For **Protocol Amendment #8: RTOG 0825/ACRIN 6686**, Phase III Double-Blind Placebo-Controlled Trial of Conventional Concurrent Chemoradiation and Adjuvant Temozolomide Plus Bevacizumab Versus Conventional Concurrent Chemoradiation and Adjuvant Temozolomide in Patients With Newly Diagnosed Glioblastoma

NCI/Local Protocol #: RTOG 0825/ACRIN 6686

NCI Protocol Version Date: October 3, 2016

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>The protocol was reformatted to comply with NCI/FDA electronic document formatting requirements.</td>
</tr>
<tr>
<td>Cover Pages</td>
<td>Contact information was updated for Drs. Gilbert, Mehta, Aldape, Zhang, and Brown.</td>
</tr>
<tr>
<td></td>
<td>NOTE: Dr. Aldape’s contact information in Section 10.2./required address for pathology submissions for central pathology review prior to randomization was not updated, as this study is closed to accrual and sites are no longer submitted pre-randomization specimens.</td>
</tr>
<tr>
<td></td>
<td>The Document History Table was updated to include this amendment.</td>
</tr>
<tr>
<td>7.6.12</td>
<td>In response to a CTEP Request for Amendment, the CAEPR for bevacizumab (Version 2.4, May 23, 2016) was revised as follows:</td>
</tr>
<tr>
<td></td>
<td>• <strong>Added New Risk:</strong></td>
</tr>
<tr>
<td></td>
<td>• <strong>Less Likely:</strong> Creatinine increased; Erythroderma</td>
</tr>
<tr>
<td></td>
<td>• <strong>Rare but Serious:</strong> Avascular necrosis; Gallbladder perforation</td>
</tr>
<tr>
<td></td>
<td>• <strong>Increase in Risk Attribution:</strong></td>
</tr>
<tr>
<td></td>
<td>• Changed to <strong>Less Likely</strong> from Also Reported on Bevacizumab Trials But With Insufficient Evidence for Attribution: Dry skin; Generalized muscle weakness; Hyperglycemia; Hypokalemia; Hyponatremia</td>
</tr>
<tr>
<td></td>
<td>• Changed to <strong>Rare but Serious</strong> from Also Reported on Bevacizumab Trials But With Insufficient Evidence for Attribution: Palmar-plantar erythrodysesthesia syndrome</td>
</tr>
<tr>
<td></td>
<td>• <strong>Deleted Risk:</strong></td>
</tr>
<tr>
<td></td>
<td>• <strong>Less Likely:</strong> Cardiac troponin I increased</td>
</tr>
<tr>
<td></td>
<td>• Also Reported on Bevacizumab Trials But With Insufficient Evidence for Attribution: Infections and infestations - Other (aseptic meningitis)</td>
</tr>
<tr>
<td></td>
<td>• <strong>Provided Further Clarification:</strong></td>
</tr>
<tr>
<td></td>
<td>• Footnote # 7 has been altered to read, “Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation.”</td>
</tr>
<tr>
<td></td>
<td>• Footnote #11 has been added and reads, “There have been reports of non-mandibular osteonecrosis (avascular necrosis) in patients under the age of 18 treated with bevacizumab.”</td>
</tr>
<tr>
<td>7.10.3 12 12.3</td>
<td>The suite address for NRG Oncology and ECOG-ACRIN was updated.</td>
</tr>
<tr>
<td>Appendix I / Sample Consent</td>
<td>To comply with NCI/FDA electronic document formatting requirements, the Sample Consent Form was removed from Appendix I and is now a stand-alone document. The following statement was added: “Appendix I/Sample Consent Form is available on the RTOG 0825 protocol-specific website as a stand-alone document.</td>
</tr>
<tr>
<td>Appendix IX/ CTSU Logistics</td>
<td>In the CTSU contact information table, RTOG was updated to NRG Oncology and the suite address was updated under the “submit data to” area. No other changes were made as other areas of this appendix are not relevant to a closed study.</td>
</tr>
</tbody>
</table>
For **Consent Amendment #8**: RTOG 0825/ACRIN 6686, Phase III Double-Blind Placebo-Controlled Trial of Conventional Concurrent Chemoradiation and Adjuvant Temozolomide Plus Bevacizumab Versus Conventional Concurrent Chemoradiation and Adjuvant Temozolomide in Patients With Newly Diagnosed Glioblastoma

NCI/Local Protocol #: RTOG 0825/ACRIN 6686

NCI Protocol Version Date: October 3, 2016

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Header/Footer</td>
<td>A version date and page numbers were added.</td>
</tr>
<tr>
<td>What side effects or risks can I expect from being in the study?</td>
<td>The introductory paragraphs were updated to current NCI standard text.</td>
</tr>
</tbody>
</table>

Under “Risks and side effects related to bevacizumab,” the risk profile for bevacizumab was amended to be consistent with the revised CAEPR for bevacizumab (Version 2.4, May 23, 2016) as follows:

- **Added New Risk:**
  - **Occasional:** Swelling and redness of the skin
  - **Rare:** Sores in the throat

- **Increase in Risk Attribution:**
  - **Changed to Occasional from Also Reported on Bevacizumab Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile):** Dry Skin; Muscle weakness
  - **Changed to Rare from Also Reported on Bevacizumab Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile):** Redness, pain or peeling of palms and soles

- **Provided Further Clarification:**
  - Damage to the jawbone which may cause loss of teeth (under Occasional) is now being reported as Damage to organs which may cause loss of teeth or loss of motion (under Occasional).

