>
<tr>
<td>58</td>
<td>128</td>
<td>7.5</td>
<td>89</td>
<td>196</td>
<td>11.6</td>
</tr>
<tr>
<td>59</td>
<td>130</td>
<td>7.7</td>
<td>90</td>
<td>198</td>
<td>11.7</td>
</tr>
<tr>
<td>60</td>
<td>132</td>
<td>7.8</td>
<td>91</td>
<td>200</td>
<td>11.8</td>
</tr>
<tr>
<td>61</td>
<td>134</td>
<td>7.9</td>
<td>92</td>
<td>202</td>
<td>12.0</td>
</tr>
<tr>
<td>62</td>
<td>136</td>
<td>8.1</td>
<td>93</td>
<td>205</td>
<td>12.1</td>
</tr>
<tr>
<td>63</td>
<td>139</td>
<td>8.2</td>
<td>94</td>
<td>207</td>
<td>12.2</td>
</tr>
<tr>
<td>64</td>
<td>141</td>
<td>8.3</td>
<td>95</td>
<td>209</td>
<td>12.4</td>
</tr>
<tr>
<td>65</td>
<td>143</td>
<td>8.5</td>
<td>96</td>
<td>211</td>
<td>12.5</td>
</tr>
<tr>
<td>66</td>
<td>145</td>
<td>8.6</td>
<td>97</td>
<td>213</td>
<td>12.6</td>
</tr>
<tr>
<td>67</td>
<td>147</td>
<td>8.7</td>
<td>98</td>
<td>216</td>
<td>12.7</td>
</tr>
<tr>
<td>68</td>
<td>150</td>
<td>8.8</td>
<td>99</td>
<td>218</td>
<td>12.9</td>
</tr>
<tr>
<td>69</td>
<td>152</td>
<td>9.0</td>
<td>100</td>
<td>220</td>
<td>13.0</td>
</tr>
<tr>
<td>70</td>
<td>154</td>
<td>9.1</td>
<td>101</td>
<td>222</td>
<td>13.1</td>
</tr>
</tbody>
</table>
### APPENDIX IX
SAMPLE DATA COLLECTION SHEETS

**Ferumoxtran-10 Infusion Flow Chart**

**NCI-Sponsored Phase 2 Study of *ferumoxtran-10* in axillary node staging in cervical cancer**

<table>
<thead>
<tr>
<th>Actual Time</th>
<th>Time Point</th>
<th>T</th>
<th>BP</th>
<th>HR</th>
<th>RR</th>
<th>O₂ Sat</th>
<th>AE Inquiry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infusion Initiation (0 min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>35 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>40 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 min post</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 min post</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>45 min post</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 hour post</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.5 hours post</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 hours post</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.5 hours post</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 hours post</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Ferumoxtran-10 Baseline Assessment Record

Past Medical History: (Include allergy history and major illnesses, surgeries)

<table>
<thead>
<tr>
<th>Height</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td></td>
</tr>
<tr>
<td>BP</td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td></td>
</tr>
<tr>
<td>Lungs (CTA or describe)</td>
<td></td>
</tr>
<tr>
<td>Heart (RRR, No MR, or describe)</td>
<td></td>
</tr>
</tbody>
</table>

Notes:

Signature of Individual Completing Form:

Subject Study ID _____________

Study Start Date _____________

Referring MD _______________
Describe any pertinent physical findings:

List all current medications:

Notes:

Signature of Individual Completing Form ____________________________
**Ferumoxtran-10 Eligibility Checklist**

