



ACRIN Protocol 6678
SUMMARY OF CHANGES

October 8, 2008

Amendment # 2

Major changes have been made to the design of the trial—the addition of a Group C, a change in overall potential sample size, and removal of randomization to Groups A and B—and to the Informed Consent forms to reflect this revision; in addition, the inclusion of participants receiving cetuximab, language reflecting the recent FDA notification on CT scanning safety, details in instances when the initial FDG-PET/CT scan needs to be repeated, instructions on how to move Group A participants to Group B if the two pre-treatment scans cannot be completed, corrections to the References so there is a single list for the body of the protocol (Appendix VIII has therefore been deleted), timing clarifications, and routine revisions to improve clarity and grammar are included:

CHANGES/ADDITIONS MADE THROUGHOUT PROTOCOL

Cover Page

Study Statistician contact information has been updated with Dr. Constantine Gatsonis replacing Dr. Suddhasatta Acharyya

Co-chair Joel Karp's information has been corrected with "Department of Radiology/Nuclear Medicine" and the fax number: "215-573-3880"

Amendment 2 and version date September 17, 2008, have been added

"Confidential" and the "This protocol was designed ..." box have been moved to accommodate placement on the single page

Table of Contents

Page numbers were adjusted to match the current clean version

Appendix I has been renamed to reflect the three Informed Consent Templates

Appendix VIII: References for Chemotherapy Regimens has been removed (references have been reduced to a single list for the entire protocol)

Schema, Pages 4–5

The Schema has been redesigned to show the addition of Group C to the study (see revised Schema below on Page 2 of 26)

On Page 5, in the NOTE below the new Schema, 1st paragraph, 1st sentence: "FDG-" has been deleted and "and" has been added

The NOTE's 2nd paragraph: has been deleted

SCHEMA

ELIGIBILITY
Patients with advanced NSCLC (stage IIIb with malignant pleural effusion or stage IV), who are being considered to undergo palliative chemotherapy. For Groups A and B, this therapy must be a platinum-based two drug chemotherapy regimen (with or without bevacizumab or cetuximab); potential participants for Group C can be planned for any treatment: standard-of-care, protocol-specific, or experimental.

OPTION 1/GROUP A

- OPTION 1 / GROUP A:**
- Two (2) FDG-PET/CT scans prior to chemotherapy – at least 24 hours between the 2 scans;
 - One (1) FDG-PET/CT scan post-cycle 1 of chemotherapy;
 - Follow-up CT scans every 6 weeks from initiation of chemotherapy for 18 weeks per standard of care;
 - Observational clinical follow-up for one year.

OPTION 2/GROUP B

- OPTION 2 / GROUP B:**
- One (1) FDG-PET/CT scan prior to chemotherapy;
 - One (1) FDG-PET/CT scan post-cycle 1 of chemotherapy;
 - One (1) FDG-PET/CT scan post-cycle 2 of chemotherapy;
 - Follow-up CT scans every 6 weeks from initiation of chemotherapy for 18 weeks per standard of care;
 - Observational clinical follow-up for one year.

OPTION 3/GROUP C

- OPTION 3 / GROUP C:**
- Two (2) FDG-PET/CT scans prior to chemotherapy— at least 24 hours, but no more than 7 days, between the 2 scans.

EXCLUSION CRITERIA FOR GROUPS A AND B

Treatment planned with other than a platinum-based two drug regimen administered at 3 week intervals. The platinum-based regimen may include bevacizumab OR cetuximab, but no other targeted drugs.

Sample Size, Page 5

The sample size language has been revised to read:

“In this prospective, multi-center trial, a maximum of 285 eligible participants will be registered to achieve the following accrual targets:

- *Combined total accrual of 228 participants to Groups A and B, with at least 171 of these in Group B.*
- *Combined total accrual of 57 participants to Groups A or C.”*

Section 1.0 Abstract, Page 6

Rationale for validating FDG-PET in NSCLC, 3rd paragraph, header: the acronym “NSCLC” replaced “non-small cell lung cancer” after first mention

Design, 4th paragraph, 1st sentence: “subsequent” has been added

Design, 5th paragraph, 1st sentence: “randomized into two” has been replaced with “enrolled into one of three” groups

Design, 5th paragraph, 4th sentence: “Groups” has been capitalized for consistency

Design, 5th paragraph, 5th sentence: “*Group C participants will undergo two FDG-PET/CT scans prior to treatment to support the test-retest reproducibility aim.*” has been added

Endpoints, 7th paragraph, 2nd sentence: a hyphen has been added to “progression-free survival”

Section 2.0 Background and Significance, Pages 7–21

Section 2.1, 1st paragraph, 7th sentence: “Section” has been capitalized for consistency

Section 2.1, 1st paragraph, 8th sentence: a comma has been removed

Section 2.1, 2nd paragraph, 1st and last sentences: the acronym “NSCLC” replaced “non-small cell lung cancer” twice in this paragraph after first mention on Page 6

Section 2.1, 2nd paragraph, 6th sentence: “undergoes” has been made plural for subject-verb agreement

Section 2.2, 1st paragraph, 1st sentence: a comma has been added

Section 2.2, 2nd paragraph, 3rd sentence: “NCI” has been spelled out to “National Cancer Institute” and “EORTC” has been spelled out to “European Organisation for Research and Treatment of Cancer” at first mention; “considered” is now in the past tense for subject-verb agreement

Page 8, Section 2.2, 3rd paragraph, 1st sentence: “of” has been deleted, and “Phase” has been capitalized in two instances

Section 2.2, 3rd paragraph, 2nd sentence: a comma has been added

Section 2.2, 3rd paragraph, 7th sentence: a hyphen has been added to “treatment-specific differences” and a semicolon has replaced “and that,” which has been deleted

Section 2.3.1, 1st paragraph, 2nd sentence: a hyphen has been added to “treatment-induced changes”

Section 2.3.1, 2nd paragraph, 1st and 2nd sentences: the acronym “NSCLC” replaced “non-small cell lung cancer” in these two sentences

Section 2.3.1, 2nd paragraph, last sentence: “p” is now lower case for consistency

Page 9, Section 2.3.1, 3rd paragraph, 4th sentence: “of” has been added

Section 2.3.1, Table 1 title: “relevance” is now lower case for consistency

Section 2.3.1, Table 1, * footnote: a hyphen has been added to “progression-free survival”

Page 10, Section 2.3.2, 2nd and 3rd paragraphs, 1st sentence of each: the acronym “NSCLC” replaced “non-small cell lung cancer” in these two sentences

Section 2.3.2, 3rd paragraph, 3rd sentence: “Section” is capitalized for consistency

Section 2.3.2, 3rd paragraph, 5th sentence: a hyphen has been added to “progression-free survival”

Page 11, Section 2.3.2, Table 3 title: “relevance” is now lower case for consistency

Section 2.3.4, section header: “Using” is now capitalized for consistency

Page 12, Section 2.4, Table 4 title: “misclassification,” “response,” and “criteria” are now lower case for consistency

Section 2.4, 3rd paragraph (1st paragraph below Table 4), 1st sentence: “p” is now lower case for consistency

Section 2.4, 3rd paragraph (1st paragraph below Table 4), last sentence: the reference has been revised from “38b” to “39”

Section 2.4, 4th paragraph (2nd paragraph below Table 4), last sentence: reference “(35)” has been added

Page 13, Section 2.4.1, 2nd paragraph (between Figure 1 and Table 5), 1st sentence: references “(35, 38, 39)” have been replaced with “(35, 40, 41)”

Page 14, Section 2.4.1, 4th paragraph (2nd on page), 2nd sentence: references “(40a, 40b, 40c)” have been replaced with “(40–42)”

Section 2.4.1, 4th paragraph, last sentence: “Lung VCAR software” has been added to item “(2)”; parentheses and a semicolon have also been added for consistency

Section 2.4.1, 5th paragraph, 1st sentence: reference “(40)” has been replaced with “(45)”

Section 2.4.1, 5th paragraph, 3rd sentence: reference “(41)” has been replaced with “(46)”

Section 2.4.2, 1st paragraph, 3rd sentence: references “(41-43)” have been replaced with “(46–48)”

Section 2.4.2, 1st paragraph, 4th sentence: “standard deviation” is spelled out at first mention and “[SD]” is put in brackets within the parentheses; reference “(41)” has been replaced with “(46)”

Section 2.4.2, 1st paragraph, 5th sentence: “standard deviation” is replaced with “SD” after first mention

Section 2.4.2, 1st paragraph, 7th sentence: “(CI)” has been deleted; “confidence interval” is spelled out here and throughout the protocol for consistency; reference “(43)” has been replaced with “(48)”

Page 15, Section 2.4.2, 2nd paragraph, 2nd sentence: a hyphen has been added to “FDG-PET” and the period at the end of the sentence has been replaced with a question mark

Section 2.5, 1st paragraph, 3rd sentence: references “(44-46)” have been replaced with “(49–51)”

Section 2.5, 2nd paragraph, 5th sentence: “change” is now “decreased” and brackets have been added around “140%-100%” in the parenthetical

Section 2.5, 3rd paragraph, 5th sentence: the space between “cannot” has been deleted

Section 2.5, 4th paragraph, 2nd sentence: reference “(47)” has been replaced with “(52)”

Section 2.5, 4th paragraph, 5th sentence: has been revised for clarity per the italicized elements to read “On the other hand, malignant diseases *that are more responsive and for which more therapeutic options are available*, such as breast cancer, *would mandate* significantly larger patient populations and longer follow up to validate FDG-PET as a predictive marker for patient outcome.”