**PLEASE NOTE:** The potential risks listed in the CAEPR for which the relationship to bevacizumab is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.
For **Protocol** Amendment #7: RTOG 0825/ACRIN 6686, Phase III Double-Blind Placebo-Controlled Trial of Conventional Concurrent Chemoradiation and Adjuvant Temozolomide Plus Bevacizumab Versus Conventional Concurrent Chemoradiation and Adjuvant Temozolomide in Patients With Newly Diagnosed Glioblastoma

**NCI/Local Protocol #:** RTOG 0825/ACRIN 6686

**NCI Protocol Version Date:** June 30, 2014 (November 3, 2014)

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
</tr>
</thead>
</table>
| Global  | Due to the transition to the NCTN and the termination of the CTSU endorsement program:  
- RTOG terminology was revised to NRG Oncology terminology where applicable and additional references to RTOG were removed where no longer applicable;  
- ACRIN terminology was revised to be specific to ECOG-ACRIN or ACR terminology as applicable;  
- NCCTG terminology was revised to Alliance terminology; and  
- CTSU endorsement language was adjusted.  
Minor spelling errors were corrected.  
The protocol was repaginated per current CTEP requirements. |
| Cover pages | The document history table was updated to include Amendment 7.  
Contact information was updated for Dr. Mehta |
| 7.6.12 | In response to a CTEP Request for Amendment, the CAEPR for bevacizumab (Version 2.3, August 1, 2013) was revised as follows:  
- **Added New Risk:**  
  - **Less Likely:** Dehydration; Wound complication  
  - **Rare But Serious:** Infections and infestations – Other (necrotizing fasciitis)  
  - **Also Reported on Bevacizumab Trials But With the Relationship to Bevacizumab Still Undetermined:** Acidosis; Activated partial thromboplastin time prolonged; Agitation; Alopecia; Anxiety; Arachnoiditis; Arterial injury; Arthritis; Ascites; Ataxia; Atelectasis; Atrioventricular block complete; Atrioventricular block first degree; Back pain; Bladder spasm; Blood antidiuretic hormone abnormal; Blurred vision; Bone marrow hypocellular; Bone pain; Breast pain; Bruising; Burn; Carbon monoxide diffusing capacity decreased; Cardiac arrest; Cataract; CD4 lymphocytes decreased; Central nervous system necrosis; Cerebrospinal fluid leakage; Chelitis; Chest wall pain; Cholecystitis; Chronic kidney disease; Cognitive disturbance; Colonic stenosis; CPK increased; Cystitis noninfective; Death NOS; Depressed level of consciousness; Depression; Dermatitis radiation; Dry eye; Dry mouth; Dry skin; Dysesthesia; Dysphagia; Dysphasia; Ear and labyrinth disorders – Other (lymphatic membrane perforation); Edema face; Edema limbs; Edema trunk; Electrocardiogram QT corrected interval prolonged; Encephalopathy; Enterocolitis; Erectile dysfunction; Esophageal pain; Esophageal stenosis; Extraocular muscle paresis; Extrapyramidal disorder; Eye disorders – Other (blindness); Eye disorders – Other (conjunctival hemorrhage); Eye disorders – Other (corneal epithelial defect); Eye disorders – Other (floaters); Eye disorders – Other (ischemic CRVO); Eye disorders – Other (macular
<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye disorders – Other (transient increased IOP &gt; or = 30 mm Hg)</td>
<td>Eye disorders – Other (vitreous hemorrhage); Eye pain; Facial nerve disorder; Facial pain; Fever; Fibrosis deep connective tissue; Flatulence; Flu like symptoms; Flushing; Forced expiratory volume decreased; Fracture; Gallbladder necrosis; Gallbladder obstruction; Gastrointestinal disorders – Other (peritonitis); Generalized muscle weakness; GGT increased; Head soft tissue necrosis; Hearing impaired; Hemolysis; Hepatic necrosis; Hot flashes; Hydrocephalus; Hypercalcemia; Hyperglycemia; Hyperhidrosis; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hyperparathyroidism; Hypertriglyceridemia; Hyperuricemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hypophosphatemia; Hypotension; Hypothyroidism; Hypoxia; Injection site reaction; INR increased; Insomnia; Irregular menstruation; Joint effusion; Keratitis; Leukoencephalopathy; Libido decreased; Lipase increased; Localized edema; Lymphocele; Lymphocyte count decreased; Memory impairment; Multi-organ failure; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder – Other (polymyalgia rheumatic); Myocarditis; Nail loss; Nasal congestion; Neck pain; Nervous system disorders – Other (increased intracranial pressure); Optic nerve disorder; Oral pain; Pain in extremity; Pain of skin; Pancreatitis; Paresthesia; Pelvic pain; Pelvic soft tissue necrosis; Phlebitis; Photophobia; Photosensitivity; Proctitis; Psychosis; Pulmonary fibrosis; Purpura; Pyramidal tract syndrome; Rash acneiform; Rectal mucositis; Rectal stenosis; Renal and urinary disorders – Other (dysuria); Renal and urinary disorders – Other (ureterolithiasis); Renal hemorrhage; Respiratory failure; Respiratory, thoracic and mediastinal disorders – Other (dry nares); Respiratory, thoracic and mediastinal disorders – Other (pulmonary infarction); Restrictive cardiomyopathy; Retinal detachment; Retinal tear; Retinopathy; Right ventricular dysfunction; Serum amylase increased; Skin and subcutaneous tissue disorders – Other (diabetic foot ulcer); Skin and subcutaneous tissue disorders – Other (skin breakdown/ decubitus ulcer); Skin hyperpigmentation; Skin induration; Soft tissue necrosis lower limb; Somnolence; Stevens-Johnson syndrome; Tinnitus; Tremor; Tumor pain; Typhilitis; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction; Urinary tract pain; Vaginal discharge; Vasculitis; Vasovagal reaction; Watering eyes; Weight gain</td>
</tr>
<tr>
<td>Increase in Risk Attribution:</td>
<td>Neutrophil count decreased</td>
</tr>
<tr>
<td>Provide Further Clarification:</td>
<td>Supraventricular tachycardia is now reported as Cardiac disorders – Other (supraventricular arrhythmias) and the following footnote (#3) was added, “Supraventricular arrhythmias may include supraventricular tachycardia, atrial fibrillation and atrial flutter.”</td>
</tr>
<tr>
<td>Decrease in Risk Attribution:</td>
<td>Vertigo</td>
</tr>
<tr>
<td>Provided Further Clarification:</td>
<td>Gastrointestinal anastomotic leak is now reported as Injury, poisoning and procedural complications – Other (anastomotic leak) and the</td>
</tr>
</tbody>
</table>
following footnote (#10) was added, “Anastomotic leak may include Gastrointestinal anastomotic leak; Gastric anastomotic leak; Large intestinal anastomotic leak; Rectal anastomotic leak; Small intestinal anastomotic leak; Urostomy leak; Vaginal anastomotic leak.”

