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TO: ALL PRINCIPAL INVESTIGATORS/NURSES/DATA MANAGERS

FROM: LEAH MADDEN  
PROTOCOL SECTION

DATE: NOVEMBER 9, 2009

RE: PROTOCOL GOG-0233 ACRIN 6671, REVISIONS 7 & 8

**Protocol Title:** Utility of Preoperative FDG-PET/CT Scanning Prior to Primary Chemoradiation Therapy to Detect Retroperitoneal Lymph Node Metastasis in Patients With Locoregionally Advanced Carcinoma of the Cervix (IB2, IIA  $\geq$ 4 cm, IIB-IVA) or Endometrium (Grade 3 Endometrioid Endometrial Carcinoma; Serious Papillary Carcinoma, Clear Cell Carcinoma, or Carcinosarcoma (Any Grade); and Grade 1 or 2 Endometrioid Endometrial Carcinoma With Cervical Stromal Involvement Over in Clinical Examination or Confirmed by Endocervical Curettage) *NCI Version 10/23/09*

**GOG Study Chair:** Michael Gold, M.D. [michael.gold@vanderbilt.edu](mailto:michael.gold@vanderbilt.edu)  
**ACRIN Study Chair:** Mostafa Atri, M.D., Dip., Epid. [Mostafa.atri@uhn.on.ca](mailto:Mostafa.atri@uhn.on.ca)

**IRB Review Recommendation:**

- No review required
- Expedited review; however, site IRB requirements take precedence
- Full board review recommended because there have been modifications to the eligibility criteria and consent.

Please direct questions about the recommended level of IRB review to your local IRB. The local IRB is responsible for making this determination. If your local IRB does not agree with the GOG's recommended level of review, please document the IRB's decision, and the rationale for the decision, in your study files

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Multiple changes have been made to GOG-0233/ACRIN 6671. These changes have resulted from the addition of endometrial cancer patients (Revision 7). Before Revision 7 could be posted we were informed that the agent ferumoxtran-10 (Combidex) was going to expire on November 16, 2009 and that the company would not manufacture any more of the agent. Subsequently, Revision 8 resulted removing all reference to ferumoxtran-10 (Combidex) and the MRI procedure component of the trial.

We have listed Revisions 7 & 8 below, in order and in their entirety.

Both Revisions 7 & 8 will become effective on November 16, 2009. Once these Amendments are approved by your local IRB, you will be running the trial under the Amendment 8 contents which reflect the addition of the endometrial cohort from Amendment 7 and the removal of the Combidex MRI procedures from Amendment 8.

**\*\*PLEASE NOTE: Your site will be unable to accrue patients to the GOG-0233/ACRIN 6671 trial until both Amendment 7 & 8 have been approved by your local IRB.**

#### **Changes made for Revision #7:**

In addition to routine corrections for grammar and clarity, Amendment 7 changes have been made to introduce a new cohort to the study (comprising patients with high risk endometrial carcinoma) and reduce the sample size target for the cervical carcinoma cohort.

- |                   |   |                                                                                                                                                                                                                      |
|-------------------|---|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| General           | - | Reference numbers have been revised to accommodate new inclusions with the introduction of a second cohort of patients to the study and to reference them in numerical order according to appearance in the protocol |
| Title Pages       | - | The title has been revised to reflect change to study                                                                                                                                                                |
|                   | - | GOG Co-Chair Matthew A. Powell, MD, has been added                                                                                                                                                                   |
|                   | - | Revision #7 has been added                                                                                                                                                                                           |
|                   | - | NCI Version Date has been updated (on every page)                                                                                                                                                                    |
| Table of Contents | - | Has been updated, including two additional Appendices and distinctions in sections related specifically to participants with cervical or endometrial cancer.                                                         |
| Schemas           | - | Page 5, the title has been revised to reflect changes to the study.                                                                                                                                                  |
|                   | - | First schema has been identified as cervical-specific.                                                                                                                                                               |
|                   | - | Schema has been revised, including the addition of a joint review of images between radiologists and gynecologic oncologists before planned lymphadenectomy.                                                         |
|                   | - | Page 6, a new endometrial-specific Schema has been added.                                                                                                                                                            |
|                   | - | Pages 6–7, Specific Aims/Objectives has been revised to include aims related to the endometrial-cancer cohort.                                                                                                       |

