SUMMARY OF CHANGES
Update Date: February 10, 2009

RTOG 0625, A Randomized Phase II Trial of Bevacizumab With Irinotecan or Bevacizumab With Temozolomide in Recurrent Glioblastoma

Study Chair: Mark R. Gilbert, MD; 713-792-4008; mrgilbert@mdanderson.org

RTOG 0625 has been updated as follows:

Section 4.0: A note was added indicating that patients must be offered the opportunity to participate in correlative components of the study, for clarity per current RTOG standard.

Sections 5.1-5.1.3.2: Regulatory preregistration requirements were updated for clarity per current RTOG standard.

Sections 7.2.6.1, 7.3.4.1, and 7.4.6.1: Drug supply information for non-international Canadian institutions was added for clarity per current RTOG standard.

Section 7.2.7: "according to good clinical practices and NCI guidelines" was added for clarity per current RTOG standard.

Section 10.0: A note was added indicating that patients must be offered the opportunity to participate in correlative components of the study, for clarity per current RTOG standard.

Appendix I/Sample Consent, About Using Tissue, Blood, and Urine for Research: In the second paragraph, the weblink was updated for "How is Tissue Used for Research."

Appendix III/Performance Scale: The Zubrod performance scale was deleted per current RTOG standard. Assessments for this study are based on the Karnofsky scale.
SUMMARY OF CHANGES
Amendment #3, Version Date: January 22, 2009

RTOG 0625, A Randomized Phase II Trial of Bevacizumab With Irinotecan or Bevacizumab With Temozolomide in Recurrent Glioblastoma

Study Chair: Mark R. Gilbert, MD; 713-792-4008; mrgilbert@mdanderson.org

RTOG 0625 has been amended as follows:

Cover page: Contact information for the senior statistician, Meihua Wang, PhD, was added per current RTOG standard.

At the request of CTEP, reference to the supply of investigational bevacizumab was deleted from the following places:

- Section 1.2.1, last paragraph
- Section 7.2.2, last paragraph
- Appendix I/Sample consent, Why is this study being done?, last paragraph

Sections 5.1-5.1.2.2: Regulatory preregistration requirements were updated per current RTOG standard.

Sections 7.8-7.8.2 and Section 7.9: Adverse event reporting logistics were updated per current RTOG standard.

Section 10.0: The RTOG Tissue Bank has been renamed the RTOG Biospecimen Resource and has moved to University of California San Francisco. The entire section was updated accordingly.

Section 10.6: The weblink was updated for the RTOG Patient Tissue Consent Frequently Asked Questions.

Section 13.2.1.2: In the first sentence, "treatment-related" was added before "medical complications" for increased clarity.

Section 13.5: The former Section 13.4 was moved to the new Section 13.5 and was expanded to describe the results of the efficacy and toxicity analysis that occurred after the temporary accrual closure in November 2007. Based on the analysis results, the study will continue to accrue until the final accrual objective is met. All sections were appropriately renumbered.

Appendix I/Sample consent, Why is this study being done? In the second-to-last paragraph, "every 4 weeks, a urine test will be performed" was corrected to "every 2 weeks..."
Appendix I/Sample consent, Risks and side effects related to bevacizumab: The risk profile was updated: (1) to be consistent with the current CAEPR (v 1.2, 6/19/07), which was added to Amendment 2 (broadcast date: 12/11/07); and (2) to be consistent with other RTOG bevacizumab trials. Specific changes were made as follows:

**Less Likely**

*Added*

- Dizziness
- Decrease in blood counts, which can lead to a risk of infection
- Anemia
- Low blood pressure
- Loss of appetite
- Weight loss; Itching, hives, welts of the skin
- Ulcers (open sores of the skin or mucous membrane that shed inflamed dead tissue)
- Nausea and/or vomiting
- Inflammation of the colon, which can result in stomach cramps and/or diarrhea
- Obstruction of the bowel

*Expanded*

- "Vagina" added after "mild to moderate bleeding in the tumor, stomach, intestines…"
- "Wheezing" added after shortness of breath
- "Generalized pain and pain and the tumor site" changed to "pain in the stomach, chests, joints, or muscles and/or pain…"
- "And/or change in or loss of voice" added after "hoarseness"