- **Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:**
  - **Added:** Dehydration; Platelet count decreased; Wound complication

- **Deleted Risk:**
  - Also Reported on Bevacizumab Trials But With the Relationship to Bevacizumab Still Undetermined: Pneumonitis; Pneumothora
For **Protocol Consent** Amendment #7: RTOG 0825/ACRIN 6686, Phase III Double-Blind Placebo-Controlled Trial of Conventional Concurrent Chemoradiation and Adjuvant Temozolomide Plus Bevacizumab Versus Conventional Concurrent Chemoradiation and Adjuvant Temozolomide in Patients With Newly Diagnosed Glioblastoma

NCI/Local Protocol #: RTOG 0825/ACRIN 6686

NCI Protocol Version Date: June 30, 2014 (November 3, 2014)

<table>
<thead>
<tr>
<th><strong>Main Consent</strong></th>
<th><strong>Will my medical information be kept private?</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main Consent</strong></td>
<td>Due to the transition to the NCTN and the termination of the CTSU endorsement program:</td>
</tr>
<tr>
<td></td>
<td>• RTOG terminology was revised to NRG Oncology terminology</td>
</tr>
<tr>
<td></td>
<td>• ACRIN terminology was revised to be specific to ECOG-ACRIN</td>
</tr>
<tr>
<td></td>
<td>• NCCTG terminology was revised to Alliance terminology.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Main Consent</strong></th>
<th><strong>Risks and side effects related to bevacizumab</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main Consent</strong></td>
<td>The risk profile for bevacizumab was amended to be consistent with the revised CAEPR as follows:</td>
</tr>
<tr>
<td></td>
<td>• <strong>Added New Risk:</strong></td>
</tr>
<tr>
<td></td>
<td>• <strong>Occasional:</strong> Dehydration; Delay in healing of wounds or spontaneous opening of wounds</td>
</tr>
<tr>
<td></td>
<td>• <strong>Rare:</strong> Flesh-eating bacteria syndrome, an infection in the deep layers of skin</td>
</tr>
<tr>
<td></td>
<td>• <strong>Decrease in Risk Attribution:</strong></td>
</tr>
<tr>
<td></td>
<td>• <strong>Changed to Reported But Undetermined from Less Likely (i.e., removed from the Risk Profile):</strong> Feeling of spinning or whirling</td>
</tr>
</tbody>
</table>

**PLEASE NOTE:** The potential risks listed in the CAEPR whose relationship to bevacizumab is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

<table>
<thead>
<tr>
<th><strong>Advanced Imaging Substudy Consent</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Making your choice</strong></td>
<td>ACRIN terminology was revised to be specific to ECOG-ACRIN.</td>
</tr>
</tbody>
</table>
For **Protocol** Update to: RTOG 0825/ACRIN 6686, Phase III Double-Blind Placebo-Controlled Trial of Conventional Concurrent Chemoradiation and Adjuvant Temozolomide Plus Bevacizumab Versus Conventional Concurrent Chemoradiation and Adjuvant Temozolomide in Patients With Newly Diagnosed Glioblastoma

NCI/Local Protocol #: RTOG 0825/ACRIN 6686

NCI Protocol Version Date: December 6, 2011
Update Date: May 1, 2014 (Broadcast May 1, 2014)

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cover pages</td>
<td>This update was added to the document history table. Peixin Zhang has replaced Minhee Won as the Statistician.</td>
</tr>
<tr>
<td>Global</td>
<td>As required by CTEP, references to the “Adverse Event Reporting System (AdEERS)” have been changed to “CTEP Adverse Event Reporting System (CTEP-AERS)” throughout the protocol.</td>
</tr>
</tbody>
</table>
| Appendix XV  | The following statement has replaced all prior text:  
|             | “AE reporting requirements for ACRIN 6686 are no longer applicable. All applicable advanced imaging has been completed and all participants in the sub-study are past the 30-day post-procedure AE reporting requirements.” |
| Informed Consent | No changes                                                                                                                                 |

Informed Consent No changes
SUMMARY OF CHANGES
Amendment #6: December 6, 2011
(Broadcast: December 16, 2011)

RTOG 0825/ACRIN 6686, Phase III Double-Blind Placebo-Controlled Trial of Conventional Concurrent Chemoradiation and Adjuvant Temozolomide Plus Bevacizumab Versus Conventional Concurrent Chemoradiation and Adjuvant Temozolomide in Patients With Newly Diagnosed Glioblastoma

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

In response to a CTEP Request for Amendment (RA) for protocols using bevacizumab (NSC 704865) RTOG 0825 was amended as follows:

Section 7.6.12: Comprehensive Adverse Events and Potential Risks list (CAEPR) version 2.2 (October 21, 2011) has replaced CAEPR Version 2.1 (May 4, 2010). Specific changes are as follows:

- The Agent Specific Adverse Event List (ASAEL) is now termed the Specific Protocol Exceptions to Expedited Reporting (SPEER) and includes grades for adverse events found on the SPEER that are used to determine if expedited reporting is required.
- Added New Risk:
  - Likely: Reproductive system and breast disorders - Other (ovarian failure)
  - Less Likely: Febrile neutropenia; Gastrointestinal obstruction
  - Also Reported on Bevacizumab Trials But With the Relationship to Bevacizumab Still Undetermined: Platelet count decreased; Palmar-plantar erythrodysesthesia syndrome

- Increase in Risk Attribution:
  - Changed to Less Likely from Reported But Undetermined: Osteonecrosis of jaw; Peripheral sensory neuropathy

- Decrease in Risk Attribution:
  - Changed to Less Likely from Likely: Diarrhea; Nausea; Vomiting; Fatigue; Headache
  - Changed to Rare But Serious from Less Likely: Acute kidney injury

- Provided Further Clarification:
  - The following footnote was added to Gastrointestinal obstruction: “Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.”
  - The following footnote was added to Osteonecrosis of jaw: “Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates.”
  - The following footnote was added to Peripheral sensory neuropathy: “Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.”
  - The following footnote was added to Reproductive system and breast disorders - Other (ovarian failure): “Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation (≥30 mIU/mL) was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of
menses and an FSH level <30 mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.”