Section 2.5, 4th paragraph, 6th sentence: “with NSCLC” has been added for clarity

Page 16, Section 2.5, 4th paragraph, 8th sentence: references “(48, 49)” have been replaced with “(53, 54)”

Section 2.5.1, 1st paragraph, 1st sentence: the acronym “NSCLC” replaced “non-small cell lung cancer”; reference “(50)” has been replaced with “(55)”

Section 2.5.1, 1st paragraph, 2nd sentence: reference “(51)” has been replaced with “(56)”

Section 2.5.1, 1st paragraph, 3rd sentence: “Section 8.6” has been updated to “Section 8.7”

Section 2.5.1, 1st paragraph, 6th sentence: references “... 52, 53)” have been replaced with “... 57, 58)”

Section 2.5.1, 1st paragraph, last sentence: a comma has been added, a hyphen has been added to “drug-specific effects,” and references “52, 53)” have been replaced with “(57, 58)”

Section 2.5.1, 2nd paragraph, 1st sentence: a period has been deleted

Section 2.5.1, 2nd paragraph, 2nd sentence: a space has been added after “≥”; a hyphen has been removed from “FDG uptake”

Section 2.5.1, 2nd paragraph, 3rd sentence: two hyphens have been deleted

Section 2.5.1, 2nd paragraph, 4th sentence: “of” has been added, “stages” has been made plural, and “ranged” has been revised to “ranging”

Section 2.5.1, 2nd paragraph, 6th sentence: a hyphen has been added to “progression-free survival” and reference “(54)” has been revised to “(59)”

Section 2.5.1, 3rd paragraph, 1st sentence: “Eastern Cooperative Oncology Group” is spelled out at first mention; parentheses have been added around “(ECOG)”; “vascular endothelial growth factor” has been spelled out at first mention; parentheses have been added around “(VEGF)”; and reference “(55)” has been revised to “(60)”

Section 2.5.1, 3rd paragraph, 4th sentence: reference “(56)” has been revised to “(61)”

Page 17, Section 2.5.1, 4th paragraph: has been added “*Recently, the results of the FLEX trial have indicated that the EGFR-targeted monoclonal antibody, cetuximab, significantly improves patient survival when added to cisplatin/vinorelbine chemotherapy (62). Accordingly, this combination therapy is now being offered as a standard treatment option for some patients with advanced NSCLC.*”

Section 2.6, 1st paragraph, 5th sentence: “standard deviation” is now “SD” after first mention and references “(57, 58)” have been revised to “(63, 64)”

Section 2.6, 1st paragraph, 7th sentence: “standard deviations” is now “SDs” after first mention

Section 2.6, 1st paragraph, 8th sentence: a hyphen has been removed from “multicenter”

Section 2.7, header: “Uptake” is capitalized for consistency

Section 2.7, 1st paragraph, 1st sentence: two commas have been added

Section 2.7, 1st paragraph, 3rd sentence: “three” has been spelled out for consistency

Section 2.7, 1st paragraph, 4th sentence: a hyphen has been deleted from “FDG uptake”

Section 2.7, 1st paragraph, last sentence: references “(28, 59, 60)” have been revised to “(28, 65, 66)”

Section 2.8, 1st paragraph, 1st sentence: references “(57, 58)” have been revised to “(63, 64)”

Page 18, Section 2.8, 1st paragraph, 7th sentence: a hyphen has been added to “progression-free survival”

Section 2.8, 2nd paragraph, 2nd, 3rd, and last sentences: a hyphen has been deleted from “FDG uptake”

Section 2.8, 3rd paragraph, 1st sentence: “Table” has been capitalized, a hyphen has been deleted from “FDG uptake,” and “30-35%” has been revised to “30% to 35%”

Section 2.8, 3rd paragraph, 3rd sentence: a hyphen has been deleted from “no less”

Section 2.8, 4th paragraph, 1st and 2nd sentences: a hyphen has been deleted from “FDG uptake” and, in the 2nd sentence, “receiver operating characteristic” has been spelled out at first mention with parentheses therefore placed around “(ROC)”

Section 2.8, 4th paragraph, last sentence: reference “(62)” has been revised to “(67)”

Section 2.9.1, 1st paragraph, 1st sentence: “*In-vitro*” has been italicized and references “(63, 64)” have been revised to “(68, 69)”

Section 2.9.1, 1st paragraph, 2nd sentence: reference “(65)” has been revised to “(70)”

Section 2.9.1, 1st paragraph, 3rd sentence: references “(66, 67)” have been revised to “(71, 72)”

Section 2.9.1, 1st paragraph, last sentence: “Only few ...” has been revised to “Few ...”

Section 2.9.1, 2nd paragraph, 2nd sentence: “*in-vitro*” has been italicized

Page 19, Section 2.9.1, 2nd paragraph, 4th sentence: references “(68, 69)” have been revised to “(73, 74)”

Section 2.9.2, 1st paragraph, 1st sentence: “and” has been deleted

Section 2.9.2, 1st paragraph, 3rd sentence: reference “(53)” have been revised to “(58)”

Section 2.9.2, 2nd paragraph, 2nd and 3rd sentences: a comma has been deleted from each sentence

Section 2.9.2, 2nd paragraph, last sentence: reference “(70)” have been revised to “(75)”

Section 2.9.2, 3rd paragraph, 1st sentence: reference “(69)” have been revised to “(76)”

Section 2.9.2, 3rd paragraph, 2nd sentence: “time points” has been moved

Section 2.9.2, 3rd paragraph, last sentence: reference “(71)” have been revised to “(76)”

Section 2.9.2, 4th paragraph, 1st sentence: “becomes clearer that it is” has been revised to “is clearly”

Section 2.9.2, 4th paragraph, 4th sentence: a hyphen has been deleted from “FDG uptake”

Section 2.9.2, 4th paragraph, 4th sentence: references “(57, 58)” have been revised to “(63, 64)”

Section 2.9.2, 4th paragraph, 5th sentence: references “(70, 72)” have been revised to “(75, 77)”

Page 20, Section 2.9.3, 1st paragraph, 4th sentence: a hyphen has been deleted from “FDG accumulation”

Section 2.9.3, 2nd paragraph, 2nd sentence: references “(73-75)” have been revised to “(78–80)”

Section 2.9.3, 3rd paragraph, 1st sentence: references “(76, 77)” have been revised to “(81, 82)”

Section 2.9.3, 3rd paragraph, 2nd sentence: the typo “manufacturers” has been corrected

Section 2.9.3, 3rd paragraph, next-to-last sentence: a hyphen has been added to “recurrence-free survival”

Section 2.9.3, 4th paragraph, 6th sentence: reference “(75a)” have been revised to “(83)”

Section 2.9.3, 4th paragraph, last sentence: reference “(78)” have been revised to “(84)”

Page 21, Section 2.10, 1st paragraph, 2nd sentence: a comma has been deleted

Section 2.10, 2nd paragraph, 3rd sentence: a comma has been added

Section 2.10, 2nd paragraph, 4th sentence: “is” has been revised to “can be” and a comma has been deleted

Section 2.10, 3rd paragraph, 2nd sentence: an apostrophe has been deleted

Section 2.10, 3rd paragraph, 4th sentence: “Phase” has been capitalized

Section 2.10, 3rd paragraph, 5th sentence: reference “(79)” have been revised to “(85)”

Section 2.10, 3rd paragraph, 6th sentence: an “s” has been added to “trials”

Section 2.10, 3rd paragraph, 7th sentence: reference “(79)” have been revised to “(85)”

Section 3.0 Study Objectives, Pages 21–22

1st paragraph, item #3: a hyphen has been added to “treatment-induced changes”

Page 22, Section 3.2.2: a hyphen has been added to “progression-free survival”

Section 3.2.4: “standard uptake values” has been deleted to leave the acronym “SUVs” after first mention; parentheses deleted

Section 3.3, 1st sentence: a hyphen has been added to “hypothesis-forming analyses”

Section 3.3.1: “the” has been deleted

Section 4.0 Study Overview, Pages 22–23

1st paragraph: has been completely revised to reflect the addition of Group C and changes to the potential number of study participants to read *“In this prospective, multicenter trial, a minimum of 228 and a maximum of 285 eligible participants, excluding those who have been classified as off-study per Section 8.6, will be registered to achieve the following accrual targets: combined total accrual of 228 participants to Groups A and B, with at least 171 of these in Group B; combined total accrual of 57 participants to Groups A and C. Accrual to Groups A and C will be closed once a combined total of 57 cases has been accrued. However, should a participant drop out of Group A or C, that participant will need to be replaced to ensure 57-total accrual.”*