**Rare But Serious**

*Added*

- Fistulas (abnormal openings or passages between internal organs or from an internal organ to the surface of the body) in the lung and/or intestinal tract
- Nasal septum perforation: a hole in the wall that divides the inside of the nose, which could result in crusting in the nose, bleeding and/or discharge from the nose, and/or whistling on intake of air and which would require surgery to repair
- Kidney failure

*Expanded*

- "Vagina" added after "serious or fatal bleeding from the tumor, brain, gut…"
- "Bowel perforation and bowel anastomotic dehiscence (a tear or hole in the gastrointestinal tract). These events may lead to serious infection and require surgery to repair. In some cases it may be fatal. " changed to "Bowel perforation
and bowel anastomotic dehiscence. Bowel perforation occurs when an opening exists in the bowel wall allowing bowel contents to spill into the abdomen. Bowel anastomotic dehiscence is a breakdown in the surgical connection between two pieces of bowel. These events are rare but can lead to serious infection and require surgery to repair.

- "Severe allergic reactions…" changed to "acute and/or severe allergic reactions…"

Appendix II/Study Parameter Table, MRI Assessments: In the last row (Optional-Advanced MRI), an X was added next to Week 2 for consistency with the information contained in footnote g.

Appendix III/Performance Scale: In the Zubrod scale 4 description, "or" was deleted after "bed" because it was included in error.
RTOG 0625, A Randomized Phase II Trial of Bevacizumab With Irinotecan or Bevacizumab With Temozolomide in Recurrent Glioblastoma

Study Chair: Mark R. Gilbert, MD; 713-792-4008; mrgilbert@mdanderson.org

RTOG 0625 has been amended as follows:

Eligibility Checklist page 2 of 3: A new question # 26 was added to correspond with new Section 3.2.10.

Section 3.2.10: This criterion was added due to the black box warning of nephrogenic systemic fibrosis with gadolinium-based contrast agents in patients with severe kidney disease.

Section 7.2.9: The updated CAEPR for Bevacizumab (NSC 704865) version 1.2, June 19, 2007 replaced the previous CAEPR.

Section 11.2.2

- In the seventh sentence, "optional" was moved from before "examinations" to after "advanced" for increased clarity.
- The last two sentences were added for increased clarity.

Section 12.2: For increased clarity,

- In the first and second lines, "M forms" and "V forms" were added parenthetically, respectively.
- The third and fourth lines were added.

Appendix I: Consent for Participation in Advanced MRI Study

- In the first paragraph, the sixth sentence was deleted for increased clarity and accuracy.

Appendix II: Study Parameter Table: To clarify the timeline for the standard and advanced MRIs, the last two rows were reorganized and the footnotes corresponding to the standard and advanced MRIs (footnotes f and g) were rewritten.

Appendix V: MRI Technical Acquisition Instructions: For increased clarity, the first sentence was rewritten and the last sentence was deleted.
Appendix VI: Imaging Study Submission and Review

- In 1.1.1, "institution" was corrected to "institutions" in the bulleted text.
- In 1.1.2, reference to the Imaging Transmittal Worksheet was added in the first bullet and the second bullet was expanded for increased clarity.
- In 1.2.1 Imaging Protocol, reference to Appendix V was deleted and reference to the Imaging Transmittal Worksheet was added to reflect current protocol logistics.

To reflect current protocol logistics: in 2.2 Electronic Transfer of MRI Images, "and Raw Spectroscopy Data" was added to the title; the first sentence was deleted; "and raw MRS data files" was added to the second sentence; and the third sentence was added.

Appendix VII: ACRIN Advanced Imaging Adverse Event Reporting Instructions:
Contact information was updated in the following places:

- Under "When to report an adverse event in an expedited manner," second paragraph, first sentence.
- Under the table text: (1) second paragraph, last sentence; (2) third paragraph, second bullet; and (3) fifth paragraph.
SUMMARY OF CHANGES
Update Date: August 9, 2007

RTOG 0625, A Randomized Phase II Trial of Bevacizumab With Irinotecan or Bevacizumab With Temozolomide in Recurrent Glioblastoma

Study Chair: Mark R. Gilbert, MD; 713-792-4008; mrgilbert@mdanderson.org

RTOG 0625 has been updated as follows:

Eligibility Checklist, question 21: The question concerning standard of care MRIs (added as question 21 in Amendment 1) was moved to the last question (current question 26) due to database needs. All affected questions were appropriately re-numbered.