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical cancer diagnosis confirmed (histological or cytological)</td>
<td></td>
</tr>
<tr>
<td>Participant &gt; 18 years of age</td>
<td></td>
</tr>
<tr>
<td>Participant has signed written informed consent document</td>
<td></td>
</tr>
<tr>
<td>Participant has signed HIPAA authorization</td>
<td></td>
</tr>
<tr>
<td>Participant is NOT pregnant or potentially pregnant</td>
<td></td>
</tr>
<tr>
<td>Leukocyte count &gt;3000/µl</td>
<td></td>
</tr>
<tr>
<td>Absolute neutrophil count &gt;1500/µl</td>
<td></td>
</tr>
<tr>
<td>Platelet count &gt;100,000/µl</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin within institutional limits</td>
<td></td>
</tr>
<tr>
<td>AST(SGOT)/ALT(SGPT) ≤ 2.5 times the institutional upper limit of normal</td>
<td></td>
</tr>
<tr>
<td>Creatinine within normal institutional limits OR, if creatinine level above institutional normal, creatinine clearance &gt;60 mL/min/1.73 m²</td>
<td></td>
</tr>
<tr>
<td>Participant is NOT receiving any other investigational agents</td>
<td></td>
</tr>
<tr>
<td>NO history of allergic reactions attributed to compounds of chemical or biologic composition similar to <em>ferumoxtran-10</em> (i.e. iron preparations, parenteral iron, parenteral dextran, parenteral iron-dextran, or parenteral iron-polysaccharide preparations)</td>
<td></td>
</tr>
<tr>
<td>NO contraindications to MR imaging (i.e. severe claustrophobia, pacemaker, aneurysm clips, defibrillators, or other institutional contraindication to MR imaging)</td>
<td></td>
</tr>
<tr>
<td>NO immunodeficiencies that predispose participant to specific or non-specific mediator release</td>
<td></td>
</tr>
<tr>
<td>Has NOT received ferumoxides within 3 months of enrollment</td>
<td></td>
</tr>
<tr>
<td>Has NO uncontrolled intercurrent illness</td>
<td></td>
</tr>
<tr>
<td>Has pre-study ferritin level &lt; 600 ng/ml AND percent saturation of transferrin level &lt; 50%</td>
<td></td>
</tr>
</tbody>
</table>

Subject Name and MRN:_________________________ Subject Study ID (if enrolled)______________

Projected Study Start Date_______________

Referring MD_________________________

**Ferumoxtran-10 Laboratory Study Results**

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline Value</th>
<th>Normal/Abnormal</th>
<th>F/U Value</th>
<th>Normal/Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactic dehydrogenase</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>---</td>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT (SGPT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT (SGOT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea Nitrogen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphorus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloride</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood Counts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Serum Iron           |   |   |
| Serum Ferritin       |   |   |
| TSAT                 |   |   |
| TIBC                 |   |   |
| PT                   |   |   |
| PTT                  |   |   |

**ECG Results:**
**Baseline**

**F/U**

**Notes:**
Signature of Individual Completing Form_________________________
## Participant Adverse Event Questionnaire

<table>
<thead>
<tr>
<th>Possible Adverse Event</th>
<th>Y = Yes</th>
<th>N = No</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body as a Whole:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain (Back)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain (Abdominal)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain (Chest/Breast)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain (Other site)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular System:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasodilation (flushing)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Digestive System:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory System:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea (Shortness of breath)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Skin and Appendages:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus (Itching)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urticaria (Hives)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweating</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other Complaint:</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX X
PET/CT IMAGING QUALITY CONTROL STANDARDS

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

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 (FWHM ≤ 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).

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.