- Renal and urinary disorders – Other (renal failure) is now reported as part of Acute kidney injury.
- Respiratory, thoracic, and mediastinal disorders – Other (rhinitis) is now reported as Allergic rhinitis.
- Skin and subcutaneous disorders – Other (rash) is now reported as Rash maculo-papular.
- Small intestinal obstruction is now reported as part of Gastrointestinal obstruction.

- Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:
  - Added: Febrile neutropenia; Colitis; Myalgia
  - Deleted: Myocardial infarction; Intracranial hemorrhage; Ischemia cerebrovascular

Appendix I/Sample Consent, Risks associated with bevacizumab: The risk profile was updated to reflect the CAEPR as follows:

- **Added New Risk:**
  - **Likely:** Loss of the normal functioning of the ovaries in a woman that can result in temporary or permanent menopause; the impact on fertility (temporary or permanent) is unknown
  - **Less Likely:** Fever associated with dangerously low levels of a type of white blood cell (neutrophils); Blockage in an organ(s)/part(s) of the digestive tract

- **Increase in Risk Attribution:**
  - **Changed to Less Likely from Reported But Undetermined:** Destruction or death of jawbone; Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning

- **Decrease in Risk Attribution:**
  - **Changed to Less Likely from Likely:** Diarrhea; Nausea or the urge to vomit; Vomiting; Fatigue or tiredness; Headache or head pain
  - **Changed to Rare But Serious from Less Likely:** Sudden decrease of kidney function

**New IND Number**
Due to reorganization of the FDA’s Office of Oncology Drug Products (OODP), bevacizumab IND 7921 was split into new INDs. As a result, RTOG 0825 was transferred to **IND 113916 (Bevacizumab – Head & Neck Cancers).** Changes were made to the **Cover Page** and **Section 7.6.**

**Additional editorial/administrative changes**
**Cover Pages:** The document history table was updated to include Amendment 6, Version Date December 6, 2011.

**Section 7.10:** The 4th paragraph was updated to reflect current process, as AdEERS paper templates are no longer available.

**Appendix I (Informed Consent), “Where can I get more information?”:** The NCI TTY number is no longer in service and has been removed.

**Appendix II (Study Parameter Table):** Line breaks were corrected in the 2nd and 3rd pretreatment columns.
Section 10.3.3 and Appendix VII (Blood/Urine Collection): Line breaks were corrected in the address for the Biospecimen Resource.
SUMMARY OF CHANGES  
Amendment #5: October 25, 2011  
(Broadcast: November 17, 2011)

RTOG 0825/ACRIN 6686, Phase III Double-Blind Placebo-Controlled Trial of Conventional Concurrent Chemoradiation and Adjuvant Temozolomide Plus Bevacizumab Versus Conventional Concurrent Chemoradiation and Adjuvant Temozolomide in Patients With Newly Diagnosed Glioblastoma

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

RTOG 0825/ACRIN 6686 was amended as follows:

**RTOG 0825**
- Global: All weblinks to sub-pages of the RTOG website were updated.

**Cover Page:** Contact information was updated for Dr. Colman.

**Section 7.10:** In the second and second-to-last paragraphs, statements referencing access to CTEP websites via the RTOG website were deleted; sites should access all CTEP websites directly.

**Section 10.3.3 and Appendix VII:** The mailing address for the RTOG Biospecimen Resource was updated.

**Section 11.4:** The link to RECIST criteria via CTEP’s website was deleted because it is no longer active.

**Appendix II:** The standard imaging contrast-enhanced MRI was noted as needing to start ≤ 28 d prior to step 1 registration, for consistency with Section 3.1.

**Appendix X/Section 3.1.2:** “on days 1 and 15 of a 28-day cycle” was added for clarity.

**ACRIN 6686**
- **Cover Page:** ACRIN Study Chair for Imaging has been updated as Dr. Jerrold Boxerman takes over the trial from Dr. A. Gregory Sorensen.

**Section 1.8.3:** 1st paragraph, 6th sentence: “1-D,” has been deleted.

**Section 2.3.1:** An extraneous period has been deleted.

**Section 11.7:** Has been extensively revised to clarify the reader study for the BIQSFP-funded ancillary study, and now reads—

> **11.7.1** All available cases with both baseline (T0) and week 22 (T2) images from the 942 cases enrolled into the study will be interpreted centrally, including both the conventional imaging arm cases from RTOG 0825 and advanced imaging arm cases from ACRIN 6686. The methods for analyzing these images will be standardized and are more fully described in the next paragraph. This will include initial visual assessments, but the manual quantitative measurements and semi-automated analyses of regions of interest will provide the majority of work and address the specific aims of the study (see Section 2.4.3).

All cases will be reviewed by board-certified radiologists with fellowship training and experience in neuro-radiology. A pair of radiologists will individually interpret the standard imaging cases from the master RTOG study and will provide the two dimensional (2-D) and volumetric (3-D) measurements using the facilities of
the ACRIN Core Laboratory. Two neuro-radiologists will perform readings at different reading sessions to ensure that the interpretations will remain independent, and the readers will perform each analysis in the case set. If the 2-D or volumetric measurements are discordant between the readers beyond a pre-defined threshold, a third radiologist will adjudicate and determine the measurement category for the dataset. A technologist will assist the reader by preparing the MRI studies for presentation and by recording the measurements. No intra-reader variability has been designed for this analysis.

