For Amendment 4 to RTOG 1203, A Randomized Phase III Study of Standard vs. IMRT Pelvic Radiation for Post-Operative Treatment of Endometrial and Cervical Cancer (TIME-C)

NCI/Local protocol #: RTOG-1203/ RTOG 1203

NCI Protocol version Date: March 16, 2015

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
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</thead>
</table>
| Global           | • “Radiation Therapy Oncology Group”, “RTOG Headquarters”, and “RTOG” were replaced with “NRG Oncology”, or deleted, as appropriate, throughout the protocol.  
                    • “NRG Oncology Biospecimen Resource” was amended to the current standard, “NRG Oncology Biospecimen Bank”, and “San Francisco” was added after “Bank” as appropriate. |
| Title pages      | • On the 1st title page, the affiliation and contact information for Dr. Weidhaas was amended.  
                    • On the 1st title page, the address for the Senior Statistician was amended.  
                    • On the 2nd title page, this amendment was added to the Document History table.  
                    • On the 3rd title page, the address for NRG Oncology was amended in the table. |
| 7.0              | The 1st paragraph was deleted to amend this section to current NRG Oncology standard text.                                                                                                                                 |
| 7.2.1            | The 2nd sentence was added to provide instructions regarding dose rounding.                                                                                                                                 |
| 7.2.2            | The phrase, “or NS” was added in the 1st sentence prior to “500 mL”.                                                                                                                                 |
| 10.7             | This section was amended to current NRG Oncology standard text.                                                                                                                                          |
| 11.2.3           | This section was added to provide instructions to sites for patients not receiving chemotherapy.                                                                                                          |
| 11.3.1 and 11.3.2| A window of “+/- 30 days” was added to the timeframes for imaging in follow up to provide increased flexibility for sites.  
                    • This section was added to provide the time points for the pap smear and the instruction that the pap smear is not required at progression/relapse. |
| 12.0             | The address for NRG Oncology was amended in the contact information.                                                                                                                                 |
| 12.2             | To amend this section to current RTQA standards, the following items were deleted:  
                    • The 5th bulleted item under “Digital data submission for IMRT”;  
                    • The 3rd bulleted item under “Digital data submission for standard treatment”.                                                                                                                                 |
| 13.2.2           | The 1st sentence was clarified to be more consistent with the hypothesis.                                                                                                                                 |
| 13.4.1           | • The 1st sentence in the 1st paragraph was clarified to be more consistent with the hypothesis.  
                    • In the 2nd sentence of the 2nd paragraph, the word, “change” was added prior to “score” for clarity.  
                    • The 6th paragraph was deleted because very few, if any, patient deaths by 5 weeks on study are expected. The handling of missing data is provided in the paragraph above the one deleted. |
| Appendix I,      | • Under “What will happen if I take part in this research study?” and under the tests and procedures in follow up, the timeframe for the pap smear was amended to be consistent with the schedule of follow-up clinic visits in Appendix II and was made specific to patients with cervical cancer.  
                    • Under “What side effects or risks can I expect from being in the study?” the word, “Pelvic” was added to the “Possible Side Effects of Radiation Therapy”, and the side effects were amended to current NRG Oncology standard text.  
                    • Under “Consent Form for Use of Tissue and Blood for Research”, the 2nd paragraph was amended to provide current information regarding the NCI information sheet. |
| Sample Consent   |                                                                                                                                                                                                 |
| Appendix II  
| Study Parameter Table | • Under “During Treatment”, the section to which sites are referred for details regarding labs was corrected from Section 11.3 to Section 11.2.  
| | • The “Pap Smear” in “Follow Up” was limited to patients with cervical cancer. In addition, the required time points for the pap smear were amended to be consistent with the follow-up clinic visits, with an asterisk (*) added to refer sites to Section 11.3.3 for further details. |
For Amendment 3 to RTOG 1203, A Randomized Phase III Study of Standard vs. IMRT Pelvic Radiation for Post-Operative Treatment of Endometrial and Cervical Cancer (TIME-C)