Note: *Group A participants who do not complete the test-retest pre-treatment imaging requirements can be considered for Group B participation (which would require new consent for this group, enrollment in this arm, and a note to file). This is an acceptable protocol variation.”*

Page 23, 2nd paragraph: 1st sentence has been deleted; “in Groups A and B” has been added to new 1st sentence; new 2nd sentence has been added to read “*Eligible participants in Group C will undergo a total of two (2) FDG-PET/CT scans and two (2) CT volumetric scans as described below.*”

3rd paragraph: 1st sentence, “Group A” has been underlined; 4th sentence, “scans” has been made plural

3rd paragraph, 3rd sentence: “The interval between the two pre-chemotherapy FDG-PET/CT scans must \geq 24 hours and \leq seven (7) days.” has been deleted

3rd paragraph: 4th sentence, “no more than 7 days” has been added to replace “within one (1) to seven (7) days”

4th paragraph: 1st sentence, “Group B” has been underlined; 2nd sentence, “Group” has been capitalized

4th paragraph: 2nd sentence, “no more than 7 days” has been added to replace “within one (1) to seven (7) days”

5th paragraph: 1st sentence, “Groups A and B:” has been added and “Groups” has been capitalized; the former 6th paragraph is now part of the 5th paragraph, beginning as the paragraph’s now-2nd sentence “Follow-up diagnostic CT imaging ...” after the deletion of two returns and “In both groups A and B,”

6th paragraph: “Group” has been capitalized in three sentences

7th paragraph: the following paragraph has been added “*Group C participants will undergo two FDG-PET/CT scans before treatment (chemotherapy and/or radiotherapy of the thoracic index lesion). The two pre-treatment FDG-PET/CT scans will be performed to assess the test-retest reproducibility of SUVs. The interval between the two pre-treatment FDG-PET/CT scans must be \geq 24 hours and \leq seven (7) days.*”

Section 5.0 Participant Selection, Pages 23–25

1st paragraph: the following paragraph has been deleted “*Eligible participants for this trial are patients with advanced NSCLC (Stage IIIB with pleural effusion or Stage IV) who meet the eligibility criteria, and who will receive platinum-based doublet chemotherapy, with or without bevacizumab, in three week cycles (50). Patients with previously treated NSCLC may participate so long as they meet the eligibility criteria.*”

1st paragraph: the following sentences have been added “*Participants interested in the trial will be consented to one of the three study arms depending on their eligibility evaluation, personal preference, and their ability to adhere to the timing sequences for each arm. The decision will be made by the referring physician, the study PI, and the research staff consenting the patient to determine the appropriate enrollment path. Eligibility is based on the option/group for which the participant is eligible and chosen. Criteria that do not apply to Group C are noted below with “(Groups A and B ONLY).”*”

Page 24, Section 5.1.2.2: “Section” has been capitalized, “5.1.4” has been revised to “5.1.5,” and “a” has been moved up in the description

Section 5.1.2.3: “Section” has been capitalized, “5.1.4” has been revised to “5.1.5,” and “a” has been moved up in the description

Section 5.1.2.4: has been added “*In a previously irradiated participant, the recurrent lesion(s) must be outside the prior radiation port or if within a prior radiation port, the lesion(s) must demonstrate radiologic progression by RECIST criteria.*”

Section 5.1.3: the following criterion has been added “Participant is being considered for therapy;”

The Section headers from 5.1.3 to 5.1.6 have been renumbered

Current Section 5.1.4.3: “**(Groups A and B ONLY)**” has been added

Former Section 5.1.6 “*Scheduled to be treated with a platinum-based, dual-agent chemotherapy regimen administered at 3 weeks intervals; bevacizumab may be administered in addition to chemotherapy;*” has been deleted

Former Section 5.1.11 “*Laboratory testing (within 4 weeks of registration) that includes at a minimum, complete blood cell count (CBC) with differential, serum glucose, blood urea nitrogen (BUN), creatinine, and Bilirubin (to include at minimum alkaline phosphatase); these tests demonstrate there are no contraindications for chemotherapy and FDG-PET/CT imaging.*” has been deleted

Page 25, Section 5.2.4: 1st sentence, “L” has been capitalized in “dL” and “d” has been deleted from “improved”; 2nd sentence, “with” has been added

Section 5.2.5: has been rewritten to read “*Prior malignancy; however, participants with basal cell or squamous cell carcinoma of the skin, or carcinoma in situ, or other cancer from which the participant has been disease free for more than 3 years are still eligible;*”

Section 5.2.7: “**(Groups A and B ONLY)**” has been added

Section 5.2.9: “**(Groups A and B ONLY)**” has been added

Section 5.2.10: OR cetuximab

Section 5.2.10: “**(Groups A and B ONLY)**” has been added

Section 5.2.11: “*Treatment planned with chemotherapy other than a platinum-based doublet, with or without the addition of either bevacizumab **OR cetuximab**, administered at 3-week cycles **(Groups A and B ONLY)**;*” has been added

Section 5.3, 4th paragraph, 1st sentence: the sentence has been made active instead of passive to read “ACRIN will provide additional resources ...”

Section 6.0 Site Selection, Page 26

Section 6.1, 1st paragraph, 3rd sentence: a hyperlink has been embedded in the URL

Section 6.1.1, 1st sentence: a space has been added to “web site” and a hyperlink embedded in the updated URL

Section 6.2: 1st sentence, “forms” has been made plural; 2nd sentence, “templates” has been added and “is” has been replaced with “are”; 4th sentence, “forms” has been made plural

Section 6.3, 1st paragraph: the 2nd sentence “*Total target accrual for this study is 228 participants.*” has been deleted

Section 7.0 Online Registration, Page 27

Section 7.0, header: “AND RANDOMIZATION SYSTEM” has been deleted

Section 7.1, 1st sentence: the clause “...to either Group A, B, or C based on inclusion/exclusion criteria and choice.” has been added to the end of the sentence

Section 7.1, last sentence: “*Please refer to the **ACRIN Procedure Manual, Section 7.1, Participant Registration** for instructions.*” has been deleted

Section 8.0 Study Procedures, Pages 27–44

Section 8.0 has been renumbered and headers have been added to call out the different scanner and other technical specifications

Section 8.0, 1st paragraph, 1st sentence: Section numbers have been updated

Section 8.0.1 Scanner Technical Specifications: header has been added

Section 8.0.2 Baseline FDG-PET/CT Scan: header has been added, 1st paragraph has been added as follows “*Minimum Acceptable Tumor FDG Uptake. If the FDG uptake of the tumor tissue is too low for quantitative analysis (SUV < 4.0), the participant will be removed from participation and replaced with another eligible study participant. In participants whose measurable tumor has a baseline SUV of less than 4.0, a 25% relative decrease of tumor FDG uptake would result in a decrease in SUV of ≤ 1 to the tumor. Data on the test-retest reproducibility of FDG-PET suggest that in an individual patient such a small absolute change in tumor FDG uptake cannot be reliably identified by PET imaging. Therefore, a baseline SUV of at least 4.0 is required for the present study which defines a metabolic response as a 25% decrease in tumor FDG uptake. We expect that the tumor SUV will be less than 4.0 in fewer than 5% of patients (26). This estimate is based on data on FDG uptake of untreated, advanced NSCLC. SUVs lower than 4.0 are observed in small lesions and in patients with bronchioloalveolar cell carcinomas (BAC). For these reasons, patients with these tumor types will not be included in the present study (see Section 8.6).*”

Page 28, Section 8.0.2, 2nd paragraph, NOTE: “baseline” has been deleted, “FDG-“ has been deleted, “and” has been added, and item “d)” has been deleted

Section 8.0.2, 3rd paragraph: has been made bold

Section 8.0.2, 4th paragraph: has been added as follows “*In addition, if the first FDG-PET/CT scan is completed prior to registration as noted above, the participant will still need to undergo a volumetric CT scan per the protocol guidelines after consent and registration to the trial is complete. The volumetric CT scan needs to be performed within the time frame indicated in the protocol for the specific group to which the participant has been registered. For Groups A and C, the first volumetric CT must be completed at least 24 hours before Imaging Visits A2 or C2. For Group B, the first volumetric CT must be completed within 7 days before treatment start.*

Please refer to Section 8.9 for the study procedure calendar.”