Some RTOG 0825 participants will participate in the advanced imaging from the ACRIN 6686 sub-study, and the central review of those data also will use two neuro-radiologists to determine the 2-D and 3-D measurements of those scans (possibly even the same two neuro-radiologists). Both data sets will be combined and used in the statistical analysis.

11.7.2 Data collected during the central sessions include: image quality, 2-D measurements of tumor area using T1 post-contrast and T2 FLAIR series, 3-D measurement of tumor volume using T1 post-contrast series, 3-D measurement of tumor volume based on the T2 FLAIR series."

Section 12.3: Has been corrected for grammatical reasons.

Section 13.7.2.3: Reference to 1-D imaging and measurements has been deleted throughout this section.
RTOG 0825/ACRIN 6686, Phase III Double-Blind Placebo-Controlled Trial of Conventional Concurrent Chemoradiation and Adjuvant Temozolomide Plus Bevacizumab Versus Conventional Concurrent Chemoradiation and Adjuvant Temozolomide in Patients With Newly Diagnosed Glioblastoma

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

RTOG 0825/ACRIN 6686 was amended as follows:

RTOG 0825

As mandated by CTEP, beginning December 31, 2010, this study will utilize CTCAE version 4.0 for AdEERS reporting of adverse events. Related changes were made to Section 7.10, 1st paragraph.

NOTE: All AE reporting on the study case report forms will continue to use CTCAE version 3.0.

ACRIN 6686

Similarly, ACRIN has updated the previous language referencing "most recent version" of the CTCAE to specify version 4.0. Revisions are included in Appendix XV, Section 8.3, 1st sentence, and in Section 8.6, in the footnote below the "Type of Report" table.

RTOG 0825/ACRIN 6686

A document version history was added to the Cover Page per current RTOG standard.
SUMMARY OF CHANGES
Amendment #3: August 2, 2010
(Broadcast: September 2, 2010)

RTOG 0825/ACRIN 6686, Phase III Double-Blind Placebo-Controlled Trial of Conventional Concurrent Chemoradiation and Adjuvant Temozolomide Plus Bevacizumab Versus Conventional Concurrent Chemoradiation and Adjuvant Temozolomide in Patients With Newly Diagnosed Glioblastoma

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

In response to a CTEP Request for Amendment (RA) for protocols using bevacizumab (NSC 704865, IND 7921) RTOG 0825/ACRIN 6686 was amended as follows:

Section 7.6.12: Comprehensive Adverse Events and Potential Risks list (CAEPR) version 2.1 (May 4, 2010) has replaced CAEPR Version 1.2 (June 19, 2007). Specific changes are as follows: (NOTE: This CAEPR version includes frequency data. The previous version did not have the categories for Likely, Less Likely or Rare but Serious. The section below utilizes CTCAE version 4.0 language unless otherwise noted.)

Added New Risk:

- **Less Likely:** Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia); Hematuria
- **Rare But Serious:** Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy)
- **Reported on Bevacizumab Trials But with the Relationship to Bevacizumab Still Undetermined:** Hepatic failure; Osteonecrosis of jaw

Increase in Risk Attribution:

Changed to Less Likely from Reported But Undetermined: Infections and infestations - Other (peri-rectal abscess); Syncope

Decrease in Risk Attribution:

Changed to Reported But Undetermined from Possible: Skin ulceration

Provided Further Clarification:

- Allergic reaction/hypersensitivity (*CTCAE version 3.0 language*) is now reported as Allergic reaction and Anaphylaxis.
- Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip) and Nasal cavity/paranasal sinus reactions (*CTCAE version 3.0 language*) is now reported as Respiratory, thoracic, and mediastinal disorders - Other (rhinitis).
- Ventricular fibrillation (*CTCAE version 3.0 language*) is now reported as Ventricular arrhythmia and Ventricular fibrillation.
- Cardiac ischemia/infarction (*CTCAE version 3.0 language*) is now reported as Acute coronary syndrome and Myocardial infarction.
- Rash/desquamation (*CTCAE version 3.0 language*) is now reported as Skin and subcutaneous tissue disorders - Other (rash).
- Leak (including anastomotic), GI: large bowel (*CTCAE version 3.0 language*) is now reported as Gastrointestinal anastomotic leak.
- Mucositis/stomatitis (functional/symptomatic) - Select (*CTCAE version 3.0 language*) is now only reported as Mucositis oral.
- The following footnotes were added to clarify those adverse events that were previously on the version 1.2 CAEPR under - Select terms (*CTCAE version 3.0 language*): #2 (Fistula, GI), #3 (Hemorrhage, GI), #4 (Perforation, GI), and #5 (Ulcer, GI).
- Infection with normal ANC or Grade 1 or 2 neutrophils - Select and Infection with normal ANC or Grade 1 or 2 neutrophils - Select (pelvis, peritoneal cavity, rectum, scrotum, skin, wound) (*CTCAE version 3.0 language*) is now reported as Infection and the following footnote (#6) added: "Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC."
- Rectal abscess/necrosis (verbatim from source documents) is now reported as Infections and infestations - Other (peri-rectal abscess).
- Dizziness (*CTCAE version 3.0 language*) is now reported as Dizziness and Vertigo.
- Neurology - Other: (Leukoencephalopathy syndrome including reversible posterior leukoencephalopathy syndrome [RPLS]) (*CTCAE version 3.0 language*) is now only reported as Reversible posterior leukoencephalopathy syndrome.
- Fistula, pulmonary/upper respiratory - Select (*CTCAE version 3.0 language*) is now reported as Bronchopleural fistula and Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula).
- Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis) (*CTCAE version 3.0 language*) is now reported as Hoarseness.
- Fistula, GU - Select (*CTCAE version 3.0 language*) is now reported as Urinary fistula and Vaginal fistula.
- Renal failure (*CTCAE version 3.0 language*) is now reported as Acute kidney injury, Renal and urinary disorders - Other (Nephrotic Syndrome), and Renal and urinary disorders - Other (renal failure).
- Cytokine release syndrome/acute infusion reaction (*CTCAE version 3.0 language*) is now reported as Infusion related reaction.
- Visceral arterial ischemia (non-myocardial) (*CTCAE version 3.0 language*) is now reported as Vascular disorders - Other (arterial thromboembolic event), and the following footnote (#8) added: "Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack, and stroke".
- The following footnote (#7) was added to Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia): "Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates".
Peripheral neuropathy (*verbatim from source documents*) is now reported as Peripheral motor neuropathy and Peripheral sensory neuropathy.