- Page 7, Methods/Methodology, enrollment target numbers have been revised for the total, cervical cohort, and new endometrial cohort; interim analysis plans have been outlined for after 40 positive cases.
  - Pages 7–8, Eligibility has been revised to specify those applicable to the cervical-cancer cohort and to include criteria for the new endometrial-cancer cohort; additional revisions have been made for consistency.
  - Page 8, Required Sample Size, revisions address the new target accrual numbers, introduction of the endometrial-cancer cohort, and optional arm of the study including participants from either disease cohort.
- Section 1.0
- Pages 9–10, 2<sup>nd</sup> paragraph, numbers have been revised to match those in Section 2.1.
  - A third paragraph has been added to address inclusion of endometrial-cancer cohort.
  - Paragraphs four and five have been revised to include endometrial cancer; clean up language; ensure that acronyms are spelled out at first mention; describe staging and grade details for each patient cohort; identify the increase of enrollees to 380 participants; and identify that seven central readers will assess PET/CT scans and seven central readers will assess the ferumoxtran-10 MRI scans.
- Section 2.0
- Pages 10–16, section subheaders have been added to this section for easier identification of background topic; references have been updated; sections have been renumbered.
- Section 2.2
- Pages 10–11, an “Endometrial Cancer” section has been added to provide the background and significance of patients with this disease being included in the study.
- Section 2.3
- Pages 11–12, instances of “patient” have been revised to “participants” in several places; “ultrasound” is spelled out at first mention; other changes have been made for grammatical reasons  
Pages 12–13, two paragraphs have been extensively revised/updated and Table 1 has been altered.
- Section 2.4
- Page 14, 2<sup>nd</sup> paragraph, a new introductory sentence has been added related to the lack of data in the literature for Combidex

use in MRI for evaluating endometrial and cervical cancer alone; the Table number has been updated.

- Section 2.5 - Page 15, 5<sup>th</sup> paragraph, “and ferumoxtran-10 MRI scan” has been added to the 2<sup>nd</sup> sentence; abdominal lymph node assessment is specified for cervical carcinoma; abdominal and pelvic lymph node assessment is specified for high-risk endometrial cancer; and reference to evaluation of diagnostic sensitivity and specificity of the preoperative ferumoxtran-1 MRI scan has been deleted.
- Section 2.6 - Pages 15–16, 4<sup>th</sup> bullet, “subjects” has been replaced with “participants” in several locations, specifying “(from either disease cohort)” in the 2<sup>nd</sup> sentence in relation to the 40 participants in the optional arm of the study; “both” is now “two” in the 2<sup>nd</sup> sentence; other changes have been made for grammatical purposes and consistency.
- Section 3.1 - Page 16, “patient” has been revised to “participant” in Sections 3.1.1 and 3.1.2; new primary objectives specific to the inclusion of the endometrial-cancer cohort have been introduced as Sections 3.1.3 and 3.1.4.
- Section 3.2 - Pages 16–18, “patient” has been revised to “participant” in Sections 3.2.1 and 3.2.2; “compare” has been revised to “evaluate” in Section 3.2.2; new secondary objectives specific to the inclusion of the endometrial-cancer cohort have been introduced as Sections 3.2.3, 3.2.4, 3.2.9, 3.2.14, and 3.2.15; other secondary aims have been revised to specify that analyses will include specific or both participant populations for the trial; the final paragraph of the section has been revised to call out specific objectives reflective of these revisions and new inclusions.
- Section 4.0 - Page 18, the Study Overview has been revised extensively to: reflect the increase in total accrual target to 380 participants and the new inclusion of the endometrial-cancer cohort; numbers related to enrollment and positive nodal cases for interim analysis, based on estimates of disease incidence, have been revised with details added.
- Section 5.0 - Pages 18–22, Sections 5.1 through 5.5: Eligibility Criteria have been revised for language consistency (i.e., making sure all Inclusion Criteria relate to “Participants” and all Exclusion Criteria relate to “Patients”); to correct grammar issues (such as 5.1.4); to specify that the pre-existing Criteria related to the Cervical Cancer cohort; to add new Sections 5.3 and 5.4 related

specifically to the new Endometrial Cancer cohort; and to renumber subsequent sections with these additions; and to introduce the endometrial cancer cohort to each discussion as appropriate.

Pages 22 and 23, Section 5.6: Gender and Minority Accrual Estimates have been revised to reflect new target accrual numbers and to add a table specific to new endometrial-cancer cohort.

Section 6.0 - Pages 23–24, minor revisions have been made to include the endometrial-cancer cohort and the inclusion of a second Informed Consent Form Template for potential participants with endometrial cancer (see Appendix III).

Section 7.1.2 - Page 24, an apostrophe has been deleted to correct for grammar.

Section 8.1 - Pages 24–25, a sentence has been added to the 1<sup>st</sup> bullet allowing for surgeon’s discretion in the event a woman with endometrial cancer is found to have lymphadenopathy above the renal hilum or extensive abdominal/pelvic lymphadenopathy (allowing for the participant to proceed to complete pelvic and para-aortic lymphadenectomy without a percutaneous biopsy of the supra-renal adenopathy).