NCI/Local protocol #: RTOG-1203/ RTOG 1203

NCI Protocol version Date: August 4, 2014

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global</strong></td>
<td>Due to the transition to the National Clinical Trials Network (NCTN), “Radiation Therapy Oncology Group”, “RTOG Headquarters”, and “RTOG” were replaced with “NRG Oncology”, or deleted, as appropriate, throughout the protocol.</td>
</tr>
</tbody>
</table>
| **Title pages** | • On the 1st title page, as required by CTEP, a sentence was added beneath the title specifying NRG Oncology as leading the trial with participation of the network of NCTN organizations: the Alliance, ECOG-ACRIN, and SWOG.  
• On the 1st title page, the affiliation and contact information for the Cost Analysis Co-Chair were updated.  
• On the 1st title page, the e-mail address for the Senior Statistician was updated.  
• The protocol number and title were added to the 2nd and 3rd title pages to amend the protocol to current NRG Oncology standards.  
• On the 2nd title page, this amendment was added to the Document History table.  
• On the 3rd title page, the table was updated to CTSU’s current text. |
| **Eligibility Checklist, Page 1** | Question 1: The phrase, “within 90 day of registration”, was deleted to be consistent with changes made in Section 3.1. |
| **Eligibility Checklist, Page 2** | • Question 8, item 2: The 3rd bullet point was amended to be consistent with changes made in Section 3.1.  
• Question 8, item 4: The 1st bullet point was amended to be consistent with changes made in Section 3.1. |
| 1.0 | The last sentence of the 4th paragraph was corrected. |
| 1.6 | In the 1st paragraph, “RTOG tissue bank” was replaced with “NRG Oncology Biospecimen Resource”. |
| 3.0 | The 2nd sentence was amended to current NRG Oncology standard text. |
| 3.1.1 | The timeframe for pathologically proven diagnosis was deleted to provide more flexibility to sites enrolling patients on study. |
| 3.1.8.2 | The 3rd bullet point was amended for clarity and to provide further instructions to sites. |
| 3.1.9.2 | The 1st bullet point was amended for clarity and to provide further instructions to sites. |
| 5.1 and 5.2 | Throughout these sections, the Radiologic Physics Center or “RPC” was amended to “Imaging and Radiation Oncology Core (IROC) Houston”, and when included, the web address for RPC was amended to the web address for IROC Houston. |
| 5.4 | This section was amended to current NRG Oncology standard text. |
| The former 5.4.2 | This paragraph was deleted, as the text is now included in Section 3.1, and the subsequent paragraph was appropriately renumbered as 5.4.2. |
| 5.5 | This section was amended to current NRG Oncology standard text. |
| 6.1.5.1 | The parenthetical phrase at the end of the section was deleted. |
| 6.4.3.1 | In the 1st sentence, “upper body” was replaced with “lower body”. |
| 6.10 | In the 1st paragraph, sentences the 7th and 8th sentences were added to provide further instructions to sites. |
| 7.5 | The 4th bulleted item was amended to current NRG Oncology standard text. |
| 7.6 | In the 2nd paragraph, “RTOG Headquarters” was replaced with “IROC Philadelphia RT”. |
| 7.7 | The 3rd paragraph was amended to current NRG Oncology standard text. |
| 7.8 | • The 4th paragraph was amended to current NRG Oncology standard text.  
• The heading of the table was corrected.  
• The heading of the section below the table was corrected. |
| 12.3 | The Radiologic Physics Center or “RPC” was amended to “Imaging and Radiation Oncology Core (IROC) Houston”, and he web address for RPC was amended to the web.
address for IROC Houston.