Appendix I: Main Study Consent

- Under "What are the costs of taking part in this study?," in the third paragraph, "Arm 2" was corrected to "Arm 1."

Appendix II: Study Parameter Table

- A row for "urine dipstick for protein" was added for consistency with information presented in Section 7.2.1.1.
- In footnote a, "lipase" was added for consistency with information presented in Section 4.1.
- In footnote d, "cycle" was added to the first sentence because it had been inadvertently missing.
SUMMARY OF CHANGES
Amendment #1, Version Date: July 18, 2007

RTOG 0625, A Randomized Phase II Trial of Bevacizumab With Irinotecan or Bevacizumab With Temozolomide in Recurrent Glioblastoma

Study Chair: Mark R. Gilbert, MD; 713-792-4008; mrgilbert@mdanderson.org

RTOG 0625 has been amended as follows:

Table of Contents

- The title for Appendix VI was changed from "Imaging Study and Review" to "Imaging Study Submission and Review."
- The title for Appendix VII was changed from "ACRIN Imaging Adverse Events Reporting Instructions" to "ACRIN Advanced Imaging Adverse Events Reporting Instructions."

Eligibility Checklist, Question 2, page 1: The former question 2 was deleted and moved to the second part of the eligibility checklist (question 26, page 3) due to database needs. Subsequent questions were appropriately renumbered.

Eligibility Checklist, Question 21, page 2: The former question 21 was deleted and moved to the second part of the eligibility checklist (question 21, page 3) due to database needs. Subsequent questions were appropriately renumbered.

Eligibility Checklist, Question 22, page 3: Wording was revised to clarify that the patient is agreeing to participate in the advanced imaging component of ACRIN 6677.

Section 2.3: Objectives for Central MRI Review were added. Subsequent sections were appropriately renumbered.

Section 2.4.1: For increased clarity and consistency with other sections of the protocol, "after two weeks of treatment" was changed to "after 2 weeks following initiation of treatment."

Section 2.4.2: For increased clarity and consistency with other sections of the protocol, "2 weeks after treatment" was changed to "2 weeks following initiation of protocol treatment" and "every" was added before "2 cycles of treatment."

Section 3.1.22: The cross reference to Section 5.2.1 was corrected to 5.2.

Section 3.2.3.3: A timeframe of within 6 months was added for consistency with the timeframe in Section 3.2.3.5.
Section 5.2

- For increased clarity, the title was changed from "Site Qualification for MR Imaging" to "Image Quality Assurance Review for MR Imaging."
- For increased clarity, the second paragraph was revised and inserted from Section 5.2.2.

Section 5.2.1: This section was revised for increased clarity.

Section 5.2.2: For increased clarity and accuracy, in the second sentence, "qualification" was changed to "image quality review" and reference to the ACRIN website was deleted.

Section 7.3.9: Neurologic adverse events were added for consistency with the informed consent.

Section 7.5.3.1: The statement in the "Remarks" column of the last row was deleted because it was included in error.

Section 7.8.4: Information was added for adverse event reporting for the magnetic resonance imaging protocol.

Sections 10.2-10.4: Tissue submission logistics were rewritten so that institutions submit all material directly to Dr. Aldape.

Section 11.2.2

- In the first sentence, reference to Appendix V was changed to a reference to the ACRIN website, to reflect current logistics.
- In the fifth sentence, reference to a list of contrast agents in Appendix V was deleted because it was deleted from the Appendix.
- The sixth sentence, concerning the standard of care MRI, was added for increased clarity and accuracy.
- In the seventh sentence, "diffusion MRI" was added for increased clarity and accuracy.
- The eighth sentence, concerning the advanced imaging sub-study, was added for increased clarity and accuracy.

Section 11.2.2.1: For increased clarity "qualification" was changed to "imaging quality assurance review" in the title and first sentence.

Section 13.1.3: Endpoints for Central MRI Review were added. Subsequent sections were appropriately renumbered.