Section 8.0.3 Number and Timing of FDG-PET/CT Scans: header has been added

Section 8.0.3, 1st paragraph: 1st sentence, “Groups A and B” has been added; 2nd sentence has been rewritten to include Group C information as follows “*All participants in Groups A and B will undergo three (3) FDG-PET/CT studies; participants in Group C will undergo two (2) FDG-PET/CT studies.*”

Section 8.0.3, final sentence: “*Eligible participants will be randomized into either group A or B during the registration visit.*” has been deleted

Section 8.0.3, 2nd paragraph, 1st sentence: “Participants in Group A” has been underlined, “Group” has been capitalized, and “... a total of three FDG-PET/CT scans: ...” has been added

Section 8.0.3, 3rd paragraph: 1st sentence, : “Participants in Group B” has been underlined, “Group” has been capitalized, “... a total of three ...” has been added, and a semicolon appears after “at:”; the last sentence has been deleted/moved to the following paragraph

Section 8.0.3, 4th paragraph, NOTE: 1st sentence, “Twenty-one ...” has been revised to “Days are listed on a 21-...”; the last sentence “*Details of the acquisition and analysis of the FDG-PET/CT scans are described in Appendices VI and VII, and an overview is provided in Section 10.*” has been added

Page 29, Section 8.0.3, new 5th paragraph: “Participants in Group C will undergo a total of two pre-chemotherapy FDG-PET/CT scans. The two pre-chemotherapy FDG-PET/CT scans will be performed at least 24 hours apart, but no longer than seven (7) days between scans. Subsequent treatment for NSCLC is not mandated for this trial group.” has been added

Section 8.0.4 CT Scans: header has been added

Section 8.0.4, 1st paragraph: “Groups” has been capitalized in three sentences; 3rd sentence, “Groups” has been made plural and “...and C ...” has been added; last sentence “**See Note above regarding performance and timing of baseline volumetric CT study if the FDG-PET/CT scan is completed prior to registration.**” has been added

Section 8.0.4, 2nd paragraph, 1st sentence: “... in Groups A and B ...” has been added

Section 8.0.5 Submission of Images to ACRIN: header has been added

Section 8.1, 1st sentence: now reads “... one of the three study groups:”

Section 8.1, 1st bullet: now reads “... specific to the group to which the patient will be registered (see Appendix I);”

Section 8.1, 3rd bullet: “..., including clinical laboratory tests completed within 4 weeks of registration that show no contraindications to begin the chosen chemotherapy regimen” has been deleted

Page 30, Section 8.1, 4th bullet: “*Review clinical laboratory tests completed within 4 weeks of registration to document that there are no contraindications to beginning the planned chemotherapy regimen (Groups A and B only; this measure is not necessary for Group C participants);*” has been added

Section 8.1, 5th bullet: “... if one has not been performed in the last 6 weeks per inclusion criteria” has been added

Section 8.1, 8th bullet: “(Groups A and B only)” has been added

Section 8.1, 9th bullet: “*Therefore, the participant will be randomized into group A or group B.*” has been deleted

Section 8.1, last sentence: “needs” has been made plural

Section 8.2, 1st sentence: “Group” has been capitalized

Section 8.2.1, header: “... and ≤ 7 Days Before Imaging Visit A2” has been added

Section 8.2.1, 1st paragraph, 2nd sentence: Section 8.6 has been updated to Section 8.7

Section 8.2.1, 1st paragraph: each of the three bulleted items ends with an asterisk

Section 8.2.1, 2nd paragraph (below the bullets), Note: has been extensively revised to read “**NOTE:** *The first FDG-PET/CT scan may be completed prior to registration; please see Note in Section 8.0 for specific guidelines and instructions. In addition, if the first FDG-PET/CT scan is completed prior to registration, the participant will still need to undergo a volumetric CT scan per the protocol guidelines after consent and registration to the trial is complete. Please refer to Section 8.9 for the study procedure calendar.*”

See Section 8.0.2 regarding minimum acceptable tumor FDG uptake necessary for participant to continue on study.”

Section 8.2.2, header: “... and ≥ 24 Hours After Visit A1 Scan” has been added

Page 31, Section 8.2.2, 4th paragraph, 2nd Note: has been added as follows “**NOTE:** *Group A participants who do not complete the test-retest pre-treatment imaging requirements can be considered for Group B participation (which would require new consent for this group, enrollment in this arm, and a note to file). This is an acceptable protocol variation. However, to ensure the 57-participant sample size, an additional participant would need to be accrued to Group A or C.*”

Section 8.2.3, header: a hyphen has been added to “21-Day”

Section 8.2.3: 1st sentence, a hyphen has been added to “21-day”; 2nd sentence, “and A2” has been added; 2nd bullet, a space is no longer underlined

Page 32, Section 8.3.1, 1st paragraph, four bullets: each end with an asterisk referring to the information included in Section 8.0.

Section 8.3.1, 2nd paragraph (below the bullets), Note: has been extensively revised to read “**NOTE:** *The first FDG-PET/CT scan may be completed prior to registration; please see Note in Section 8.0 for specific guidelines and instructions. In addition, if the first FDG-PET/CT scan is completed prior to registration, the participant will still need to undergo a volumetric CT scan per the protocol guidelines after consent and registration to the trial is complete. Please refer to Section 8.9 for the study procedure calendar.*

See Section 8.0.2 regarding minimum acceptable tumor FDG uptake necessary for participant to continue on study.”

Section 8.3.2, header: a hyphen has been added to “21-Day”

Section 8.3.2, 1st sentence: a hyphen has been added to “21-day” and “Visit” has been capitalized

Section 8.3.3, header: a hyphen has been added to “21-Day”

Section 8.3.3: 1st sentence, a hyphen has been added to “21-day”; 2nd sentence, “and B2” has been added

Page 33, Section 8.4, 1st bullet, 2nd paragraph, NOTE: a hyphen has been added to “progression-free survival”

Pages 33–34, Section 8.5 has been added for Group C procedures:

8.5 “Group C Participants

Participants in Group C will undergo two FDG-PET/CT scans, the first obtained per standard of care and the second for research purposes only. Each FDG-PET/CT study includes a PET emission scan and a low-dose CT scan for attenuation correction. Participants in Group C will also undergo two volumetric CT scans of the chest beyond the standard of care for research purposes.

8.5.1 Imaging Visit C1: Pre-Treatment

Imaging Visit C1 will occur 7 days or fewer before Visit C2 imaging. All C1 or C2 imaging must be completed prior to treatment. Each participant will undergo FDG-PET/CT and CT scans, as described in Appendices VI and VII, using the same scanner at each study visit.

- *Perform serum glucose test prior to administration of FDG*;*
- *Perform pre-treatment, non-contrast CT scan for tumor volumetry*;*
- *Perform pre-treatment FDG-PET/CT scan.**

****NOTE:** The first FDG-PET/CT scan may be completed prior to registration; please see Note in Section 8.0 for specific guidelines and instructions. In addition, if the first FDG-PET/CT scan is completed prior to registration, the participant will still need to undergo a volumetric CT scan per the protocol guidelines after consent and registration to the trial is complete. Please refer to Section 8.9 for the study procedure calendar.*

See Section 8.0.2 regarding minimum acceptable tumor FDG uptake necessary for participant to continue on study.

8.5.2 Imaging Visit C2: Pre-Treatment — ≥ 24 Hours After Visit C1 Scan and No More Than 7 Days Between Scans

Imaging Visit C2 will occur at least 24 hours but no more than seven (7) days after the Visit C1 FDG-PET/CT scan, before the participant has received any treatment. The scan

can be done on the same day of start of treatment (but must be done prior to administration of pre-medication, chemotherapy, or radiotherapy to exclude acute effects on tumor FDG uptake and FDG biodistribution).

Each participant will undergo FDG-PET/CT and CT scans, as described in Appendices VI and VII, using the same scanner as his/her Visit C1 scan(s).

- Perform serum glucose test prior to administration of FDG;
- Perform pre-treatment, non-contrast CT scan for tumor volumetry;
- Perform pre-treatment FDG-PET/CT scan;
- Assess for any adverse events since Imaging Visit C1.

NOTE: If a clinical diagnostic CT scan is performed on the same day as the FDG-PET/CT scan or the CT scan for tumor volumetry, the acquisition of the latter studies must be delayed for at least 30 minutes after IV contrast agent administration.”

Subsequent Sections have been renumbered

Page 34, Section 8.6, 1st paragraph: 1st sentence, “will need to be” has been added; last sentence, the acronym “DMC” for “Data Management Center” is used throughout after first mention

Section 8.6.1: “Section” has been capitalized, Section 8.2.1 has been updated to Section 8.0.2, and a hyphen has been removed from “FDG uptake”

Section 8.6.3: has been revised to read “If a participant in Group A or C does not undergo both test-retest imaging requirements, an additional participant will need to be recruited for either Group A or C to ensure the 57-participant sample size; imaging will continue as scheduled for the Group A participant or the participant can be enrolled in Group B (see Note in Sections 4.0 and 8.2.2).”

Section 8.6.4: “/treatment” has been added

Section 8.6.5: “(for Groups A and B only)” has been added

Page 35, New Section 8.7 Off-Protocol Imaging Criteria has been created from the former Section 8.6.7

Subsequent sections have been renumbered

Section 8.7: has been added as follows “Participants will be taken off-protocol imaging (will not undergo any additional FDG-PET/CT scan[s] or CT tumor volumetric scan[s]) for the reasons identified below, but we will continue to collect survival data for these participants as itemized below. These participants will remain on-study.

