



ACRIN 6678

SUMMARY OF CHANGES

November 19, 2009

Amendments # 3 & # 4

The following summary of changes includes revisions made for Amendments 3 (beginning below) and 4 (see Page 7) to the protocol.

Amendment 3 has been developed to explain the timing of test-retest FDG-PET/CT and volumetric CT imaging, to ensure volumetric CT is described for each time point, to make test-retest volumetric CTs in Groups A and C optional (this imaging relates to an Exploratory Endpoint and has proven to be a logistic barrier hindering accrual), and for routine revisions to improve clarity and grammar, including:

Amendment 4 focuses the trial on FDG uptake from scans taken pre- and post-therapy initiation (Groups A and B) and on the reproducibility of the FDG-PET/CT prior to any treatments (Groups A and C). All volumetric CT scans are optional, and the post-cycle 2 FDG-PET/CT scan (Image B3) in Group B is optional. Potential participants will consent to all scans; the study and treating physicians will decide, with the participant, whether to complete all scans requested in the trial.

The baseline diagnostic RECIST FDG-PET/CT scan can be submitted to ACRIN if it has been completed within 28 days prior to treatment initiation. Recommendations are included relating to timing should the diagnostic RECIST FDG-PET/CT need to be repeated.

Eligibility has also been revised: Groups A and B are now open to all cytotoxic chemotherapy regimens, with or without bevacizumab or cetuximab. Patients already treated with or to-be treated with other targeted agents alone (e.g., gefitinib or erlotinib) are excluded from the trial. Group C now includes Stages IIIA, IIIB, and IV disease.

REVISIONS FOR AMENDMENT #3 (v.August 5, 2009)

Cover Page

Amendment 3 and version date August 5, 2009, have been added

Table of Contents

Page numbers were adjusted to match the current clean version

Schema, Pages 4–5

The Schema has been revised to identify all volumetric CT scans, to allow for optional scans in the test-retest component for Groups A and C (see new Footnotes), and to explain timing variations allowable for the test-retest scans in Groups A and C (see new NOTE)

Page 5, a new NOTE has been added directing the reader to Section 8.0.5 for examples of test-retest scenarios for Groups A and C

Section 1.0 Abstract, Page 6

Design, 5th paragraph, 2nd sentence: "... and two volumetric CT ..." and "... and one volumetric CT scan ..." have been added

Design, 5th paragraph, new-3rd sentence: "NOTE" has been added in reference to one optional test-rest volumetric CT scan in Group A

Design, 5th paragraph, now-4th sentence: "... and one volumetric CT scan ..." and "... and two volumetric CT ..." have been added

Design, 5th paragraph, now-6th sentence: "... and should undergo two volumetric CT ..." has been added

Design, 5th paragraph, new-7th sentence: Reference to optional status of test-retest volumetric CT scans has been added

Section 2.6 Rational for Assessing the Test-Retest Reproducibility of FDG-PET, Page 17

Section 2.6, 1st paragraph, 3rd sentence: "... of FDG-PET and volumetric CT imaging ..." and "... in Groups A and C" have been added

Section 2.6, 1st paragraph, new 4th-sentence: has been added to describe the optional status of one test-retest volumetric CT scan for Group A and both test-rest volumetric CT scans for Group C

Section 4.0 Study Overview, Pages 23–24

3rd paragraph, 1st sentence: "... should undergo ..." has been added; "CT volumetric" has been revised to "volumetric CT" for consistency; and "...; in Group A, however, one of the two (2) pre-treatment volumetric CT scans is optional, but strongly encouraged" has been added

3rd paragraph, 2nd sentence: "... should undergo ..." has been added; "CT volumetric" has been revised to "volumetric CT" for consistency; and "...; these two (2) volumetric CT scans are optional, but strongly encouraged" has been added

3rd paragraph, new-3rd and 4th sentences: have been added as follows—"*Test-retest volumetric CT scans do not need to be completed on the same days as the FDG-PET/CT scans, but do need to be completed within specified time frames between scans and prior to treatment initiation. See Section 8.0.5 for examples of possible timing scenarios.*"

Group A, 4th paragraph, 1st sentence: "..., two volumetric pre-chemotherapy CT scans (one of which is optional, but strongly encouraged), ..." has been added; "... and one volumetric CT scan ..." has been added

4th paragraph, 2nd sentence: "two" has been deleted; "... scans—two ..." has been added; "... and one mandatory and one optional volumetric CT ..." has been added; an em dash has been added

4th paragraph, 4th sentence: "7" is now "seven (7)"