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
CONFIDENTIAL

- 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
### MRI TECHNIQUE CHART

### GE MRI Scanners

<table>
<thead>
<tr>
<th>Scan Name</th>
<th>Plane</th>
<th>Sequence</th>
<th>TR (ms)</th>
<th>TE (ms)</th>
<th>FOV (cm)</th>
<th>Flip</th>
<th>Matrix</th>
<th>Averages (NEX)</th>
<th>Slice Thickness (mm)</th>
<th>Slice Gap (mm)</th>
<th>ETL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localizer</td>
<td>3-plane</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Axial</td>
<td>FSE</td>
<td>4500 - 5500</td>
<td>80-100</td>
<td>180°</td>
<td>24-40</td>
<td>256 x 256</td>
<td>2-4</td>
<td>3</td>
<td>0</td>
<td>8 to 16</td>
</tr>
<tr>
<td>T2</td>
<td>Sagittal</td>
<td>FSE</td>
<td>4500 - 5500</td>
<td>80-100</td>
<td>180°</td>
<td>24-40</td>
<td>256 x 256</td>
<td>2-4</td>
<td>3</td>
<td>0</td>
<td>8 to 16</td>
</tr>
<tr>
<td>T2*</td>
<td>Axial</td>
<td>GRE</td>
<td>2000 - 2100</td>
<td>12 and 21</td>
<td>60-70</td>
<td>24-40</td>
<td>256 x 128</td>
<td>2-4</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>T2*</td>
<td>Left Obturator</td>
<td>GRE</td>
<td>2000 - 2100</td>
<td>12 and 21</td>
<td>60-70</td>
<td>22-30</td>
<td>256 x 128</td>
<td>2-4</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>T2*</td>
<td>Right Obturator</td>
<td>GRE</td>
<td>2000 - 2100</td>
<td>12 and 21</td>
<td>60-70</td>
<td>22-30</td>
<td>256 x 128</td>
<td>2-4</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Axial</td>
<td>FSPGR</td>
<td>175</td>
<td>1.8</td>
<td>80°</td>
<td>22-30</td>
<td>256 x 128</td>
<td>2-4</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Coronal</td>
<td>FSPGR</td>
<td>175</td>
<td>1.8</td>
<td>80°</td>
<td>22-30</td>
<td>256 x 128</td>
<td>2-4</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>T1 3D</td>
<td>Axial</td>
<td>FAME</td>
<td>4.5-13</td>
<td>1.4-5</td>
<td>8° to 15°</td>
<td>24-40</td>
<td>256 x 256</td>
<td>2-4</td>
<td>1-2</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

### Siemens MRI Scanners

<table>
<thead>
<tr>
<th>Scan Name</th>
<th>Plane</th>
<th>Sequence</th>
<th>TR (ms)</th>
<th>TE (ms)</th>
<th>FOV (cm)</th>
<th>Flip</th>
<th>Matrix</th>
<th>Averages (Acq)</th>
<th>Slice Thickness (mm)</th>
<th>Slice Gap (mm)</th>
<th>Turbo Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localizer</td>
<td>3-plane</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Axial</td>
<td>TSE</td>
<td>5000 - 6000</td>
<td>80-100</td>
<td>160°</td>
<td>24-40</td>
<td>256 x 256</td>
<td>2-4</td>
<td>3</td>
<td>0</td>
<td>8 to 12</td>
</tr>
<tr>
<td>T2</td>
<td>Sagittal</td>
<td>TSE</td>
<td>5000 - 6000</td>
<td>80-100</td>
<td>160°</td>
<td>24-40</td>
<td>256 x 256</td>
<td>2-4</td>
<td>3</td>
<td>0</td>
<td>8 to 12</td>
</tr>
<tr>
<td>T2*</td>
<td>Axial</td>
<td>GRE</td>
<td>3000</td>
<td>12</td>
<td>75°</td>
<td>24-</td>
<td>256 x 256</td>
<td>2-4</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Scan Name</td>
<td>Plane</td>
<td>Sequence</td>
<td>TR (ms)</td>
<td>TE (ms)</td>
<td>FOV (mm)</td>
<td>Matrix</td>
<td>Averages (NSA)</td>
<td>Slice Thickness (mm)</td>
<td>Slice Gap (mm)</td>
<td>Turbo Factor</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>-------</td>
<td>----------</td>
<td>---------</td>
<td>---------</td>
<td>----------</td>
<td>--------</td>
<td>----------------</td>
<td>---------------------</td>
<td>-----------------</td>
<td>--------------</td>
<td></td>
</tr>
<tr>
<td>Localizer</td>
<td>3-plane</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Axial</td>
<td>FSE</td>
<td>4500-5500</td>
<td>80-100</td>
<td>180°</td>
<td>24-40</td>
<td>256 x 256</td>
<td>2-4</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Sagittal</td>
<td>FSE</td>
<td>4500-5500</td>
<td>80-100</td>
<td>180°</td>
<td>24-40</td>
<td>256 x 256</td>
<td>2-4</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>T2*</td>
<td>Axial</td>
<td>FFE</td>
<td>3000-3500</td>
<td>12 and 21</td>
<td>20° to 30°</td>
<td>24-40</td>
<td>256 x 128</td>
<td>2-4</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>T2*</td>
<td>Left Obturator</td>
<td>FFE</td>
<td>3000-3500</td>
<td>12 and 21</td>
<td>20° to 30°</td>
<td>22-30</td>
<td>256 x 128</td>
<td>2-4</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>T2*</td>
<td>Right Obturator</td>
<td>FFE</td>
<td>3000-3500</td>
<td>12 and 21</td>
<td>20° to 30°</td>
<td>22-30</td>
<td>256 x 128</td>
<td>2-4</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Axial</td>
<td>T1 FFE</td>
<td>175</td>
<td>1.8</td>
<td>80° to 90°</td>
<td>22-30</td>
<td>256 x 128</td>
<td>2-4</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Coronal</td>
<td>T1 FFE</td>
<td>175</td>
<td>1.8</td>
<td>80° to 90°</td>
<td>22-30</td>
<td>256 x 128</td>
<td>2-4</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>T1 3D</td>
<td>Axial</td>
<td>THRIVE</td>
<td>4.5-13</td>
<td>1.4-5</td>
<td>8° to 15°</td>
<td>24-40</td>
<td>256 x 256</td>
<td>2-4</td>
<td>1-2</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