- Groups A and B Only: Participants who receive less than 2 cycles of first-line chemotherapy. These participants will go off-imaging, and will not undergo any additional FDG-PET/CT studies. For these participants, overall survival will be determined and correlated with changes in tumor FDG uptake from the baseline FDG-PET/CT scan compared to FDG-PET/CT scan completed after one cycle of chemotherapy.
- Groups A and B Only: Participants are expected to have diagnostic follow-up imaging visits every 6 weeks from initiation of chemotherapy (i.e. every other chemotherapy cycle) for a maximum of 18 weeks, however, the participant will go off-protocol imaging if the participant shows progression, at which point, the secondary endpoint of progression-free survival has been reached.
- All Groups: Participants experience any serious adverse events related to the investigational component of the trial. These participants will go off-protocol imaging (no additional study imaging will be performed) but will be followed for progression and one-year survival.”

Current Section 8.8, header: “(Groups A and B Only)” has been added

Section 8.8.1.1, 1st paragraph, 1st sentence: the acronym “NSCLC” is used and reference “(50)” has been revised to “(55)”

Section 8.8.1.1, 1st paragraph, 2nd sentence: reference “(51)” have been revised to “(56)”

Section 8.8.1.1, Table 5: was formerly numbered “Table 1,” “regimens” has been made plural, and “(data from Milton and Miller [56] except where indicated otherwise)” has been added

Page 36, Section 8.8.1.1, Table 5: the last four rows have been added to include cetuximab data as follows

Sandler (2006) (60)	<i>paclitaxel/carboplatin</i>	444	15	10.3
	<i>paclitaxel/carboplatin + bevacizumab</i>	434	35	12.3
Pirker (2008) (62)	<i>cisplatin/vinorelbine</i>	568	Not available	10.1
	<i>cisplatin/vinorelbine + cetuximab</i>	557	Not available	11.3

Section 8.8.1.1, 2nd paragraph below Table 5, 3rd sentence: a hyphen has been deleted from “FDG signal” and references “(52, 53)” have been revised to “(57, 58)”

Section 8.8.1.1, 2nd paragraph below Table 5, 4th sentence: “*in-vitro*” has been italicized, a comma has been added, and a hyphen has been removed from “FDG uptake”

Section 8.8.1.1, 2nd paragraph below Table 5, last sentence: a hyphen has been added to “drug-specific effects” and references “(52, 53)” have been revised to “(57, 58)”

Section 8.8.1.2, 1st paragraph, 1st sentence: “...in Groups A and B; Group C can be scheduled for any therapeutic regimen” has been added to the end of the sentence

Section 8.8.1.2, 1st paragraph, 2nd sentence: “the study” has been replaced with “therapy in Groups A and B” and “or cetuximab” has been added to the end of the sentence

Page 37, Section 8.8.1.2, 1st paragraph, 5th sentence: a hyphen has been deleted from “FDG uptake” and a “C” added to the end of “NSCLC”

Section 8.8.1.2, 1st paragraph, 7th and 8th sentences: a hyphen has been deleted from “FDG uptake” in two locations

Section 8.8.1.2, 1st paragraph, 9th sentence: “n” has been made lower case for consistency

Section 8.8.1.2, 1st paragraph, 13^h sentence: two commas have been added

Section 8.8.1.2, 2nd paragraph, 3rd sentence: a comma has been replaced with a colon

Section 8.8.1.2, 3rd paragraph, 1st sentence: “or cetuximab” has been added

Section 8.8.1.2, 3rd paragraph, 2nd sentence: references “(80, 81)” have been revised to “(86, 87)”

Section 8.8.1.2, 3rd paragraph, 1st sentence: reference “(56)” has been revised to “(61)”

Section 8.8.3, 1st paragraph, last sentence: a hyphen has been deleted from “FDG uptake”

Section 8.8.3, 2nd paragraph, only sentence: reference to Appendix VIII has been deleted

Page 38, Section 8.9.1, Group A Study Procedures Table, introduction: "... -- at least 24 hours between scans ...", "... but prior to second cycle ...", and "diagnostic" have been deleted

Section 8.9.1, Group A Study Procedures Table, 1st column, 7th row under blue header row: "/Randomization" has been deleted

Section 8.9.1, Group A Study Procedures Table, 4th column, 1st row under blue header row: has been revised to read "... 1 to 7 days between A1 and A2 ..."

Section 8.9.1, Group A Study Procedures Table, 5th column, 1st row under blue header row: a period has been replaced with a comma and footnote #5 is now footnote #6

Section 8.9.1, Group A Study Procedures Table, 6th column, 1st row under blue header row: "from initiation of chemotherapy" has been added

Section 8.9.1, Group A Study Procedures Table, 4th column, 11th row under blue header row: footnote #5 has been added

Page 39, Section 8.9.1, Group A Study Procedures Table, footnote #4: 1st sentence, "baseline" has been deleted, "FDG" has been deleted, "and" has been added, and item "d)" has been deleted; 2nd sentence, "... that the ..." has replaced "...: The ..."

Section 8.9.1, Group A Study Procedures Table, footnote #5: has been added "*For Group A, the first volumetric CT must be completed within 7 days before treatment starts.*"; former footnote #5 is not footnote #6

Page 40, Section 8.9.2, Group B Study Procedures Table, introduction: "... but prior to the start of the second chemotherapy cycle..." and "... but prior to the third chemotherapy cycle ..." have been deleted

Section 8.9.2, Group B Study Procedures Table, 1st column, 7th row under blue header row: "/Randomization" has been deleted

Section 8.9.2, Group B Study Procedures Table, 5th column, 11th row under blue header row: footnote #5 has been added

Section 8.9.2, Group B Study Procedures Table, 6th column, 1st row under blue header row: "from initiation of chemotherapy" has been added

Page 41, Section 8.9.2, Group B Study Procedures Table, footnote #4: 1st sentence, "baseline" has been deleted, "FDG-" has been deleted; "and" has been added. and item "d)" has been deleted; 2nd sentence, "... that the ..." has replaced "...: The ..."

Section 8.9.2, Group B Study Procedures Table, footnote #5: has been added "*For Group B, the first volumetric CT must be completed within 7 days before treatment starts.*"; former footnote #5 is not footnote #6

Pages 42–43, Section 8.9.3, Group C Study Procedures Table: has been added as follows on the next page

8.9.3 Group C: Two (2) FDG-PET/CT scans with CT tumor volumetry prior to start of treatment (at least 24 hours between scans).

STUDY PROCEDURES	REGISTRATION VISIT	IMAGING VISIT C1: Pre-Treatment	IMAGING VISIT C2: Pre-Treatment
<i>Time Frames</i>	<i>Before start of treatment</i>	<i>Before start of treatment</i>	<i>≥ 24 hours after C1 scans, but no more than 7 days later</i>
<i>Signed Informed Consent Form</i>	X		
<i>Confirmation of Eligibility</i>	X		
<i>Medical History</i>	X		
<i>Physical Examination</i>	X		
<i>Confirmation of Diagnosis¹</i>	X		
<i>Registration</i>	X		
<i>Serum Pregnancy Test</i>	X		
<i>Diagnostic CT²</i>	X		
<i>Serum Glucose³</i>		X	X
<i>FDG-PET/CT</i>		X ⁴ (Standard of Care)	X (Research)
<i>Non-Contrast CT Tumor Volumetry</i>		X ⁵ (Research)	X (Research)
<i>Clinical Assessment</i>			
<i>Adverse Event Assessment</i>		X	X

¹ Confirmation by histopathologic diagnosis.

² Baseline diagnostic CT scan results will need to be confirmed at registration or a diagnostic CT will need to be scheduled if results are unavailable for verification.

³ Prior to each FDG administration.

⁴ NOTE: The first baseline FDG-PET/CT scan may be completed prior to registration if: a) the PET/CT scanner has been qualified for the 6678 protocol; b) all parameters and scanning techniques are completed per protocol guidelines; and c) all subsequent PET/CT scans are performed on the same scanner or the same scanner model. Please note that the PET scan must include serum glucose testing prior to scanning and the timing and scheduling of the scan must fall within protocol guidelines.

⁵ For Group C, the first volumetric CT must be completed at least 24 hours before Imaging Visit C2.”