Section 8.3 - Pages 26–27, Sections 8.3.1 through 8.3.3 have been extensively revised to include technical difficulty, unresected lymph node, retroperitoneal fibrosis, parameters specific to the cervical- or endometrial-cancer cohort.

Section 8.3.1.1- Page 26, has been added to describe joint review of the PET/CT and MR images between the radiologists and the surgeon prior to lymphadenectomy to ensure the images are considered in surgical planning and that involved lymph nodes are removed by the surgeon.

Section 8.3.2 - Page 26, 9<sup>th</sup> bullet has been revised to specify that conversion to a trans-peritoneal approach for lymphadenectomy is inappropriate for participants from the cervical-cancer cohort.

Page 26, 10<sup>th</sup> (final) bullet has been added to specify that conversion between three lymphadenectomy approaches (extra-peritoneal, trans-peritoneal, and laparoscopic) is allowable for participants from the endometrial-cancer cohort.

Section 8.3.4 - Pages 27–28, Section 8.3.4’s modified or aborted lymph node sampling options have been revised to explain that extent of

tumor spread found at laparotomy, should it render lymphadenectomy not standard-of-care therapy, is an acceptable reason for surgeons to abort lymphadenectomy; this aborted lymph node sampling will not be considered a protocol violation unless the procedure is aborted when it should not have been or if the procedure was done incorrectly.

- Section 8.4 - Pages 28–29, revisions have been made to include the endometrial-cancer cohort (Section 8.4.1.1); describe procedures in the event the PET/CT identifies interperitoneal or supra-renal lymph node disease is detected (new Section 8.4.2.1) among participants with endometrial carcinoma; and to add a hyphen for grammatical consistency (Section 8.4.4).
- Section 8.5 - Pages 29–31, changes have been made for grammatical consistency, to update references, and to specify instructions for participants with cervical versus endometrial carcinoma.
- Section 9.0 - Pages 31–41, Study Procedures: Sections have been split into Cervical-Cancer specific (Sections 9.1 through 9.10) and Endometrial-Cancer specific (Sections 9.11 through 9.19). Most revisions described below are reflected in both Sections; to avoid repetition, both Sections are described together below.

Revisions include the following:

- Sections 9.1 and 9.11: A chest CT is allowable in place of a chest X-ray to exclude metastases at Registration provided the CT has already been completed;
- Language has been included throughout to specify cervical or endometrial cancer (for example, the Eligibility Criteria mentioned in Sections 9.1 and 9.11 alludes to the sections specific to either the cervical or endometrial cancer Criteria);
- Corrections have been made throughout for grammatical purposes;
- Sections 9.2 and 9.11, Visit 1 has been split into Sections 9.2.1 and 9.2.2, as well as 9.11.1 and 9.11.2, to clarify the option of Visit 1—administering the ferumoxtran-10 agent on the same day as the PET/CT scan (in the event that the MR is scheduled for the following day)—or on a Visit 1.5 subsequent day, as long as the ferumoxtran-10 administration can be completed within one week of the PET/CT scan;
- Sections 9.2 and 9.12, Visit 1 no longer needs to be completed within 7 days after the Registration Visit (this revision is reflected in the Sections 9.10 and 9.19 Study Procedures Tables, as well);
- Sections 9.3 and 9.13, Visit 2, 1<sup>st</sup> bullet has been revised for grammatical and consistency purposes;

- Sections 9.4 and 9.14, Visit 3: The header has been revised for clarification and the 1<sup>st</sup> bullet has been added to describe the image review between radiologists and surgeon prior to lymph node sampling;
- Section 9.5, Visit 4: The header has been revised for clarification and periods have been changed to semicolons for consistency;

**NOTE:** Visit 4 criteria differ between the cervical and the endometrial cohorts because no therapeutic regimen is mandated in this protocol for the endometrial cohort while chemotherapy should begin within 4 weeks of the Visit 1 PET/CT scan in the cervical cohort.