13.4.2 The 6th paragraph and Table 13-1 were amended.

<table>
<thead>
<tr>
<th>Appendix I, Sample Consent</th>
<th>Under “Will my medical information be kept private?”, “Radiation Therapy Oncology Group (RTOG)” was replaced with “NRG Oncology” in the 1st bullet of the 2nd paragraph.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendix II Study Parameter Table</td>
<td>The timeframe for “Disease Documentation” was amended to be consistent with changes made in Section 3.1.</td>
</tr>
<tr>
<td>Appendix IV AJCC Staging System, Cervical Cancer</td>
<td></td>
</tr>
</tbody>
</table>
|   | - Primary Tumor, Tis, asterisk (*) moved to *TMN Categories* column from *FIGO stages* column.  
|   | - Primary Tumor, T4: The following language has been added (*italics*): “Tumor invades mucosa of bladder or rectum, and/or extends beyond true pelvis (*bullous edema is not sufficient to classify a tumor as T4)*”  
|   | - Distant Metastasis, M0: The following language has been deleted: No distant metastasis (*no pathologic M0; use clinical M to complete stage group)*”  
|   | - The description of Distant Metastasis, M1, was corrected. |
| Appendix IV AJCC Staging System, Endometrial Cancer |  
|   | - Primary Tumor, Tis*: deletion of “0” from *FIGO Stage* column  
|   | - Primary tumor, T1c stage deleted.  
|   | - Primary Tumor, T3a: The following language has been deleted: “Tumor invades involves serosa and/or adnexa (direct extension or metastasis)”  
|   | - Primary Tumor, T4: The following language has been deleted: “Tumor invades bladder mucosa and/or bowel mucosa (bullous edema is not sufficient evidence to classify a tumor as T4).”  
|   | - Anatomic Stages/Prognostic Groups: “Carcinomas*” was added prior to the stages. |
**For Protocol Update of: RTOG 1203 A Randomized Phase III Study Of Standard Vs. IMRT Pelvic Radiation For Post-Operative Treatment Of Endometrial And Cervical Cancer (TIME-C)**

NCI/Local Protocol #: RTOG 1203

NCI Protocol Version Date: September 16, 2013 *(April 29, 2014)*

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>As required by CTEP, references to the &quot;Adverse Event Reporting System (AdEERS)&quot; have been changed to &quot;CTEP Adverse Event Reporting System (CTEP-AERS)&quot; throughout the protocol</td>
</tr>
<tr>
<td>Title Page</td>
<td>This update was added to the Document History table</td>
</tr>
<tr>
<td>7.7.1</td>
<td>The link for the NCI Guidelines was updated</td>
</tr>
<tr>
<td>7.7.2</td>
<td>Pregnancy language was revised per current standard</td>
</tr>
<tr>
<td>10.2.2</td>
<td>Clarifying text was added to indicate that, if sites are unable to submit a tumor block or punch, 10-15 unstained slides is an acceptable alternative as currently stated in the Specimen Collection Summary Table in section 10.4</td>
</tr>
</tbody>
</table>
RTOG 1203, A Randomized Phase III Study Of Standard Vs. IMRT Pelvic Radiation For Post-Operative Treatment Of Endometrial And Cervical Cancer (TIME-C)

Study Chairs:  Ann Klopp MD, PhD;  Phone: 713-563-2444;  aklopp@mdanderson.org
Anamaria Yeung, MD; Phone: 352-265-0287;  areyna@ufl.edu

RTOG 1203 has been amended as follows:

Section 6.3.4 - 6.3.5: Bowel contouring was clarified.

Section 6.7.2.6: The standard structure names for TRIAD submission were updated.

Section 6.3.6: This section was deleted and moved to section 6.3.5.

Section 10.4: The following statement was added for clarity "Unstained slides are permitted if sites are unable to provide block or punches."

Appendix I: The date next to "Possible Side Effects of Cisplatin" was removed. This date was added in error.
RTOG 1203, A Randomized Phase III Study Of Standard Vs. IMRT Pelvic Radiation For Post-Operative Treatment Of Endometrial And Cervical Cancer (TIME-C)

Study Chairs: Ann Klopp MD, PhD; Phone: 713-563-2444; aklopp@mdanderson.org
Anamaria Yeung, MD; Phone: 352-265-0287; areyna@ufl.edu

RTOG 1203 has been amended as follows:

Title Page:
- Dr. Stephanie Shook’s last name (Pugh) and e-mail address has been updated.
- The IND# field for Cisplatin in the Protocol Agents table was revised per current RTOG standard
- The Document History table has been updated for this amendment
- The Participating Sites list was revised per current RTOG standard

Eligibility Checklist: Question 3 was updated to include “chest x-ray.” Questions 8-11 were condensed into one question to clarify that the criteria for only one scenario needed to be met. The corresponding numbers were numbered accordingly. Question 26 was added to correspond with ineligibility criteria in section 3.2.12.