Section 9.0 Data Collection and Management, Pages 44–46

Section 9.1.2, 2nd sentence: “the” and “, PA” were added

Section 9.1.3, 3rd sentence: a hyphen has been added to “case-specific calendar”

Section 9.1.3, 4th sentence: “DMC” replaces “Data Management Center”

Section 9.2.1, 1st sentence: a hyphen has been added to “case-specific calendar”

Section 9.2.1, 2nd sentence: a hyphen has been added to “participant-specific data”

Section 9.2.1, 4th sentence: a space has been added to “web site”

Section 9.2.1, 5th sentence: “(RA)” has been added after “research associate” at first mention

Section 9.2.3, 1st sentence: a space has been added to “web site”

Page 45, Section 9.2.4, 1st sentence: has been corrected to read “data are”

Section 9.2.4, 2nd and 3rd sentences: “research associate” has been replaced with “RA” in two locations

Section 9.2.4, 3rd sentence: “Data Management Center” has been replaced with “DMC”

Section 9.2.5, last sentence: “the” has been deleted and “ACR” is now “ACRIN”

Section 9.4.1, 3rd sentence: “Complimentary” has been corrected to “Complementary,” “Biostatistics Center” has been replaced with “BC,” and “Data Management Center” has been replaced with “DMC”

Section 9.4.1, 5th sentence: a comma has been deleted

Section 9.4.1, 6th sentence: “research associate” has been deleted

Section 9.4.1, 7th sentence: “Data Manager (DM)” has been deleted

Section 9.4.1, 8th sentence: “DM at the” has been deleted

Section 9.4.1, 11th sentence: “C” has been added to “DMC”

Section 9.4.1, 12th sentence: “Data Management Center” has been replaced with “DMC”

Page 46, Section 9.4.2, 1st sentence: “Protocol DM” has been replaced with “DMC”

Section 9.4.2, 2nd sentence: “C” has been added to “DMC”

Section 9.5, 4th sentence: a hyphen has been added to “as-needed basis”

Section 9.6.1, 1st sentence: “Biostatistics Center (BC)” is now “BC”

Section 9.6.1, 2nd sentence: “Data Management Center (DMC)” is now “DMC”

Section 9.6.2, 2nd sentence: “Biostatistics and Data Management Center (BDMC)” is now “BDMC” and “the” has been deleted

Section 9.6.2, 3rd sentence: “department” has been made lower case and been moved to appear after “(PDRC)”

Section 9.6.2, 4th sentence: “(QA)” has been added

Section 9.6.3, 1st sentence: “Quality Assurance” has been replaced with “QA,” “the” has been added, “are” has been added, and “in the event of” has been added

Section 10.0 Imaging Protocol: PET and CT Scans, Pages 46–49

Section 10.1, 1st sentence: “Appendix” has been amended to “Appendices”

Page 47, Section 10.2, header: “Interpretation” has been capitalized

Section 10.2.2, 1st paragraph, 1st sentence: “standardized uptake values (SUVs)” has been replaced with “SUVs”

Section 10.2.2, 1st paragraph, 5th sentence: “interest” has been made singular

Section 10.2.2, 2nd paragraph, 1st sentence: “Appendix” has been capitalized

Section 10.2.3, 1st paragraph, last sentence: “Appendix” has been capitalized

Page 48, Section 10.2.4, header, “Assessment” and “According” have been capitalized

Section 10.3 has been added and reads as follows:

“10.3 FDA Preliminary Public Health Notification for CT scans

As of July 14, 2008, the FDA has released a preliminary public health notification to health professionals regarding possible malfunction of electronic medical devices caused by CT scanning. Please refer to the FDA website for the notification (<http://www.fda.gov/cdrh/safety/071408-ctscanning.html>) and to Section 12.5.3 for adverse event reporting requirements.”

Subsequent Sections have been renumbered

Section 10.4, 1st paragraph, 1st sentence: “used” has been moved to appear after “PET/CT system”

Section 10.4, 1st paragraph, 2nd sentence: a comma has been added

Section 10.4, 1st paragraph, 4th sentence: a comma was deleted and references “(82–85)” have been replaced with “(88–91)”

Section 10.4, 1st paragraph, 5th sentence: reference “(86)” has been revised to “(92)”

Section 10.4, 1st paragraph, 6th and 7th sentences: reference “(87)” has been revised to “(93)” in two locations

Section 10.4, 1st paragraph, 8th sentence: “United States” is now “US”

Section 10.4, 1st paragraph, 9th sentence: a comma has been added

Section 10.4, 2nd paragraph, 1st sentence: “Group” has been capitalized

Section 10.4, 2nd paragraph, 3rd sentence: the “/” has been removed and a hyphen added to “test-retest reproducibility”

Section 10.4, 2nd paragraph, 4th sentence: “also” has been moved in the sentence

Section 10.4, 2nd paragraph, 5th sentence: now begins “Unless the diagnostic pre-chemotherapy CT scan has been conducted prior to registration, these ...”; a comma has been added; “cycle one” has been revised to “cycle 1”; “-chemotherapy” has been added to “post-chemotherapy”; and “of chemotherapy” has been deleted

Section 10.4, 2nd paragraph: the final three sentences have been deleted

Section 10.4, 3rd paragraph, 3rd sentence: “volumetric” has been added, “... beyond the standard of care for research purposes.” replaces “... for measurement of tumor volume.”

Section 10.4, 3rd paragraph, 4th sentence: now begins “Unless the diagnostic pre-chemotherapy CT scan has been conducted prior to registration, these ...” and, in two locations, “-chemotherapy” has been added to “post-chemotherapy” and “of chemotherapy” has been deleted

Page 49, Section 10.4, 4th paragraph: has been added as follows

“In Group C, participants will undergo one FDG-PET/CT scans per standard of care and one for research purposes only. Each FDG-PET/CT study includes a PET emission scan and a low-dose CT scan for attenuation correction. In Group C, these FDG-PET/CT scans for assessment of test-retest reproducibility are the first and second FDG-PET/CT scans, conducted prior to the initiation of treatment. Participants in Group C will also undergo two volumetric CT scans of the chest beyond the standard of case for research purposes. Unless the diagnostic pre-chemotherapy CT scan has been conducted prior to registration, these scans will be performed at the same time as the FDG-PET/CT studies, i.e. two studies pre-treatment.”

Section 11.0 Image Submission, Page 49

Section 11.0, 1st paragraph, 1st sentence: “FTP” has been amended to “sFTP”; a space has been added to “web site”; and a hyperlink has been added to the URL

Section 11.1, 1st paragraph, 1st sentence: “FTP” has been amended to “sFTP”

The Section headers for 11.1.1 through 11.1.5 have been made bold

Section 11.1.1, 1st sentence: “image” has been revised to “data”

Section 11.1.2, 1st sentence: “FTP” has been amended to “sFTP” in two locations and “ACR” has been amended to “ACRIN”

Section 11.1.2, 3rd sentence: “Imaging Transmittal Worksheet (ITW)” has been revised to “ITW”

Section 11.1.3, 1st sentence: “Imaging Transmittal Worksheet” has been revised to “ITW” and “Lab” has been capitalized

Section 11.1.5, 1st sentence: “Imaging Transmittal Worksheet” has been revised to “ITW”

Section 12.0 Adverse Event Reporting, Pages 50–54

Page 51, Section 12.5.3, 3rd bullet after “Claustrophobia”: has been added with revisions to include the recent FDA warning regarding CT scans and electronic medical devices as follows

- *“Malfunction of implanted electronic medical devices, e.g., pacemakers, neurostimulators, insulin pumps (see note below).”*

NOTE: *As of July 14, 2008, FDA released a preliminary public health notification of possible malfunction of electronic medical devices caused by CT scanning. Site should use CT scout views to determine if implanted or externally worn electronic medical devices are present and if so, their location relative to the programmed scan range. See Section 10.3 for FDA warning and their recommendations.”*

Page 51, Section 12.6, 2nd paragraph, 1st sentence: “case report form (CRF)” replaces “CRF” at first mention and “DSMC” is no longer spelled out

Section 12.6, 3rd paragraph, 1st sentence: “Section” has been capitalized

Section 12.6, 4th paragraph, 2nd sentence: “Grades” has been capitalized

Section 12.6, 5th paragraph, 1st sentence: “Section” has been capitalized and “National Cancer Institute’s Cancer Imaging Program (NCI/CIP)” has been spelled out at first mention

Page 52, Section 12.7.1, 1st paragraph, last sentence: “IRB” is no longer spelled out

Section 12.7.2, 1st paragraph, last sentence: “NCI/CIP” and “IRB” are no longer spelled out

Page 53, Section 12.8.3, 1st sentence: “Grade 3-5” is now “Grade 3, 4, or 5”

Section 12.8.4: now begins “Expected ...” instead of “For expected ...”

Section 12.8.5, 1st sentence: “NCI/CIP” and “IRB” are no longer spelled out

Page 54, Section 12.9.3: “report” is now singular

Section numbering has been corrected for 12.9.4 through 12.9.6

Section 12.9.4: 1st sentence, “report” is now singular; 2nd sentence, a hyphen has been deleted from “24 hours”

Section 12.9.6: “IRB” is no longer spelled out

Section 13.0 Ethical Considerations, Pages 54–55

1st paragraph, 1st sentence: brackets and parentheses have been switched

2nd paragraph, 1st sentence: “IRB” is no longer spelled out

2nd paragraph, 3rd sentence: “copies” has been made plural, a hyphen has been added to “IRB-approved,” and “forms” has been made plural

Page 55, 3rd paragraph, 1st sentence: “a copy of the” has been deleted and “forms” has been made plural

3rd paragraph, 2nd sentence: “This” has been revised to “The” and “forms” has been made plural

3rd paragraph, 3rd sentence: “the” has been revised to “an”

Section 15.0 Publication Policy, Page 55

1st paragraph, 2nd sentence: “the” has been deleted and “participating” has been revised to “participation”

1st paragraph, last sentence: a hyperlink has been embedded in the URL

Section 16.0 Institutional Monitoring and Auditing, Pages 55–56

2nd paragraph, 1st sentence: “to provide” has been changed to “provides” and “CRFs” is no longer spelled out

2nd paragraph, last sentence: “also” has been moved

3rd paragraph, 3rd sentence: “Cancer Imaging Program (CIP) of the NCI” has been revised to read “NCI/CIP”