4th paragraph, new-6th and 7th sentences: have been added as follows—"*The mandatory pre-treatment volumetric CT scan must be performed no more than 14 days before the start of chemotherapy; the optional volumetric CT scan would therefore be performed within one (1) to seven (7) days after the first volumetric CT scan and no more than seven (7) days before the start of chemotherapy. Test-retest volumetric CT scans do not need to be completed on the same days as the FDG-PET/CT scans, but do need to be completed within specified time frames between scans and prior to treatment initiation.*"

Group B, 5th paragraph, 1st sentence: "a" has been deleted; "... and volumetric CT ..." has been added; "scans" is now plural

5th paragraph, 2nd sentence: "... and volumetric CT ..." has been added; "scans" is now plural

Groups A and B, 6th paragraph, 1st sentence: "... and volumetric CT ..." has been added

7th paragraph, 2nd sentence: "Groups" is plural; "and C" has been added

Group C, 8th paragraph, 1st sentence: "mandatory" has been added; "... and two optional, but strongly encouraged, volumetric CT ..." has been added

8th paragraph, new-4th and 5th sentences: have been added as follows—*“The mandatory pre-treatment volumetric CT scan must be performed no more than 14 days before the start of chemotherapy; the optional volumetric CT scan would therefore be performed within one (1) to seven (7) days after the first volumetric CT scan and no more than seven (7) days before the start of chemotherapy. Test-retest volumetric CT scans do not need to be completed on the same days as the FDG-PET/CT scans, but do need to be completed within specified time frames between scans and prior to treatment initiation.”*

9th paragraph, 2nd sentence: two commas have been deleted

Section 8.0 Study Procedures, Pages 28–45

Page 28, Section 8.0.1, 1st sentence: “and volumetric CT” and “and VII” (in relation to an Appendix reference) have been added

Section 8.0.2, 4th paragraph, 1st sentence: “will” has been revised to “may”

Section 8.0.2, 4th paragraph, 2nd sentence: “The” has been revised to “Each”

Section 8.0.2, 4th paragraph, new-3rd sentence: *“Test-retest volumetric CT scans do not need to be completed on the same days as the FDG-PET/CT scans, but do need to be completed within specified time frames between scans and prior to treatment initiation.”*

Section 8.0.2, 4th paragraph, now-4th sentence: “must” has been replaced with “should”

Section 8.0.2, 4th paragraph, new-5th sentence: has been added as follows—*“However, the volumetric CT portion of imaging Visit A2 is optional and the volumetric CT portion of Imaging Visits C1 and C2 are also optional; all volumetric CT pre-treatment scans are strongly encouraged.”*

Page 29, Section 8.0.3, 4th paragraph, 2nd sentence: a close-parenthesis has been added

Section 8.0.4, 1st paragraph opener: “Volumetric CT.” has been added

Section 8.0.4, 1st paragraph, 1st sentence: “At the time of ...” has been replaced with “Within similar timeframes as ...”

Section 8.0.4, 1st paragraph, new-3rd, 4th, and 5th sentences: have been added as follows—*“Test-retest reproducibility of volumetric CT imaging will be assessed only prior to treatment in Groups A and C. Although strongly encouraged, the second of these two volumetric CT pre-treatment scans (A2) is optional in Group A and both volumetric CT scans are optional in Group C. Volumetric CT scans do not need to be completed on the same days as the FDG-PET/CT scans, but do need to be completed within the specified time frames between scans and prior to treatment initiation. The site investigator and treating physicians will determine whether a participant will undergo the optional volumetric scans based upon the health of the participant and scheduling barriers.”*

Page 30, Section 8.0.4, 2nd paragraph opener: “Diagnostic CT.” has been added

Section 8.0.4, 3rd paragraph opener: “Contrast Media.” has been added

Section 8.0.5, Timing Scenario Guidance for Test-Retest FDG-PET/CT and Volumetric CT Scans (Groups A and C Only): has been added

Section 8.0.6 has been renumbered from previous-Section 8.0.5

Page 31, Section 8.2, 1st sentence: “(see Section 10.4 for details)” has been added

Section 8.2, 3rd sentence: “...; one of the pre-treatment volumetric CT scans is optional (A2), but strongly encouraged” has been added

Section 8.2.1, 1st paragraph, 2nd sentence: “or” is now “and”

Section 8.2.1, 1st paragraph, new-3rd sentence: has been added as follows—“*The volumetric CT A2 image is optional but strongly encouraged.*”

Section 8.2.1, 1st paragraph, now-4th sentence: “volumetric” has been added

Section 8.2.1, 2nd bullet: “mandatory” has been added

Pages 31–32, Section 8.2.1, NOTE, new-4th sentence: has been added as follows—“*Test-retest volumetric CT scans do not need to be completed on the same days as the FDG-PET/CT scans, but do need to be completed within specified time frames between scans and in relation to treatment.*”