Section 1.2: 1st paragraph, the word “compared” was deleted in the 3rd sentence.

Section 3.0: A statement was added about contacting RTOG per current RTOG standard.

Section 3.1.3.3: Eligibility was modified to include chest x-ray as an option.

Section 3.1.7: Eligibility was modified to allow creatinine ≤ 1.5.

Section 3.2.12: Women who are breastfeeding was added as a criteria for patient ineligibility.

Section 4.2.2: “at baseline and following treatment” was added for clarity.

Section 4.2.3: A clarifying note was added to the end of this section

Section 5.0: Instructions for accessing TRIAD and OPEN were added per current RTOG standard.

Section 5.0: Access requirements for OPEN and TRIAD were added per current RTOG standard.

Section 5.1.1: 2nd paragraph, last sentence was revised per current RTOG standard.

Section 5.1.2: This section was updated to add TRIAD information per current RTOG standard.

Section 5.3: Access requirements for TRIAD were added.

Section 5.4 and 5.5: These sections were renumbered accordingly.
Section 5.4.4: “Non-Canadian” was deleted from the heading

Section 5.4.4.1: Instructions were updated for international institutions that do not have an approved LOI for this protocol

Section 5.5: Heading was revised for clarity

Section 5.5.1: Section was revised for clarity

Section 5.5.2: Instructions were updated for RTOG Headquarters access when the OPEN system is not accessible.

Section 6.0: A note was added about data submission to TRIAD. Radiation Therapy was added as parenthetical text for clarity; the timeframe for starting radiation therapy following hysterectomy was changed from 49 days to 63 days (9 weeks).

Section 6.2.2.2: The sentence “In patients with…” was added to the section on vaginal contouring to address the scenario of distended rectum during simulation.

Section 6.3.5 and 6.3.6: Additional details about contouring and an example image of bone marrow contours was provided for clarification.

Section 6.4.3.2: The word “tumor” was deleted.

Section 6.7.1: Instructions for submitting required structures was added.

Section 6.7.2.1: “Small bowel” was changed to “bowel” since large bowel is included in the bowel contour.

Section 6.7.2.2: The critical structure values for Variation Acceptable and Deviation Unacceptable for the rectum have been revised.

Section 6.7.2.6: “Standard Structure Names for TRIAD submission” and corresponding table were added per current RTOG standard.

Section 6.10 This section was updated to clarify 2 fractions of 6 Gy vaginal cuff brachytherapy should be prescribed.

Section 6.11: The compliance criteria was revised for clarity.

Section 7.0: Chemotherapy was added as parenthetical text for clarity; the timeframe for starting concurrent chemotherapy following hysterectomy was changed from 49 days to 63 days to match with the time to start radiation therapy (9 weeks).

Section 7.1: The reference to the package insert was revised for clarity

Section 7.4: Adjuvant chemotherapy is now permitted for any patients enrolled on the study at the physician’s discretion.

Section 7.7: This section was updated per current RTOG standard.

Section 7.7.1: The reference citation date and link were updated in the 1st paragraph. The rest of the section was updated per current RTOG standard.

Section 7.7.2: This section was updated per current RTOG standard.
Section 7.7.3: First paragraph, the 2nd sentence was deleted, and the subsequent paragraphs regarding Second Malignancy were added to update this section to current CTEP text.

Section 7.8: AdEERS expedited reporting requirements were updated per current RTOG standard. The word “investigational” agent was revised to “commercially available” agent in the 1st footnote of the AdEERS expedited reporting requirements table; the “Note” at the end of the table was removed; an effective date to denote the revision to the table was added.

Section 9.1.5: Section was added to instruct caution when using anticonvulsants during cisplatin therapy.

Section 10.2 – 10.8: The numbering was corrected in these sections.

Section 10.2: Specimen submission instructions were updated per current RTOG standard.

Section 10.3.2 – 10.3.3: The references to specific protocol sections were updated.

Section 10.4: The table was updated per current RTOG standard.