Therefore, subsequent descriptions of revisions will be addressed separately per disease-specific Procedural section:

- Section 9.6, Visit 5: The header has been revised for clarification and a period has been changed to a semicolon for consistency;
- Section 9.7, Visit 6: The header has been revised for clarification and a period has been changed to a semicolon for consistency;
- Section 9.8, Visits 7–14: The header has been revised for clarification and a period has been changed to a semicolon for consistency;
- Section 9.9, Visits 15–20: The header has been revised for clarification and a period has been changed to a semicolon for consistency;
- Section 9.10, Study Procedures Table: The Table header row has been revised in several places to fix Visits descriptions to match the prior Procedures revisions; the Procedures column on the far left has been revised to include "Ferritin Level" at Registration, split the Registration Chest X-ray (or alternative chest imaging per Section 9.1 revision) and Follow Up Chest X-rays (at investigator's discretion), add reference to use of Glucagon with MRI, add Images Review between radiologists and surgeon before lymph node surgery; and delete repetition of Visit 1 pregnancy testing; Visit 1.5 language has been added; and the footnotes have been revised for clarity, consistency, and renumbering of Section 2.3 to 2.6;
- Again, Sections 9.11 through 9.20 relate specifically to the new endometrial-cancer cohort and are all new material. Most of the revisions described above are reflected within these new Sections

- Section 11.0 - Pages 45–46, Data Collection Forms: Language has been updated throughout the descriptive paragraph for GOG-related Data Collection submissions; the Forms table itself has been updated to specify that the OSC Form will be for primary cervical cancer only, the OSE Form for primary endometrial cancer has been added for completion at Registration; the Operative report is now to be submitted via postal mail or uploaded via SEDES; and the Primary disease “Stained” Slides, Pathology Report, and Form F may also be uploaded now by SEDES; and “Section” has been capitalized in two places.
- Section 12.0 - Pages 46–55, Image Procedures have been revised to include the endometrial-cancer cohort among descriptions and to update Section and Appendix numbers.
- Page 46–47, Section 12.1.1: A sentence has been added in the NOTE related to attempts to perform T2\* sequencing early within 30 minutes of Glucagon injection; in the first paragraph under the NOTE in Section 12.1.1, a parenthesis has been added in relation to extending MRI coverage up to the renal hilum for the endometrial-cancer cohort; two sentences have been added in the final paragraph of the section to describe mandatory use of gadolinium with participants with endometrial cancer versus optional use in participants with cervical cancer and explaining that diffusion-weighted imaging (DWI) is optional for both cohorts; and other changes have been made for grammar and clarity.
  - Page 47, Section 12.1.2: An MR Imaging section describing fasting (4 hours before) and other pre-scan procedures prior to MR imaging has been added; subsequent Section numbering has been revised.
  - Pages 47–54, Sections 12.1.3 through 12.2.7: Revisions have been made to update the number of participants to 380 (Section 12.1.3, 1<sup>st</sup> sentence, 1<sup>st</sup> paragraph), for clarity, consistency (use of “ferumoxtran-10” instead of “Combidex” MRIs throughout the protocol, capitalization of “Section”), and to update ACRIN-related email addresses, as well as References, Section, and Appendix numbers.
  - Page 55, Section 12.3 has been revised to identify the revised study objectives section numbers and to describe the single reader study, number of readers, and number of scans to be obtained—  
132 scans comprising:

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

- Section 13.0                      Pages 55–61, Drug Information revisions comprise replacing a period with a comma for the IND number of the Section 13.2 header; capitalization of “Section” in multiple places throughout the section; update to Table number for Table 3 in Section 13.2.2; update of Appendix number in Sections 13.2.6 and 13.3.1; and minor changes for consistency and clarity (including moving the URL for the NCI Investigational Drug Accountability Record Form to immediately follow description of same)
- Section 14.0                      Pages 61–62, Clinical Staging and Lymphatic Evaluation: This Section has been revised to update Appendix numbers and predominantly to include cervical- and endometrial-cohort specific content, including timing of clinical and surgical staging for each cohort (1<sup>st</sup> paragraph), addition of trans-peritoneal lymph node sampling for endometrial-cancer cohort participants only (2<sup>nd</sup> paragraph), the collection of all additional regions of lymph node sampling in addition to the common 8 regions for both cohorts (2<sup>nd</sup> paragraph), change of header for Section 14.1 (to “Lymph Node Procedures” from “Lymph Node Sampling”), inclusion of “Cervical cancer only—” (Section 14.1.1 header), “Cervical or endometrial carcinomas—” (Section 14.1.2 header), and new Section 14.1.3 related to “Endometrial cancer only—*Trans-peritoneal Pelvic and Abdominal Lymph Node Sampling:*”
- Section 15.1                      Page 62, under Pathology Information, language has been added to specify that the eight regions of interest will be collected for both disease cohorts and that additional regions sampled in participants with endometrial cancer only will be performed at the surgeon’s discretion; a final sentence has been added to the paragraph to specify that: “H and E stained slides documenting tumor type and grade (and cervical stromal invasion if histologically documented) should be submitted along with complete pathology reports.”
- Section 16.0                      Pages 63–77, in several places in this Section, reference to the CTCAE has been revised from “version 3” or “v3” to the “most recent version”; references have been updated (Section 16.6.1); revisions have been made for style and to update numbering in Tables (Sections 16.6.5, 16.8, 16.10, and 16.11.1) and