Section 13.1.4.1: For increased clarity and consistency with other sections of the protocol, "2 weeks after chemotherapy" was changed to "2 weeks following initiation of
Section 13.1.4.2: For increased clarity and consistency with other sections of the protocol, "2 weeks after treatment" was changed to "2 weeks following initiation of protocol treatment" and "every" was added before "2 cycles of treatment."

Section 13.2.1.3

" In the first sentence, Section 13.4.2 was corrected to Section 13.5.2.

In the last sentence, "temozolomide and irinotecan" was corrected to "bevacizumab and irinotecan."

Section 13.5.4: Statistical methods were added for central MRI review to provide explicit information for this component of the trial. Subsequent sections were appropriately renumbered.

Section 13.5.5

- In the second sentence, "performed" was corrected from "performs."
- In the second sentence, for increased clarity "at" was deleted before "2 weeks" and "after" was changed to "every."

Appendix I: Main Study Consent

- Under "Why is this study being done?," the last paragraph was added. It had previously been included at the beginning of "Risks and side effects associated with bevacizumab" but was moved because the use of research versus commercial bevacizumab poses no risk to the patient.
- Under "During the study," the following wording was corrected in the third-to-last paragraph:
  - In the first sentence, "Arm 1 versus Arm 2" was corrected to "Arm 2 versus Arm 1"
  - In the third sentence, "Arm 1" was corrected to "Arm 2" and "bevacizumab and temozolomide" was corrected to "bevacizumab and irinotecan"
  - The fourth sentence was deleted and was replaced with the second sentence
  - In the second-to-last sentence, "Arm 1" was corrected to "Arm 2" and "Arm 2" was corrected to "Arm 1"
  - In the last sentence, "bevacizumab plus irinotecan" was corrected to "bevacizumab plus temozolomide" and "Arm 2" was corrected to "Arm 1"
• Under "Risks and side effects related to bevacizumab"/rare but serious, "heat failure" was corrected to "heart failure"

Appendix I: Consent for Participation in Advanced MRI Study

• In the first paragraph, first sentence, "will" was added before "undergo" for increased clarity.
• In the first paragraph, the fourth through sixth sentences have replaced the original fourth sentence for increased clarity and accuracy regarding the timing and number of scans.
• In the second paragraph, first sentence, possible associated problems were added.
• In the second paragraph, second sentence, "however" was deleted for increased clarity.
• In the third paragraph, the last two sentences were replaced by more extensive information regarding gadolinium.
• In the fourth paragraph, last sentence, blood was deleted because it was inadvertently included.
• Under "Where can I get more information?," a reference to ACRIN's Web site was added for information about MRI scans.

Appendix II: Study Parameter Table

• In the first row, last column, reference to footnote d was deleted because it was inadvertently included.
• To clarify the timeline for the standard and advanced MRIs, the last row was rewritten to distinguish between the standard and advanced MRIs, footnote f was revised, and footnote g was added.

Appendix V: MRI Technical Acquisition Instructions: The imaging parameters were removed and a reference to see the ACRIN website was added.

Appendix VI: Imaging Study Submission and Review

• In the first sentence of the first paragraph "qualification" has been deleted and replaced by "image quality assurance."
• In the third sentence of the first paragraph "qualification" has been deleted and replaced by "the imaging quality assurance review."
• In the first sentence of the fifth paragraph "Michael Nahill at mnahill@phila.acr.org" has been deleted and replaced by "Jim Gimpel at jgimpel@phila.acr.org."
• In 1.1 the title of the section "MRI Imaging Qualification" has been deleted and replaced by "ACRIN Imaging Quality Assurance Review."
• In 1.1.1 the title of the section "ACRIN Equipment Qualification" has been deleted and replaced by "Institution MRI Scanners."
In 1.1.2 the title of the section "Submission of Qualification Test Cases" has been deleted and replaced by "Submission of Test Cases for Image Quality Assurance Review."

The first bullet under 1.1.2 Submission of Test Cases for Image Quality Assurance Review has been revised and now states:
Submit for review one standard of care MRI exam to include the MRI sequences using the parameters listed on the ACRIN website at http://www.acrin.org/6677_protocol.html

In 1.1.3 the title of the section "Qualification Rationale" has been deleted and replaced by "Image Quality Assurance Review Rationale."