Section 11.2: “The Pre-Treatment Evaluation” section was deleted, because these evaluations are included in Sections 3 and 4 as applicable per current RTOG standard. Subsequent sections were renumbered as needed.

Section 11.2 – 11.6: The numbering was corrected.

Section 11.3.1: Chest CT was changed to Chest x-ray. The requirement for any activity at the time of death was removed. Audiogram was modified to state that it is highly recommended at baseline and 4-6 weeks after radiation. Corresponding change made to Appendix I (Sample Consent) and Appendix II (Study Parameter Table).

Section 11.3.2: A Chest CT was added as an evaluation at years 1 and 3 from start of tx during follow-up. Corresponding change made to Appendix I (Sample Consent) and Appendix II (Study Parameter Table).

Section 12.2 – 12.3: Instructions for submitting data via TRIAD were added per current RTOG standard.

Appendix I (Sample Consent):

What will happen if I take part in this research study?:

- “Before you begin the study”, the History and physical examination in the 1st bullet was revised to include a record of the patient’s weight and ability to carry out activities of daily living to be consistent with Pre-treatment assessments listed in Appendix II (Study Parameter Table). “Chest x-ray” was added.
- “When you are finished receiving all treatment you will have the following tests and procedures”: The timeframe for follow-up beginning 4-6 weeks after completion of RT was revised for clarity; the history and physical exam in the 1st bullet was changed to a physical exam and revised to include a record of the patient’s weight; “CT scan” was changed to “x-ray of the chest;” the bullets under “1 and 3 years form the start of your radiation therapy” were revised for clarity. Corresponding change made to Appendix II (Study Parameter Table).

What side effects or risks can I expect from being in the study?:

The risk profile for Radiation Therapy has been revised to be consistent with the current format of CTEP provided lists of side effects.
The risk profile for Cisplatin was revised with the current CTEP provided list of side effects for this commonly-used oncology drug.

**What are the costs of taking part in this study?:**
The web link to access a copy of the “Clinical Trials and Insurance Coverage” informational brochure is no longer active; therefore the last paragraphs have been removed.

**Consent Form for Use of Tissue and Blood for Research,** “About Using Tissue, Blood, and Urine for Research”, the “Risk” section was enhanced to be consistent with current RTOG standard/ NCI Group Banking Committee recommendations for genetic testing risks.

**Appendix II (Study Parameter Table):**
- The pre-treatment CTCAE toxicity evaluation was removed, as it was indicated as a pretreatment assessment in error.
- A note was added indicating a chest CT or chest x-ray can be performed during “pre-treatment.”
- Chest x-ray was added as a follow up assessment.
- Follow up Chest CT assessments were changed to “1 and 3 years form the start of treatment.”
- An audiogram was added as an assessment during week 5 of RT treatment.
- A note was added regarding the Audiogram assessment “highly recommended for patients receiving chemo.”
- “Physical exam” was added to the performance status/weight category.

**Appendix V:** Specimen submission instructions were updated to current RTOG standard. “STF” (Specimen Transmittal Form) was changed to “ST” per current RTOG Standard.
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Study Chairs: Ann Klopp MD, PhD; Phone: 713-563-2444; aklopp@mdanderson.org
Anamaria Yeung, MD; Phone: 352-265-0287; areyna@ufl.edu

RTOG 1203 has been updated as follows:

Title Page:
- The phone number for the Quality of Life Co-Chair, Karen Gil, PhD has been corrected.
- The Document History table has been updated with the RTOG Group Activation date, to align with the new NCI Protocol Setup and Assignments Policy for newly activated trials managed within the CTSU RSS, effective October 1, 2012.

Section 7.7.1: The section of reference for the AdEERS Expedited Reporting Requirements table was added in the 2nd paragraph.

Section 11.4.1: The total length of time for follow up was added as parenthetical text for clarity.

Section 11.5.1: The additional languages for which the Expanded Prostate Cancer Index Composite (EPIC) is available and validated have been removed, as RTOG currently has permissions for the Spanish language only.

Section 11.5.2.1: The additional languages for which the FACT-G with Cervix Subscale (FACT-Cx) is available and validated have been removed, as RTOG currently has permissions for the Spanish language only.