### Philips MRI Scanners

<table>
<thead>
<tr>
<th>Scan Name</th>
<th>Plane</th>
<th>Sequence</th>
<th>TR (ms)</th>
<th>TE (ms)</th>
<th>FOV (mm)</th>
<th>Matrix</th>
<th>Averages (NSA)</th>
<th>Slice Thickness (mm)</th>
<th>Slice Gap (mm)</th>
<th>Turbo Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localizer</td>
<td>3-plane</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Axial</td>
<td>FSE</td>
<td>4500-5500</td>
<td>80-100</td>
<td>180°</td>
<td>24-40</td>
<td>256 x 256</td>
<td>2-4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>T2</td>
<td>Sagittal</td>
<td>FSE</td>
<td>4500-5500</td>
<td>80-100</td>
<td>180°</td>
<td>24-40</td>
<td>256 x 256</td>
<td>2-4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>T2*</td>
<td>Axial</td>
<td>FFE</td>
<td>3000-3500</td>
<td>12 and 21</td>
<td>20° to 30°</td>
<td>24-40</td>
<td>256 x 128</td>
<td>2-4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>T2*</td>
<td>Left Obturator</td>
<td>FFE</td>
<td>3000-3500</td>
<td>12 and 21</td>
<td>20° to 30°</td>
<td>22-30</td>
<td>256 x 128</td>
<td>2-4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>T2*</td>
<td>Right Obturator</td>
<td>FFE</td>
<td>3000-3500</td>
<td>12 and 21</td>
<td>20° to 30°</td>
<td>22-30</td>
<td>256 x 128</td>
<td>2-4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>T1</td>
<td>Axial</td>
<td>T1 FFE</td>
<td>175</td>
<td>1.8</td>
<td>80° to 90°</td>
<td>22-30</td>
<td>256 x 128</td>
<td>2-4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>T1</td>
<td>Coronal</td>
<td>T1 FFE</td>
<td>175</td>
<td>1.8</td>
<td>80° to 90°</td>
<td>22-30</td>
<td>256 x 128</td>
<td>2-4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>T1 3D</td>
<td>Axial</td>
<td>THRIVE</td>
<td>4.5-13</td>
<td>1.4-5</td>
<td>8° to 15°</td>
<td>24-40</td>
<td>256 x 256</td>
<td>2-4</td>
<td>1-2</td>
<td>0</td>
</tr>
</tbody>
</table>
APPENDIX XII
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 XIII

COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA)/CLINICAL TRIALS AGREEMENT (CTA)

The study agent will be provided via NCI Pharmaceutical Branch under the CIP/DCTD/NCI Clinical Trials Agreement with AMAG Pharmaceuticals Inc.