Appendices (Section 16.7); and email addresses for ACRIN staff have been updated (Section 16.11.2)

Section 17.0 Page 77, 3<sup>rd</sup> paragraph, 1<sup>st</sup> sentence has been updated to reflect change to Appendix numbers and the inclusion of a second Informed Consent Form specific to the endometrial cohort

Section 20.0 Pages 78–79, Section 20.0, 2<sup>nd</sup> paragraph, 1<sup>st</sup> sentence has been revised for style; Section 20.2, 2<sup>nd</sup> paragraph, 1<sup>st</sup> sentence has been revised because CRF is spelled out in preceding paragraph; Section 20.3, 3<sup>rd</sup> sentence, “Section” is capitalized for consistency and style

Section 21.0 Pages 79–86, the Statistical Considerations section has been extensively revised to specify which objectives relate to cervical cancer only, to include new objective related specifically to the endometrial-cancer cohort, and to describe which assessments will include both disease cohorts. Specifically:

- Headers have been added under Section 21.0 (21.0.1 indicating “Cervical Carcinoma Only”; 21.0.2 indicating “Endometrial Cancer Only”; 21.0.3 indicating “Both Cervical and Endometrial Cancers”); Section 21.0.1 has been revised to describe analyses related only to the cervical-cancer cohort; Sections 21.0.2 and 21.0.3 are new; minor revisions have been made to now-21.0.4 for grammar and consistency;
- Page 81, Section 21.1, Study Design and Endpoints now includes endpoints specific to cervical cancer only, endometrial cancer only, and cervical and endometrial cancer combined, including two new Primary Aims (2<sup>nd</sup> and 3<sup>rd</sup> bullets under Section 21.1.1);
- Page 81, Section 21.1.1, 2<sup>nd</sup> paragraph 1<sup>st</sup> sentence describes that seven radiologists will be recruited to read the PET/CT scans, and seven different radiologists will be recruited to read the MRI scans;
- Pages 81–82, References have been updated and changes have been made for style, clarity, and consistency;
- Page 82, Section 21.1.2, Specific Aims and Analysis Plans, 1<sup>st</sup> paragraph, 1<sup>st</sup> sentence, reference to the two separate cohorts has been added, former reference b) relating to “analysis of the original scan interpretations performed at the participating sites” has been removed, and former c) is now b);

- Section 21.1.2, 2<sup>nd</sup> paragraph, former-3<sup>rd</sup> and 4<sup>th</sup> sentences relating to modifications while comparing PET alone have been deleted;
- Section 21.1.2, former-3<sup>rd</sup> paragraph related to the analysis of site interpretation of imaging has been deleted;
- Page 83, Section 21.1.2, now-3<sup>rd</sup> paragraph, reference to CTCAE “v3” has been deleted;
- Section 21.1.2, final paragraph, section references have been revised for consistency;
- Page 83, Section 21.2, 1<sup>st</sup> paragraph, 1<sup>st</sup> sentence has been altered to reflect that 40 positive cases from the two cohorts combined will be used in interim analysis; 3<sup>rd</sup> sentence has been updated with a new 50% minimal acceptance value ; and the final sentence has been added to explain that the analysis will be done without consideration of the cancer cohorts and using 40 positive cases;
- Pages 83–83, Section 21.2, 2<sup>nd</sup> paragraph, 2<sup>nd</sup> sentence, the null-hypothesis’ true mean sensitivity value has been changed from 60% to 50%;
- Section 21.3, Sample Size, Accrual Rate, 1<sup>st</sup> paragraph, 1<sup>st</sup> sentence, numbers have been updated to reflect the new 380-participant sample size target for both cohorts, the breakdown of 165 patients with cervical cancer and 215 patients with endometrial cancer;
- Section 21.3, 1<sup>st</sup> paragraph, 2<sup>nd</sup> sentence, “patients” is now “participants” and the accrual of 40 participants “from either disease cohort” has been specified;
- Section 21.3, 1<sup>st</sup> paragraph, 3<sup>rd</sup> sentence, Section 2.3 has been updated to Section 2.6;
- Section 21.3, 1<sup>st</sup> paragraph, 4<sup>th</sup> sentence, reference to completion timeline has been deleted;
- Section 21.3, 1<sup>st</sup> paragraph, 5<sup>th</sup> sentence, the approximate number of enrolled woman who actually have positive lymph nodes has been revised from “20-25%” to “20%” and the expected total number of positive nodes in the study is now “about 76”;