In 1.2 Imaging Protocol the reference to "Appendix VI" has been changed to "Appendix V."

In 1.2.1 Imaging Protocol "For more detailed information, contact Michael Nahill at mnahill@phila.acr.org" has been deleted.

In the first sentence of 2.0 MRI Image Submission Instructions "section" has been deleted.

In the sixth sentence of 2.1 under 2.0 MRI Image Submission Instructions "at imagearchive@phila.acr.org" has been added.

In the second sentence under 2.2 Electronic Transfer of MRI Images "Michael Nahill (mnahill@phila.acr.org; 215-940-8810)" has been deleted and replaced by "the ACRIN Image Management Center at imagearchive@phila.acr.org."

In the fourth sentence under 2.3 Removal of Confidential Participant Information "Michael Nahill (mnahill@phila.acr.org; 215-940-8810; 215-717-2754) or Anthony Levering (alevering@phila.acr.org; 215-574-3244)" has been deleted and replaced by "the ACRIN Image Management Center at
imagearchive@phila.acr.org."

In the second sentence of 2.4 CD Transfer "Michael Nahill (mnahill@phila.acr.org; 215-940-8810; 215-717-2754)" has been deleted.

In the first sentence of 2.5 Image Quality Control "contributing" has been deleted and replaced by "participating" and "for adequate quality" has been deleted.

Appendix VII: ACRIN Advanced Imaging Adverse Event Reporting Instructions

The title "Expected Adverse Events" has been changed to "Expected Adverse Events for Advanced Imaging Study."
The expected adverse events for gadolinium have been revised
The following clarification has been inserted as the fourth sentence in the first paragraph under section Recording of Adverse Events: For the standard MRI imaging, sites should follow standard of care practice per the local institution's policies and procedures.

Appendix VIII: Imaging Reimbursement

The imaging reimbursement for the standard MRI and advanced MRI components of the trial have been revised.
• In the first sentence of the third paragraph "sub-study" has been deleted and replaced by "ACRIN 6677 trial."

• The following statement, "For additional information please refer to the ACRIN website, http://www.acrin.org/6677_protocol.html. The form is listed under protocol specific contents as 0625/0677 CRS," has been added to this appendix to provide clarification for participants looking for further information about the reimbursement process.
SUMMARY OF CHANGES
Update Date: March 1, 2007

RTOG 0625, A Randomized Phase II Trial of Bevacizumab With Irinotecan or Bevacizumab With Temozolomide in Recurrent Glioblastoma

Study Chair: Mark R. Gilbert, MD; 713-792-4008; mrgilbert@mdanderson.org

To clarify the ACRIN imaging component of this trial, RTOG 0625 has been updated as follows:

Index: Appendices VI, VII, VIII re-titled per changes described below.

Eligibility Checklist, question 21: Added. All subsequent questions re-numbered.

Section 3.1.22: Added.

Sections 5.2-5.2.2: Re-written.

Section 5.3: First paragraph re-written.

Section 11.2.2: Appendix cross-reference corrected.

Section 11.2.2.1: Added.

Section 11.2.3: Appendix cross-reference corrected.

Section 11.2.4: Appendices cross-references corrected.

Section 12.2: Due dates for MRIs corrected.

Appendix II: Footnote f re-written.

Appendix VI:

- "Advanced" deleted from title.
- First paragraph: Last 2 sentences modified.
- Third paragraph: Appendix cross-reference corrected.
- Fifth paragraph: Appendix cross-reference added.
- Sixth paragraph: Contact information updated.
- Sections 1-1.1.3: Re-written.
- Sections 2-2.2: Re-written and re-numbered. All subsequent sub-sections re-numbered.
- Sections 2.2-2.4: Contact information updated.
Appendix VII:

- "Advanced" deleted from title.
- Expedited Reporting to NCI, RTOG, and/or ACRIN: #5 re-written.

Appendix VIII:

- "Advanced" deleted from title.
- #3 and second-to-last and last paragraphs: Re-written.

The following additional changes were made:

**Cover page:** Phone number for Dr. Gilbert updated.

**Schema page:** Arm 2 cycle length corrected for consistency with the rest of the protocol.