Page 56, 3rd paragraph, 7th sentence: “also” has been moved

3rd paragraph, last sentence: a hyperlink has been embedded in the URL

Section 16.1, 1st paragraph, last sentence: “CRFs” is no longer spelled out

Section 16.2, 1st paragraph, 1st sentence: “CRFs” is no longer spelled out

Section 17.0 Statistical Considerations, Pages 57–64

Section 17.1, 1st paragraph, 2nd sentence: a hyphen has been added to “progression-free survival” and “SUVs” is no longer spelled out

Section 17.1, 2nd paragraph, 1st sentence: “randomized into two” has been revised to “enrolled into one of three groups”

Section 17.1, 2nd paragraph, 3rd sentence: has been added as follows “*Group C will undergo two PET scans prior to treatment only and will contribute only to the test-retest reproducibility analysis; no follow-up imaging during therapy is required, and Group C participants may choose any therapy (or none).*”

Section 17.1, 2nd paragraph, 4th sentence: “Groups” has been capitalized

Section 17.1, 2nd paragraph, last sentence: “from initiation of chemotherapy” has been added

Section 17.1, 3rd paragraph, 1st sentence: a comma has been deleted

Section 17.1.1, 1st sentence: “SUVs” is no longer spelled out

Section 17.1.1, 5th sentence: “interest” has been made singular

Section 17.1.1, 7th sentence: “also” has been moved

Section 17.1.2, 1st paragraph, 2nd sentence: references “(26, 58)” have been revised to “(26, 64)”

Section 17.1.2, 1st paragraph, 3rd sentence: reference “(58)” has been revised to “(64)”

Section 17.1.2, 1st paragraph, 4th sentence: a comma has been added

Section 17.1.2, 1st paragraph, 3rd sentence: “Section” has been capitalized

Page 58, Section 17.1.2, 2nd paragraph, 1st sentence: a comma has been deleted

Section 17.2.1, 1st paragraph: “Primary endpoint:” has been made bold

Section 17.2.1, 2nd paragraph, 1st sentence: “1-year” has been replaced with “one-year”

Section 17.2.1, 2nd paragraph, 2nd sentence: “smaller” has been replaced with “sooner” and “1-year” has been replaced with “one-year”

Section 17.2.1, 3rd paragraph, 1st sentence: “1-year” has been replaced with “one-year”

Section 17.2.1, 3rd paragraph, 3rd sentence: “or cetuximab” has been added, “also” has been moved, and reference “(90)” has been revised to “(94)”

Section 17.2.1, 4th paragraph, next-to-last sentence: reference “(62)” has been revised to “(67)”

Section 17.2.1, 4th paragraph, last sentence: references “(88, 89)” have been revised to “(95, 96)”

Page 59, Section 17.2.2, each Secondary Endpoint has been revised from a numerical value (1 through 4) to a roman numeral value (i through iv)

Section 17.2.2, Secondary endpoint (i), 2nd paragraph, 2nd sentence: “1-year” has been replaced with “one-year”

Section 17.2.2, Secondary endpoint (ii), 2nd paragraph, 2nd sentence: “the” has been deleted, “... as well as, ...” has been deleted, and “and” has been added

Per previous CTEP request, under Secondary endpoint (iii), the term “predictive” has been changed to “diagnostic” in the first and second sentences of the section

Section 17.2.2, Secondary endpoint (iii), 2nd paragraph: 1st sentence, “1-year” has been replaced with “one-year”; 2nd sentence, “Group” has been capitalized

Section 17.2.2, Secondary endpoint (iv), 1st paragraph, 1st sentence: “SUVs” is no longer spelled out

Section 17.2.2, Secondary endpoint (iv), 2nd paragraph, 1st sentence: “group A” has been revised to “Groups A and C” and reference “(90)” has been revised to “(97)”

Section 17.2.2, Secondary endpoint (iv), 2nd paragraph, 2nd sentence: “still” has been moved

Section 17.2.2, Secondary endpoint (iv), 2nd paragraph, 4th sentence: “QA” is no longer spelled out

Section 17.2.2, Secondary endpoint (iv), 2nd paragraph, 5th sentence: references “(57, 58)” have been revised to “(63, 64)”

Section 17.2.2, Secondary endpoint (iv), 2nd paragraph, last sentence: reference “(91)” has been revised to “(98)”

Page 60, Section 17.2.3, 3rd paragraph, 3rd sentence: reference “(92)” has been revised to “(99)” and reference “(93)” has been revised to “(100)”

Section 17.2.3, 3rd paragraph, 5th sentence: “also” has been moved and reference “(91)” has been revised to “(101)”

Section 17.2.3, 5th paragraph, 1st sentence: has been revised to read “... from participants in Groups A and C”

Section 17.2.3, 5th paragraph, last sentence: “SD” is no longer spelled out

Section 17.2.3, 7th paragraph, last sentence: “of” has been added

Page 61, Section 17.2.3, 9th paragraph, 2nd sentence: a comma has been added

Section 17.2.3, 9th paragraph: 3rd sentence, a hyphen has been removed from “FDG uptake”

Section 17.2.3, 13th paragraph: 1st sentence, two commas have been added

Section 17.3, 1st paragraph: has been extensively revised (new text is in red below) to read “*The planned sample size is a minimum of 228 and a maximum of 285 eligible participants, excluding those who have been classified as off-study per Section 8.6, to achieve the following accrual targets: combined total accrual of 228 participants to Groups A and B, with at least 171 of these in Group B; combined total accrual of 57 participants to Groups A and C. Accrual to Groups A and C will be closed once the enrollment has reached 57 in those arms. Cases are to be accrued over 2 years. There is no formal interim analysis planned for this study. However, the accrual rate will be closely monitored and any barriers to recruitment identified in the trial will be addressed in a timely manner, as outlined in Section 6.3.*”

Section 17.4.1: has been extensively revised to read

“Using parameter estimates from previous studies and justifiable effect sizes, it appears that a sample size of 228 participants enrolled to Groups A and B will provide over 80% power for testing the primary endpoint, as well as the secondary endpoints i and ii. Of the 228 participants, at least 171 participants must be assigned to Group B. The remaining 57 will be in Groups A or C. There must also be a total of 57 among Groups A and C to provide adequate power to assess secondary endpoint iv. Thus, the total accrual to all groups could be as high as 285 (228 in Group B plus 57 in Group C). The minimum of patients to be included would be 228 (171 in Group B and 57 in Group A). According to the calculations, this breakdown will provide sufficient (over 80%) power for evaluation of the secondary endpoint iii and allow for construction of 95% simultaneous confidence intervals of reasonable size for evaluating the secondary endpoint iv. An attrition rate of about 15% is assumed in the calculations.”

Page 62, Section 17.4.2, 1st paragraph, 1st sentence: “(26)” has been deleted

Section 17.4.2, 1st paragraph, 2nd sentence: reference “(5)” has been revised to “(26)”

Section 17.4.2, 1st paragraph, last sentence: a hyphen has been removed from “FDG uptake”

Section 17.4.2, 3rd paragraph, 4th sentence: “1-year” has been replaced with “one-year”

Section 17.4.2, 3rd paragraph, 5th sentence: “1-year” has been replaced with “one-year,” “to” has been added, and “a” has been added

Section 17.4.2, 4th paragraph, 1st sentence: a comma has been added and a comma has been deleted

Section 17.4.2, 4th paragraph, 2nd sentence: reference “(90)” has been revised to “(94)”

Section 17.4.2, 4th paragraph, 3rd sentence: reference “(60)” has been revised to “(102)” and reference “(88)” has been revised to “(103)”

Page 63–64, Section 17.4.3, the Secondary endpoint numerals (1 through 4) have been revised to Roman numerals (i to iv)

Page 63, Section 17.4.3, For secondary endpoint i, 1st paragraph, 1st sentence: “of” has been added

Section 17.4.3, For secondary endpoint i, 1st paragraph, 2nd sentence: two commas have been deleted

Section 17.4.3, For secondary endpoint i, 1st paragraph, 3rd sentence: “a” has been added, two commas have been deleted, “it is” was deleted, and “, is” was replaced with “=”

Section 17.4.3, For secondary endpoint i, 1st paragraph, 4th sentence: a comma was deleted and a comma was added

Section 17.4.3, For secondary endpoint ii, 1st paragraph, 1st sentence: a hyphen was added to “progression-free survival”

Section 17.4.3, For secondary endpoint ii, 1st paragraph, 2nd sentence: a comma was added

Section 17.4.3, For secondary endpoint ii, 1st paragraph, 3rd sentence: an apostrophe was added and “-free” was added to “progression-free survival”

Section 17.4.3, For secondary endpoint ii, 1st paragraph, 4th and 5th sentences: two commas were added to each sentence, and a comma was deleted from the 5th sentence

Section 17.4.3, For secondary endpoint ii, 1st paragraph, 6th sentence: a comma has been deleted

Section 17.4.3, For secondary endpoint iii, 1st paragraph, 1st sentence: reference “(60)” has been revised to “(102)”