- Section 21.3, 1<sup>st</sup> paragraph, 6<sup>th</sup> sentence, the anticipated number of women from the endometrial cohort with positive lymph nodes in the abdomen that will not complete biopsy is 15% and from the cervical cancer cohort is 8%; a comma has been deleted;
- Section 21.3, 1<sup>st</sup> paragraph, 7<sup>th</sup> sentence, the number of women with reference standard information is estimated to be 30 from the cervical cancer cohort and 36 from the endometrial cancer cohort;
- Section 21.3, 1<sup>st</sup> paragraph, new-9<sup>th</sup> sentence has been added allow for the enrollment figures to be revised if the number of positive nodes is below the projected numbers;
- Section 21.3, 1<sup>st</sup> paragraph, final sentence has been revised for interim analysis once 40 positive cases from the two cohorts combined have been collected;
- Page 84, Section 21.4, Power Consideration/Stratification Factor: Section 21.4.1, Considerations for Primary Aims, 1<sup>st</sup> paragraph, 2<sup>nd</sup> sentence, the number of sample cases positive for sensitivity and negative for specificity has been updated to 30;
- Page 84, Section 21.4.1, 1<sup>st</sup> paragraph, final sentence, “ $r_2$ ” contains a subscript “2” for consistency;
- Section 21.4.1, table immediately following the 1<sup>st</sup> paragraph has been updated;
- Section 21.4.1, sentence following first section table described the following table (which has also been updated) as it relates to a possible increase in sample size of cases to 36 (positives or negatives);
- Pages 84–85, Section 21.4.1, paragraph immediately following 2<sup>nd</sup> table of the section, half length value has been updated to “0.14, assuming the true sensitivity of 80% for cervical cancer and 70% for endometrial cancer”; further, the sentence defines nod-positive and node-negative case values (30 each for cervical cancer cohort and 36 each for endometrial cancer cohort);
- Page 85, Section 21.4.2, Considerations for Secondary Aims, 2<sup>nd</sup> paragraph, 1<sup>st</sup> sentence has been revised to specify that it relates to the cervical cancer cohort; to allow for detection of

a “23%” (as opposed to a “21%”) or higher difference in sensitivity between PET/CT and PET alone; and to remove the  $r_1$  value;

- Section 21.4.2, 2<sup>nd</sup> paragraph, 5<sup>th</sup> sentence, revisions explain that the power to detect a difference of “15% (0.8 vs 0.95)” between modality sensitivities (revised from “10% [0.8 vs 0.9]”) is about “68%” (revised from “50%”);
- Section 21.4.2, 2<sup>nd</sup> paragraph, final sentence, now states that the power exceeds 80% for detecting a difference of “17% (0.5 vs 0.97)” where it was previously “15% (0.8 vs .95)”;
- Section 21.4.2, new-3<sup>rd</sup> paragraph relating to design for the endometrial cancer cohort has been added;
- Page 85, Section 21.5.2 now describes the disease-specific Informed Consent Form Templates found in Appendix III

- References - Pages 87–92, have been renumbered and re-ordered to reflect the order in which they appear in the protocol.
- Appendix II - Pages 95–97, Clinical Staging for Carcinoma of the Corpus Uteria (FIGO Classification) has been added; subsequent Appendices have been renumbered.
- Appendix III - Pages 98–121, Sample Consents for Research Study, Templates #1 (Cervical Cancer) and #2 (Endometrial Cancer): a new consent form specifically for potential participants with endometrial cancer has been added (as Template #2, starting on Page 109), and the original Sample Consent (now Template #1, starting on Page 97) for the trial has been revised to reflect revisions applicable to potential participants with cervical cancer.

**NOTE:** The following itemized revisions are largely reflected in Template #2, with the exceptions of: 1) Template #1 only contains reference to the chemotherapy Visit, mandated for participants with cervical cancer only, and 2) the inclusion in Template #2 of the use of gadolinium during MRI (see Overview table and final sentence, 1<sup>st</sup> paragraph under “What Happens With I Have an MRI Scan?”).

***Template #1: Cervical Cancer***

- Page 97, the title has been updated and shortened for patients;