**Modified Agent Specific Adverse Events List (ASAEL) Reporting Requirements:**

- **Added:** Pain; Wound dehiscence; Weight loss; Hematuria
- **Deleted (*CTCAE version 3.0 language*):** Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10⁹/L); Rigors/chills; Hemorrhage, pulmonary/upper respiratory: lung

**Deleted Risk:**

- **Possible (*CTCAE version 3.0 language*):** Hypotension; Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10⁹/L); Rigors/chills; Creatinine; Bronchospasm, wheezing
- **Reported on Bevacizumab Trials But with the Relationship to Bevacizumab Still Undetermined (*verbatim from source documents*):** Platelets; Cardiac arrest; Hypopigmentation; Hyperglycemia; Hypoglycemia; Hypomagnesemia; Cataract; Watery eye; Urinary frequency

**Appendix I/Sample Consent, Risks associated with bevacizumab:** The risk profile was updated to reflect the CAEPR.

*Based upon the analysis of the first 360 patients entered, the rate of patients not being randomized due to ineligibility, insufficient tissue, progression, patient refusal, or other reasons, was very much underestimated (35% vs. originally projected 15%). So a slightly higher nonrandomized rate of 35% was adopted to recalculate the targeted sample size for the study. With that rate 942 patients would have to be entered in order to have 612 patients randomized. The sample size was therefore revised from 720 to 942 patients.*

Related changes were made to the following sections:

- **Schema Pages:** required sample size updated
- **Section 1.8.3:** 1st sentence updated
- **Section 6.10.2:** 1st and last sentences updated
- **Section 11.7.1:** 1st sentence updated
- **Section 13.2.1:** Last three sentences added
- **Section 13.2.3:** Last sentence updated
- **Section 13.3:** Last paragraph added
- **Section 13.6:** Table 13.7 updated
- **Section 13.7.1:** 2nd-to-last sentence updated
- **Appendix I, How many people will take part in the study:** Updated

*Time frame prior to step 2 registration was clarified in the following places, for consistency with the eligibility checklist:*

- **3.1.4**
- 3.1.5
- 3.1.7
- 3.1.10
- 3.1.11.1
- 3.1.12.1
- 3.1.12.2
- 3.1.13
- 3.1.13.1
- 3.1.14
- 3.1.17
- 3.2.6.3
- 3.2.6.4
- 3.2.6.9
- 3.2.6.11
- Appendix II: Pretreatment assessments, ≤ 14 d prior to step 2 registration and ≤ 1 wk prior to step 2 registration

Other Changes:

Cover Pages: Contact information was updated for Dr. Mehta, Dr. Aldape, and Dr. Brown.

Study Participants: NCCTG was added as an endorsing cooperative group via the endorsement plus option.

Section 1.8: Background details have been added explaining the rationale for new Aims included to assess the MacDonald Criteria with Biomarker, Imaging Quality of Life Study (BIQSFP) funding.

Section 2.4.3: Three new BIQSFP-driven study Aims have been added.

Section 3.1.6.1: The timeframe for scanning was changed from "1 week prior to registration" to "10 days prior to the start of radiation therapy" for logistical reasons. Corresponding changes were made to the Eligibility Checklist.

Section 3.1.11.3.1: Instructions were added for calculating the UPC ratio for clarity.

Sections 6.6.1-6.6.3: Compliance criteria was revised and expanded for clarity and accuracy. Subsequent sections were appropriately renumbered.

Sections 7.1-7.1.2: Instructions for unblinding were expanded for clarity. RTOG business hours were corrected.

Section 7.4.1, last sentence: Adverse events was qualified as "treatment-related" adverse events for clarity.
Section 7.6.3, 2nd paragraph, 4th-to-last sentence: "week six of radiation" was deleted after "third dose" because it was included in error.

Section 7.6.3, 2nd-to-last paragraph, sentences 6, 7 and 10: Instructions for obtaining open-label bevacizumab were revised for clarity and accuracy.

Section 7.8.2.2, 2nd paragraph: In the first sentence, adverse events was qualified as "treatment-related" adverse events for clarity. The second-to-last sentence was rewritten and expanded for clarity.

Sections 10.3.3 and 10.5: Per current RTOG Biospecimen Resource standard, buffy coat collection was changed to whole blood collection.

Section 10.5: Instructions for serum, plasma and urine collection were revised and expanded per current RTOG Biospecimen Resource standard.

Section 10.6: Reimbursement information was revised per current RTOG standard.

Section 11.4, "NOTE" accompanying the heading: "Radiologist" was changed to "MD" for logistical reasons.

Sections 11.4.6-11.4.6.1: A definition of pseudo-progression was added for clarity.

Section 11.7: Details of the reader study design for BIQSFP component of the study assessment have been added.

Section 12.1

- The Adverse Event Form was deleted because it was included in error.
- The timing was corrected for the Treatment Summary Form.
- The timing was corrected for the Salvage Treatment Guideline Questionnaire

Section 12.3

- For clarity, the following statement was added underneath the header: "ATTENTION: Sites are to submit all cases to ACRIN for image archiving. This is not be confused with the ACRIN 6686 Advance Imaging Component."
- For clarity, the following statement was added for each scan collection: "Each scan must be accompanied by an ITW MRI submission form"

Section 13.3: Ending parentheses added to first sentence due to inadvertent omission.