Section 17.4.3, For secondary endpoint iii, 1st paragraph, 2nd sentence: reference “(88)” has been revised to “(103)” and reference “(89)” has been revised to “(104)”

Section 17.4.3, For secondary endpoint iii, 1st paragraph, 2nd line item in series that “follows: ...”: an apostrophe has been deleted

Page 64, Section 17.4.3, For secondary endpoint iii, 2nd paragraph, 1st sentence: “number” has been made singular

Section 17.4.3, For secondary endpoint iii, 2nd paragraph, 3rd sentence: “Group” has been capitalized

Section 17.4.3, For secondary endpoint iv, 1st paragraph, 4th sentence: “a” has been added

Section 17.4.3, For secondary endpoint iv, 1st paragraph, last sentence: “55” has been revised to “57”; “... and Group C ...” has been added; and “combined” has been added

References, Pages 65–71

Reference “38b” has been revised to “39”

Reference “40” has been added

Reference “39” has been revised to “41”

Reference “40” has been deleted

Reference “40a” has been revised to “42” and the typo for lead author “Yuan” has been corrected **AJR**

Reference “40b” has been revised to “43”

Reference “40c” has been revised to “44”

References “41” through “54” have been revised to “45” through “58”

Reference “59” has been added

Reference “55” has been revised to “60”; reference “60” has been updated with the publication of the study results

Reference “61” has been added

Reference “62” has been added

References “56” through “75” have been revised to “63” through “82”

Reference “75a” has been revised to “83”

Reference “76” has been revised to “84”

Reference “77” has been revised to “85”

Reference “86” has been added

Reference “87” has been added

References “78” through “83” have been revised to “88” through “93”

Reference “94” has been added

References “84” through “88” have been revised to “95” through “98”

Reference “94” has been added

References “99” through “102” has been added

Reference “88” has been revised to “103”

Reference “89” has been revised to “104”

References “90” through “92” have been deleted

Appendix I Informed Consent Form Templates, Pages 72–96

With the addition of Group C, the previous single Informed Consent for participants randomized to either Group A or Group B would no longer suffice; therefore, three new Informed Consent Form Templates have been created to accommodate six different consent scenarios. These scenarios are outlined on a cover page to the informed consent forms to aid in understanding the distinctions.

Appendix II ACRIN 6678 Eligibility Checklist, Page 97

1st sentence: the URL has been updated

Appendix IV ACRIN 6678 Protocol-Specific Application Information, Page 98

2nd sentence: a comma and space have been added after “(PSA)”; “and” has been deleted; and “..., and obtaining qualification from ACRIN for the CT Volumetric imaging.” has been added to the end of the sentence

3rd sentence: a space has been added to “web site”

4th sentence: the URL has been updated

Appendix V ACRIN Qualification Procedures for PET Imaging, Page 100

1st sentence: the URL has been updated

2nd sentence: a hyperlink has been added to “petcorelab@phila.acr.org”

Appendix VI PET Imaging Acquisition Parameters and Image Data Analysis, Pages 101–107

1st sentence: the typo in “Analysis” has been corrected and the URL has been updated

2nd sentence: a hyperlink has been added to “petcorelab@phila.acr.org”\

Under 1. Participant Preparation, 1st paragraph, 1st sentence: “water” replaces “sugar free beverages”

Under 1. Participant Preparation, 1st paragraph, 3rd bullet: “affects” has been corrected to “effects”

Under 1. Participant Preparation, 1st paragraph, 4th bullet: “also” has been deleted

Page 102, Under 3. FDG-PET/CT Imaging, 1st bullet, 1st sentence: now begins “PET scanning ...”

Under 3. FDG-PET/CT Imaging, 1st bullet, 2nd sentence: “... between injection and the start of the PET scanning for ...” replaces “... of beginning scanning on ...” and “in uptake” replaces “of acquisition”

Under 3. FDG-PET/CT Imaging, 4th bullet: “minimum” has been added

Under 4. Image Reconstruction, 1st bullet: “randoms” has been made plural and the typo has been corrected in “manufacturers”

Under 5. Blinded Central Image Analysis, 1st bullet: a hyphen has been added to “attenuation-corrected PET images”

Under 5. Blinded Central Image Analysis, 2nd bullet: a hyphen has been deleted from “FDG uptake”

Under 5. Blinded Central Image Analysis, 3rd bullet, 1st sentence: “A circular region of interest ...” replaces “Circular regions of interests ...”; “0.75 to” has been added; and a hyphen has been removed from “FDG uptake”

Under 5. Blinded Central Image Analysis, 3rd bullet, 2nd sentence: “immediately” has been added and “..., at the same traverse location.” has been added

Under 5. Blinded Central Image Analysis, 3rd bullet, 3rd sentence: has been deleted

Page 103, Under 5. Blinded Central Image Analysis, 4th bullet, 4th sentence: “the” has been added

Under 5. Blinded Central Image Analysis, 5th bullet, 1st sentence: a hyphen has been deleted from “FDG uptake”

Under 5. Blinded Central Image Analysis, 6th bullet, 3rd sentence: a hyphen has been deleted from “FDG uptake”

Under 5. Blinded Central Image Analysis, 8th bullet, 3rd sentence: a hyphen has been deleted from “FDG uptake”

Under 5. Blinded Central Image Analysis, 9th bullet, 1st sentence: “1.0” replaces “one”

Under 5. Blinded Central Image Analysis, 10th bullet, 1st sentence: a hyphen has been deleted from “FDG uptake”

Under 6. Local Image Interpretation, 2nd bullet, 2nd sentence: “Image Management Center” has been capitalized

Under 6. Local Image Interpretation, 3rd bullet: a hyphen has been deleted from “FDG uptake” in two locations

Under 6. Local Image Interpretation, 4th bullet: “Section” has been capitalized

Section 7.2: a hyphen has been deleted from “FDG injection”

Sections 7.2.1.1 through 7.2.1.5: “PET” has been added before “scan” in five locations

Pages 104–105, Sections 7.2.2.1 through 7.2.2.3: “PET” has been added before “scan” in three locations

Page 105, Section 7.3.2, 3rd sentence: “Section” has been capitalized

Section 7.4.1: “been” has been deleted and “Section” has been capitalized

Page 106, Section 10.2.2: “an” has been added

Section 10.2.3: a hyphen has been deleted from “FDG uptake”

Appendix VII CT Acquisition Parameters and Image Data Analysis, Pages 108–116

1st paragraph, 1st sentence: the URL has been updated

Under Acquisition and Analysis of the CT Scans, “scan” has been changed to “scanner” in five locations among the Single Platform and Dual Platforms bullet points

Under Acquisition and Analysis of the CT Scans, 3rd bullet, Dual Platforms: a space was deleted from “standalone”

Page 109, Under CT Volumetry, 2.1 Image Acquisition, 3rd paragraph, 1st sentence: “Group A” is now “Groups A and C”

Under CT Volumetry, 2.1 Image Acquisition, 3rd paragraph, 2nd sentence: “..., in Group A, ...” has been added

Page 110, Under CT Volumetry, 2.2 Volume Measurements and Image Analysis Core Credentialing, 4th paragraph, last sentence: “laboratory” and “of” have been added

Under CT Volumetry, 2.2 Volume Measurements and Image Analysis Core Credentialing, 4th paragraph, 1st bullet, 1st sentence: “FTP” has been revised to “sFTP”

Under CT Volumetry, 2.2 Volume Measurements and Image Analysis Core Credentialing, 5th paragraph, 3rd sentence: “Group A” is now “Groups A and C”

Page 111, Under CT Volumetry, 2.2.1 Baseline Scans, 1st paragraph, 4th sentence: “the” has been added

Under 3.1 Image Acquisition, Table 2, footnote #1: “also” has been moved and “be” has been added

Page 112, Under CT Volumetry, 3.2.1 Local CT Interpretation, 1st paragraph, 1st sentence: “generally” has been moved

Under CT Volumetry, 3.2.1 Local CT Interpretation, 1st paragraph, 3rd sentence: “Also” has been moved to the front of the sentence and capitalized

Under CT Volumetry, 3.2.2 Response Evaluation Criteria in Solid Tumors (RECIST), 1st paragraph, 3rd bullet: “following” has been replaced with “followed”

Page 114, Under CT Volumetry, 3.2.2 Response Evaluation Criteria in Solid Tumors (RECIST), Duration of Stable Disease, 1st sentence: a typo in “from” has been corrected

Page 115, Under CT Volumetry, 4.3 Reconstructing CT Images Produced on a PET/CT for Volumetric Analysis, 1st sentence: “also” has been moved

Page 116, Under CT Volumetry, 4.4 Required CT Test Case Submission, 1st paragraph, last sentence: “FTP” has been revised to “sFTP”

Under CT Volumetry, sFTP Transfer, header: “sFTP Transfer” was previously “FTP Transfer”

Under CT Volumetry, sFTP Transfer, 1st paragraph, 1st sentence: “FTP” has been revised to “sFTP”

Under CT Volumetry, sFTP Transfer, 2nd paragraph: a space has been added to “web site” and the URL has been revised

Appendix VIII has been deleted