Section 8.2.1, NOTE, now-5th sentence: “... 8.0.5 for timing guidance and Section ...” have been added

Page 32, Section 8.2.2, 1st paragraph, 1st sentence: “and volumetric CT” has been added and “scans” is now plural

Section 8.2.2, 1st paragraph, new-2nd sentence: has been added as follows—“*Only the A2 volumetric CT scan is considered optional; it is strongly encouraged.*”

Section 8.2.2, 2nd bullet: “optional” and an asterisk have been added

Section 8.2.2, 3rd bullet: an asterisk has been added

Section 8.2.2, new-2nd NOTE: has been added as follows—“* **NOTE:** *Test-retest volumetric CT scans do not need to be completed on the same days as the FDG-PET/CT scans, but do need to be completed within specified time frames between scans and prior to treatment initiation. See Section 8.0.5 for timing guidance.*”

Section 8.2.2, now-3rd NOTE, 1st sentence: “FDG-PET/CT” has been added

Page 33, Section 8.3, 1st paragraph, 1st sentence: “(see Section 10.4 for details)” has been added

Page 34, Section 8.5, 3rd sentence: “may” has replaced “will”; “... optional—but strongly encouraged—...” has been added

Page 35, Section 8.5.1, 1st paragraph, 3rd sentence: “and CT” has been deleted; “... and may undergo optional volumetric CT scans (strongly encouraged) ...” has been added

Section 8.5.1, NOTE, new-3rd and 4th sentences: have been added as follows—“*Test-retest volumetric CT scans do not need to be completed on the same days as the FDG-PET/CT scans, but do need to be completed within specified time frames between scans and prior to treatment initiation. See Section 8.0.5 for timing guidance.*”

Section 8.5.2, 2nd paragraph: “and CT” has been deleted; “... and may undergo optional volumetric CT scans (strongly encouraged) ...” has been added

Section 8.5.2, 2nd and 3rd bullets: asterisks have been added

Section 8.5.2, 2nd NOTE: has been added as follows—“* **NOTE:** *Test-retest volumetric CT scans do not need to be completed on the same days as the FDG-PET/CT scans, but do need to be completed within specified time frames between scans and prior to treatment initiation. See Section 8.0.5 for timing guidance.*”

Page 36, Section 8.6.3, 1st sentence: “FDG-PET/CT” and “... for the FDG-PET/CT component” have been added

Page 39, Section 8.8.2, header: “... Per Institutional Standard of Care” has been added

Section 8.8.2, former-2nd sentence: has been deleted

Section 8.8.2, now-2nd sentence: "... and filed within the participant's study chart" has been deleted

Page 41–42, Section 8.9.1, Group A, "... one (1) mandatory, one (1) optional ..." has been added, "scan(s)" has been added, and "... one (1) mandatory ..." has been added

Section 8.9.1, Table, 12th row, 3rd, 4th, and 5th columns: parentheticals have been added to explain the optional versus mandatory status of the volumetric CT scans

Section 8.9.1, Footnotes have been revised and renumbered, including within the table, to explain the optional test-retest volumetric CT component for Group A

Pages 44–45, Section 8.9.3, Group C: "mandatory" and "two (2) optional" have been added

Section 8.9.3, 13th row, 3rd and 4th columns: parentheticals have been added to explain the optional status of the volumetric CT scans

Section 8.9.3, Footnotes have been revised and renumbered, including within the table, to explain the optional test-retest volumetric CT component for Group C

Section 10.4, Radiation Dose to the Participant, Pages 50–51

2nd paragraph, 4th sentence: "two to" has been added

2nd paragraph, new-5th sentence: has been added as follows—"*(The second pre-chemotherapy test-retest volumetric CT scan [A2] is optional, but strongly encouraged.)*"

4th paragraph, 3rd sentence: has been revised to read—"... any chemotherapy, if scheduled"

4th paragraph, 4th sentence: "will" has been replaced with "may" and "...; these volumetric CT scans are optional, but strongly encouraged" has been added

4th paragraph, final sentence: has been deleted

Section 11.0 Image Submission, Page 51

1st paragraph, 4th sentence: the email address for Triad Support has been revised

Section 11.1.2, 3rd sentence: the email address for Triad Support has been revised

Section 12.6 Reporting of Adverse Events, Page 54

Footnote below table, "CTCAE" is spelled out at first mention and "v3.0" has been revised to "most recent version)"

Section 12.7.3 Expedited Reporting to NCI and ACRIN, Page 55

"v3.0" has been revised to "most recent version)"