Section 13.7.2.3: Rationale descriptions, analytical criteria, and power calculations for the BIQSFP-driven Aims have been introduced.

REFERENCES: New REFERENCES in support of the BIQSFP-driven Aims have been
introduced.

Appendix I/Consent Form for Use of Tissue, Blood, and Urine for Research: The web link was updated in the second paragraph.

Appendix I/Consent Form for ACRIN 6686: Advanced Imaging Sub-Study

- Under About Advanced Imaging Study, second paragraph: "the investigational" has been added.
- Above the schema, three time points was corrected to four time points; the schema has been revised to show the four time points.
- In second paragraph of the risks sections/gadolinium contrast agent: triple dose was corrected to double dose.
- In third paragraph, effects/affects typo has been corrected.

Appendix II

- Urine protein row: UPC ratio was added next to urine protein for clarity
- CD4 count row: "if lymphocyte count <500 mm³" was added to the first time point in the adjuvant phase because it was inadvertently omitted.

Appendix VII: Blood and urine collection instructions were updated to current RTOG Biospecimen Resource standard.
SUMMARY OF CHANGES
Update: September 29, 2009
(Broadcast September 29, 2009)

RTOG 0825/ACRIN 6686, Phase III Double-Blind Placebo-Controlled Trial of
Conventional Concurrent Chemoradiation and Adjuvant Temozolomide Plus
Bevacizumab Versus Conventional Concurrent Chemoradiation and Adjuvant
Temozolomide in Patients With Newly Diagnosed Glioblastoma

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

RTOG 0825/ACRIN 6686 has been updated as follows:

Eligibility Checklist-Step 2 (page 3 of 5): The second question 29 was renumbered to
question 30.

Eligibility Checklist-Step 2 (page 4 of 5): Questions 15 and 16 were added for database
purposes.

Section 6.6: At the end of 2nd sentence, 46 Gy was corrected to 60 Gy.

Section 10.3.3/Urine: "And (3) and on day 28" was corrected to "and (3) on day 28."

Section 10.4: A section for storage conditions was added per current RTOG standard.
Subsequent sections and cross-references were appropriately renumbered.

Section 10.6: Reimbursement information was updated to current RTOG standard.

Section 12.2: The web address was updated for the DDSI submission.

Appendix V/Step 3: The last sentence ["This form is faxed to CTSU (215-569-0206)
within 1-week of the completion of each assessment"] was deleted because it was
included in error.

Appendix VI: Mailing instructions were updated for urine specimens.

Note: These are editorial/administrative changes to the protocol. NCI requires that these
changes be documented on the protocol title page as "Update Date."
SUMMARY OF CHANGES
Amendment #2: August 27, 2009
(Broadcast: September 29, 2009)

RTOG 0825/ACRIN 6686, Phase III Double-Blind Placebo-Controlled Trial of Conventional Concurrent Chemoradiation and Adjuvant Temozolomide Plus Bevacizumab Versus Conventional Concurrent Chemoradiation and Adjuvant Temozolomide in Patients With Newly Diagnosed Glioblastoma

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

RTOG 0825/ACRIN 6686 has been amended as follows:

Clarifying text concerning the relationship between verifying physician and automated drug shipment was added to the following sections:

- Eligibility Checklist-Step 1, question 6
- Eligibility Checklist-Step 2, question 4
- Eligibility Checklist-Step 3, question 4
- Section 7.6.3
- Section 7.6.3.2

Information was corrected concerning instructions for CTSU sites to apply for an RTOG username and password. Sites participating through CTSU must apply for an RTOG username and password immediately after registering, to enable access to the Neurocognitive Training Procedure Letter on the 0825 forms section of the RTOG website, not to enable electronic data submission to RTOG Headquarters. The correction was made to the following places:

- Final Cover Page
- End of Eligibility Checklist
- Section 5.0
- Appendix IX: CTSU Procedures for Patient Enrollment, point 5

Cover Page: The following boxed text was added per current RTOG standard:

This protocol was designed and developed by the Radiation Therapy Oncology Group (RTOG) of the American College of Radiology (ACR). 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 RTOG nor does RTOG assume any responsibility for unauthorized use of this protocol.

Eligibility Checklist-Steps 1, 2, and 3: The page numbers associated with the header
were clarified throughout.

**Section 3.1.2:** The last bullet was added. Per Section 10.2, sites **must** submit tissue directly to Dr. Aldape in order to obtain the MGMT analysis. Patients from sites not following the protocol-specified process for obtaining MGMT results will be made ineligible.

**Section 5.3:** The last paragraph (concerning RTOG telephone registration) was deleted because telephone registration is not applicable to this study.

**Section 10.3.3:** In the first two bullets, the collection for serum/plasma/buffy coat cells and urine was corrected from 28 days prior to registration to 28 days prior to treatment. Corresponding corrections were made to **Appendix II**.

**Section 12.1:** The due date for the Follow-Up Form (F1) was corrected from "At the conclusion of protocol therapy, then q 6 months X 1 year..." to "At the conclusion of protocol therapy, then q 3 months X 1 year..."

**Section 13.4:** The treatment allocation scheme was clarified as follows

- The 3rd sentence, ("This results in 9 strata and randomization will be conducted within each stratum"), was added
- "in each stratum" was added to the 5th and 6th sentences
- "in each stratum, resulting in equal allocation for the trial overall" was added to the 7th sentence

**Section 13.5.5:** The last 6 sentences were added to explain the sensitivity analysis plan.

**Section 13.7.1:** The section was revised to include reference to the consecutive nature of case accrual and to delete reference to equal stratification and division of cases between the two study arms.

**Appendix I:** Under During the Study, 7th paragraph, the 3rd through 5th sentences were revised to clarify the patient's chances of being placed in either treatment group at each enrollment phase.