The agent used in this protocol, which is supplied by CIP/DCTD/NCI, is provided to the NCI under a Clinical Trials Agreement (CTA) between the Pharmaceutical Company(ies) [hereinafter referred to as “Collaborator”] and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the “Intellectual Property Option to Collaborator” contained within the terms of award, will apply to the use of the Agent in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a Participant participating on the study or Participant’s family member, the individual should sign a confidentiality agreement.

2. Only one investigational agent will be used in this study. Therefore, there is to be no “Multi-Party data.”

3. Clinical Trial Data and Results and Raw Data developed under a collaborative agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate. All data made available will comply with HIPAA regulations.

4. Any manuscripts reporting the results of this clinical trial will be provided to CIP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator’s confidential and proprietary data, in addition to Collaborator(s)’s intellectual property rights, are protected. Copies of abstracts will be provided to CIP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations will also be forwarded to CIP prior to release. Copies of any manuscript, abstract, and/or press release/ media presentation will be sent to:

    Lalitha Shankar, MD
    Molecular Imaging Branch, CIP, DCTD, NCI
    6130 Executive Boulevard, Room 6048
    Bethesda, MD  20892-7412
    FAX 301-480-3507
    E-mail: shankarl@mail.nih.gov
APPENDIX XIV
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 16.10 – Table D2 and 16.10.2);
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.

Non-Serious Combidx (ferumoxtran-10) 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. Determine the regulatory reporting requirements for the IND (see sections 16.8 – Table D1 and 16.9.2);
4. Complete the AE form and paper template of AdEERS, if applicable (only unexpected grade 2 require expedited reporting) with all the information reported or assessed;
5. Have the PI sign and date the AE form and the paper template of AdEERS;
6. For AEs that require expedited reporting, provide documentation of the report/assessment and the completed paper AE form and paper template of AdEERS to the GOG data manager for data entry and submission to the clinical database and electronic AdEERS within the appropriate timeframe to ensure meeting the regulatory reporting timeframe;
7. For routine reporting of AEs, only the AE form will need completion. The completed AE form will be provided to the GOG data manager for data entry and submission to 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.

**Serious Combidex (ferumoxtran-10) 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 IND (see sections 16.8 – Table D1 and 16.9.2);
4. Complete the AE form and paper template of AdEERS with all the information reported or assessed;
5. Have the PI sign and date the AE form and the paper template of AdEERS;
6. For expedited AE reporting, provide documentation of the report/assessment and the completed paper AE form and AdEERS form to the GOG data manager for data entry and submission to the clinical database and electronic AdEERS within the appropriate timeframe to ensure meeting the regulatory reporting timeframe.

**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.

**Non-Serious Combidex (ferumoxtran-10) AE – Routine and Expedited Reporting**

1. Review the documentation and completed AE form and paper template of AdEERS, if applicable (only unexpected grade 2 require expedited reporting per sections 16.8 – Table D1 and 16.9.2) for the ferumoxtran-10 AE forwarded by the ACRIN RA for completion;
2. Data enter and submit the AE form into the clinical database and the AdEERS information into the electronic AdEERS, if applicable, within the specified regulatory reporting timeframe.

**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 D1 and 16.9.2) for the imaging AE forwarded by the ACRIN RA to ensure forms are completed;
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.

**Serious Combidex (ferumoxtran-10) AE – Routine and Expedited Reporting**
1. Review the documentation and completed AE form and paper template of AdEERS (see sections 16.8 – Table D1 and 16.9.2) for the imaging AE forwarded by the ACRIN RA to ensure forms are completed;
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 16.10 – Table D2 and 16.10.2);
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.