- Page 97, 4<sup>th</sup> paragraph, language issues have been corrected among the 1<sup>st</sup> two sentences, creating a single sentence;
- 5<sup>th</sup> paragraph, a comma has been added to the 1<sup>st</sup> sentence;
- Page 98, under “How Many People Will Take Part in the Study?”: target accrual has been updated with descriptions of the numerical breakdown between the two disease cohorts;
- Page 98, under “What Am I Being Asked to Do in the Study?”: consistency revisions have been made; under 1<sup>st</sup> paragraph, 5<sup>th</sup> bullet, clarification has been added to explain that previous chest imaging may replace the need for baseline pre-registration chest X-ray;
- Page 99, under “Description of the MRI Scan”: 2<sup>nd</sup> paragraph, 5<sup>th</sup> sentence, “... before the scan” has been added for clarity; new-7<sup>th</sup>, 8<sup>th</sup>, and 9<sup>th</sup> sentences have been added in relation to use of Glucagon during the MR scan;
- Page 99, under “After You Have the Scans that Are Part of the Research Study”: 1<sup>st</sup> paragraph, 5<sup>th</sup> sentence, “lymph” has been added before “nodes”;
- Page 99, header for “Overview of Timeline and Procedures Associated with Study” has been revised to specify that the timeline and procedures are specific to participants with cervical cancer;
- Page 100, in “Overview ...” table, 2<sup>nd</sup> column, “Day 2” row, reference to the use of the Glucagon agent has been added;
- Other consistency changes have been made throughout the Overview;
- Page 100, under “What Happens When I Have a PET/CT Scan?”: 1<sup>st</sup> paragraph, 4<sup>th</sup> sentence has been revised to describe the FDG as a “radioactive tracer, a type of glucose (sugar) ...” and the former-5<sup>th</sup> sentence has been deleted to avoid repetition;
- Page 101, changes under “Are There Risks Associated with a PET/CT Scan?” and in the header for “What Happens When I Have an MRI Scan?” have been made for grammatical reasons;

- Page 102, under “What Is Ferumoxtran-10?”: final sentence, reference has been updated and “or endometrial cancer” has been added;
- Page 102, consistency changes have been made under “Are There Risks Associated with Ferumoxtran-10?”;
- Page 103, under “What Is a Lymph Node Dissection? ...”: 2<sup>nd</sup> paragraph, 2<sup>nd</sup> sentence, a comma has been deleted;
- Page 105, under “Are There Reproductive Risks?”: 1<sup>st</sup> paragraph, 2<sup>nd</sup> sentence has been corrected for clarity, creating a new-3<sup>rd</sup> sentence.

**Template#2: Endometrial Cancer** has been added

- Appendix IV - Page 121, the beginning of the sentence has been corrected.
- Appendix V - Pages 122–123, under “Content of Procedure”: #5, item c), “bifurcation of the aorta” replaces “mid right common iliac artery”.
- Under “Content of Procedure”: #5, item e), reference to bilateral retroperitoneal drains has been removed
  - Under “Content of Procedure”: #6, item c), has been replaced
- Appendix VI - Pages 124–125, under “Content of Procedure:” item A, #3, “this will be sent as Common Iliac Lymph Nodes.” has been added as the final sentence.
- Appendix VII - Pages 126–127, “Transperitoneal Lymphadenectomy” is new.
- Appendix XI - Pages 131–136, reference to the endometrial-cancer cohort has been added beneath the header on the first page of the Appendix and to the Ferumoxtran-10 Eligibility Checklist (which has been altered to outline highlights for both disease cohorts and to reference Section 5.0 for disease-specific Eligibility Criteria.
- Appendix XVI- Pages 144–146 has been updated with revised Table numbers to match the protocol and changes have been made for consistency.

**Changes made for Revision #8:**

- General - Reference numbers have been revised to accommodate removal of MR and Combidx components

- Section and Appendix numbers have been updated in light of removed components
- Title Pages
  - The title has been revised (at all occurrences)
  - The Agent name and associated identifying numbers have been removed
  - Revision #8 has been added
  - NCI Version Date has been updated (on every page)
- Table of Contents
  - Has been updated, including removing four Appendices

The following contain revisions to delete all Combidex MRI details, including reference to the optional arm of the study inclusive of an extra MR scan pre-ferumoxtran-10 administration, as well as reference to the involvement of AMAG Pharmaceuticals in AE reporting, auditing, and access to participant files going forward under this Amendment:

- Schemas and overviews of Aims, Methods, Eligibility, and Sample Size, Pages 5–8
- Section 1.0 , Abstract, Page 9
- Section 2.0, Background and Significance, Pages 13 and 14
- Section 3.0, Specific Aims/Objectives, Pages 14 and 15—including Primary and Secondary Aims related to the Combidex MR component
- Section 4.0, Study Overview, Page 15
- Section 5.0, Participant Selection, Pages 16–18, including the following specifics related to former Section numbers:
  - Section 5.2.9 and 5.4.9, cessation of breastfeeding related to unknown impact of ferumoxtran-10
  - Sections 5.2.12 and 5.2.13, as well as 5.4.11 and 5.4.12, contraindication to MR and history of allergic reactions to chemical or biologic compounds similar to Combidex
  - Sections 5.2.14 and 5.4.13, predisposition to specific or non-specific mediatory release due to immunodeficiency
  - Section 5.2.15 and 5.4.14, previous exposure to ferumoxides within 2 weeks of enrollment
  - Section 5.2.16 and 5.4.15, elevated pre-study ferritin levels
  - Section 5.2.18 and 5.4.17, exposure to other investigational agents within a 30-day period
- Section 8.3.1.1, under Treatment Modifications, Page 22
- Section 8.5, Evaluation Criteria, Page 25
- Section 9.0, Study Procedures, Pages 26–32