**Appendix II**

- In the adjuvant phase, "d 28 of each cycle (± 3 d)" was changed to "d 28 (± 3 d) of each cycle" for clarity.
- In the CBC row in the adjuvant phase, "and at 21 d (± 48h)" was added for consistency with Section 7 of the protocol.
- The assessment schedule for PT INR was corrected as follows:
  - In the row for PT INR for patients not on warfarin, assessments were removed during chemo-RT and in the adjuvant phase.
A row for PT INR for patients on full-dose anticoagulants was added, with assessments occurring pre-treatment, during chemo-RT, and in the adjuvant phase.

**Appendix V:** Under Step 1-Examiner Certification, point 3: Instructions for obtaining username and password for training video were updated.

**Appendix VI:** All text except for reference to the RTOG web site was deleted. Sites should access the RTOG website for this appendix.

**Appendix XA:** In the row for PT INR, patients not on warfarin was corrected to patients on full-dose anticoagulants.
SUMMARY OF CHANGES
Amendment #1: July 20, 2009
(Broadcast: September 29, 2009)

RTOG 0825/ACRIN 6686, Phase III Double-Blind Placebo-Controlled Trial of Conventional Concurrent Chemoradiation and Adjuvant Temozolomide Plus Bevacizumab Versus Conventional Concurrent Chemoradiation and Adjuvant Temozolomide in Patients With Newly Diagnosed Glioblastoma

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

RTOG 0825 has been amended as follows:

An advanced imaging substudy, ACRIN 6686, was added. Modifications were made to the following sections:

Title Pages: Altered to include ACRIN protocol number and ACRIN as a collaborator/coordinating group in the study; to specify ACRIN Study Chairs; and to add ACRIN as the Imaging Group.

Schema: A second Schema page has been added for the imaging component.

Eligibility Checklist-Step 1, intro language: Advanced imaging certification requirements added.

Eligibility Checklist-Step 2, question #29: Added.

Section 1.7: Added.

Section 2.4: Added.

Section 3.0: Introductory sentence added.

Section 3.1.6.2, final sentence and parenthetical: Added.

Section 3.2.10: Added.

Section 5.1.5: Added.

Section 6.0, header: Altered to include "/Functional Imaging"; corresponding change made to Index.

Section 6.10: Added.
Section 7.10: NOTE added.

Section 7.11: NOTE added.

Section 11.3.1: Header and Section number added.

Section 11.3.2: Added.

Section 12.3: Header revised; NOTE added.

Section 12.4: Added.

Section 13.0: NOTE added.

Section 13.7: Added.

References: Additional references added.

Appendix I, Consent Form for Advanced Imaging Component: Added.

Appendix II: Advanced Imaging parameters introduced and distinguished from Standard Imaging; footnote added; additional clarifying table for Advanced Imaging time points added.

Appendix XII, title: Altered to specify "Standard MR" imaging; corresponding change made to Index.

Appendix XIII: Added; corresponding change made to Index.

Appendix XIV: Added; corresponding change made to Index.

Appendix XV: Added; corresponding change made to Index.

Other modifications:
Title Page: Email address for Dr. Wang updated.

Eligibility Checklist-Step 2, (page 6 of 7), question 14: Added for internal database needs.

Section 3.1.6: "Prior to registration" clarified as "Prior to step 1 registration"; corresponding change was made to Eligibility Checklist-Step 2, (page 3 of 7), question 7

Section 5.3, 2nd-to-last paragraph: Email address for web support updated.
Section 7.3.4.2: Last sentence expanded to last 4 sentences for clarity.

Section 7.8.2.1, last bullet: "Grade 3 or 4" corrected to "Grade 4."

Section 7.8.2.2, 2nd paragraph, 1st sentence: "10/L" corrected to "10^9/L"  

Section 10.3 and Appendix VII: Contact information for RTOG Biospecimen Resource updated.

Sections 11.3.1 and 11.5.1: Parenthetical note concerning CT option added for clarity.

Section 12.3

- TRIAD contact information: Updated.
- Item/Due table: "Scans obtained in follow-up, after protocol treatment…" and "Scans obtained during salvage treatment..." deleted because they were included in error.

Appendix I

- Risks and side effects related to temozolomide, rare but serious, last bullet: "while" corrected to "white"
- Risks and side effects related to bevacizumab, rare but serious: Extraneous bullet point deleted.
- Risks and side effects related to antibiotic treatment for Pneumocystis pneumonia prevention: For clarity, introductory paragraph expanded and parenthetical note deleted.
- About Using Tissue, Blood, and Urine for Research, third paragraph, 1st sentence: "before you before your start treatment" corrected to "before you start treatment"

Appendix II

- Pre-treatment/first column: "possibly" corrected to "possible"
- Assessments/3rd row: "CT" replaced with ** footnote referencing Section 3.1.6 for details.
- Assessments/10th row: "Creatine" corrected to "Creatinine"

Appendix V

- STEP 1-Examiner Certification, point 3: Instructions for obtaining username and password for training video clarified.
- NC/QOL Endpoint Diagram, Wk6: MRI deleted because it was included in error.

Appendix XA
• MRI/CT (blood detection): Reference to footnote ** added.
• ** Footnote: Last sentence added.

Appendix XII: 1\textsuperscript{st} sentence, last paragraph rewritten for clarity and accuracy.
SUMMARY OF CHANGES
Update: April 15, 2009
(Broadcast 4/15/09)

RTOG 0825, Phase III Double-Blind Placebo-Controlled Trial of Conventional Concurrent Chemoradiation and Adjuvant Temozolomide Plus Bevacizumab Versus Conventional Concurrent Chemoradiation and Adjuvant Temozolomide in Patients With Newly Diagnosed Glioblastoma

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

RTOG 0825 has been updated as follows:

Cover Page: Contact information was updated for Dr. Chakravarti and Dr. Armstrong.

Section 12.3: The MR code designation was added for all scans.

Note: These are editorial/administrative changes to the protocol. NCI requires that these changes be documented on the protocol title page as "Update Date."