- Section 12.0, Image Procedures, Pages 37–44
- Section 12.1, Combidex MRI, has been completely deleted and subsequent sections renumbered
- Section 13.2, Ferumoxtran-10, Page 45, had been completely deleted
- Section 16.0, Adverse Events Reporting, Pages 48–55
- Section 20.0, Institutional Audits, Pages 56 and 57
- Section 21.0, Statistical Considerations, Pages 58–63
- References, Pages 64–68, have been renumbered after removing citations from deleted text
- Appendix III, Sample Consents for Research Study, Pages 73–90
- Appendix XI, Credential Procedures for PET/CT Imaging for This Study, Page 100
- Former-Appendices X and XI, Ferumoxtran-10 Dosing Chart and Sample Data Collection Sheets, have been deleted in their entirety; subsequent Appendices have been relabeled
- Former-Appendix XIII, MRI Technique Chart, has been deleted in its entirety; subsequent Appendices have been relabeled
- Former-Appendix XV, Cooperative Research Development Agreement (CRADA)/Clinical Trials Agreement (CTA), relating specifically to the IND study agent, has been deleted in its entirety; subsequent Appendix has been relabeled
- Now-Appendix XII, GOG-0233/ACRIN 6671 Responsibilities and Roles for Reporting of Adverse Events and Serious Adverse Events, Pages 105–106

Addition revisions include:

- Section 12.1.1 - Page 40, under “Oral contrast” 1<sup>st</sup> paragraph, a hyphen has been added to “MD-Gastroview<sup>®</sup>” for consistency  
Under “Oral contrast” 2<sup>nd</sup> paragraph, the “L” of “mL” has been capitalized for consistency
- Section 16.0 - Pages 46–55, have been reviewed and revised in response to Recommendations from CTEP based on review and approval of protocol Amendment #7
- Section 17.0 - Page 55, 1<sup>st</sup> paragraph, “Conference” has been capitalized
- Section 20.0 - Page 56, 2<sup>nd</sup> paragraph, the first sentence has related to timing of institutional on-site audits has been updated to the following:

“All participating institutions that enroll participants will be audited. The timing of the initial on-site audit will depend upon several factors, including the rate of accrual (both study-wide and site-specific), the number of evaluable participants enrolled at an individual site, the status of the protocol and pending amendments, and monitoring status. Generally, audits will be conducted after the number of evaluable participants

reaches 20% of targeted accrual, either study-wide and/or site-specific. Audits are typically scheduled to occur at least 3 months after an institution has been monitored, providing that monitoring did not identify issues that mandate immediate auditing. This schedule may be altered in the event of pending protocol amendments. Closure of the study to accrual will trigger auditing of all participating institutions not yet audited. Additionally, site-specific circumstances may prompt an audit at any time.”

- Appendix II - Pages 73 and 83, 3<sup>rd</sup> paragraph, “FDG” has been defined at first mention
- 1<sup>st</sup> sentence under “Why is this study being done?”: “FDG-” has been added before “PET/CT” for consistency
  - Pages 74 and 83, 1<sup>st</sup> bullet under “During the study ...”: “FDG-” has been added before “PET/CT” for consistency
  - Header for “Description of the FDG-PET/CT scan”: “FDG-” has been added before “PET/CT” for consistency
  - Pages 76 and 85, under “Are there risks associated with a PET/CT scan?”: 2<sup>nd</sup> paragraph, “People” and “they” have been replaced with “you” in three places
  - Pages 77 and 86, under “What is a lymph node dissection? What is the procedure?” 5<sup>th</sup> paragraph, 2<sup>nd</sup> sentence, a hyphen has been added to “long-term”
  - Pages 78 and 87, under “How long will I be in the study?” 2<sup>nd</sup> paragraph, 3<sup>rd</sup> bullet, a serial comma has been added
  - Pages 80 and 89, under “What are my rights as a participant?” 1<sup>st</sup> paragraph, 3<sup>rd</sup> sentence, a “decide” is now present tense as a grammatical correction

Again, all other changes are related to the deletion of the Combidex MRI.

**Please update all copies of the protocol at your institution with these changes. Do not discard the old version. Please retain a copy of earlier versions of the protocol in your regulatory binder as historical documentation.**