Section 17.1 Study Design and Endpoints, Page 59

2nd paragraph, 2nd sentence: ".../CT and one to two volumetric CT ..." has been added in two places

2nd paragraph, new-3rd sentence: has been added as follow—"*(One of the two pre-therapy volumetric CT scans is optional.)*"

2nd paragraph, now-4th sentence: ".../CT and one volumetric CT ..." has been added; ".../CT and two volumetric CT ..." has been added

2nd paragraph, now-5th sentence: ".../CT ..." has been added; "..., and up to two optional volumetric CT scans, ..." has been added

Appendix I, Informed Consent Form Templates, Pages 74–98

Page 74, Cover page, 4th paragraph: a typo has been corrected in “Institutional”

Page 77, Group A Informed Consent Form Template, under “Standard medical procedures ...” 2nd paragraph, 1st sentence: “... and two (2) other CT scans (also 1 to 7 days apart) ...” and “... FDG-PET/CT and one (1) other CT scan ...” have been added

Under “Standard medical procedures ...” 2nd paragraph, new-2nd and 3rd sentences: have been added as follows—“*Your study doctor will try to take imaging scans on the same day as possible, or on days when you are already scheduled to be at the facility for care. You may not receive one (1) of the two (2) pre-treatment CT scans if your study doctor and treating doctors decide it is in your best interest or if time becomes an issue.*”

Page 78, under “The PET/CT scanner ...” 1st paragraph, 3rd sentence: “30-90 minutes” has been revised to “50-70 minutes”

Under “Time Required” 2nd paragraph, 4th sentence: “... and two (2) other CT scans (also 1 to 7 days apart ...” and “... FDG-PET/CT and one (1) other CT scan...” have been added

Page 79, Study Chart, 2nd row, 2nd column: “(maybe not the same day as the FDG-PET/CT—ask your study doctor about what works best for you)”^{**} has been added

Study Chart, 3rd row, 2nd column: “(maybe not the same day as the FDG-PET/CT—ask your study doctor about what works best for you)”^{**} has been added

Study Chart, 2nd paragraph below the table: Footnote has been added as follows—“** What is important to part of the study is making sure you complete these four scans before you start chemotherapy. However, you may not receive one (1) of the CT scans prior to chemotherapy if your study and treating doctors find it in your best interest or if time becomes an issue.*”

Page 86, Group B Informed Consent Form Template, under “The PET/CT scanner ...” 1st paragraph, 3rd sentence: “30-90 minutes” has been revised to “50-70 minutes”

Page 93, Group C Informed Consent Form Template, under “Standard medical procedures ...” 2nd paragraph, 1st sentence: “... and two (2) other CT scans (also 1 to 7 days apart) ...” has been added

Under “Standard medical procedures ...” 2nd paragraph, new-2nd and 3rd sentences: have been added as follows—“*Your study doctor will try to take imaging scans on the same day as possible, or on days when you are already scheduled to be at the facility for care. You may not receive the two (2) pre-treatment CT scans if your study and treating doctors decide it is in your best interest or if time becomes an issue.*”

Page 94, under “The PET/CT scanner ...” 1st paragraph, 3rd sentence: “30-90 minutes” has been revised to “50-70 minutes”

Under “Time Required” 2nd paragraph, 4th sentence: “... and two (2) other CT scans (also 1 to 7 days apart ...” has been added

Study Chart, 2nd row, 2nd column: “(maybe not the same day as the FDG-PET/CT—ask your study doctor about what works best for you)”^{**} has been added

Study Chart, 3rd row, 2nd column: “(maybe not the same day as the FDG-PET/CT—ask your study doctor about what works best for you)”^{**} has been added

Page 95, Study Chart, 2nd paragraph below the table: Footnote has been added as follows—“** What is important to the study is making sure you complete all four scans before you start any treatment. You may not receive the two (2) pre-treatment CT scans if your study and treating doctors decide it is in your best interest or if time becomes an issue.*”

Appendix V, ACRIN Qualification Procedures for PET Imaging, Page 102

1st paragraph, 2nd sentence: the email address for the PET Core Lab has been updated

Appendix VI, PET Imaging Acquisition Parameters and Image Data Analysis, Page 103

2nd sentence: the email address for the PET Core Lab has been updated

Appendix VII, CT Acquisition Parameters and Image Data Analysis, Page 118

Under "Removal of Confidential Participant Information" final sentence: the email address for Triad Support has been updated

Under "sFTP Transfer" 1st paragraph, final sentence: the email address for Triad Support has been updated

REVISIONS FOR AMENDMENT #4 (v.November 16, 2009)

Cover Page

Dr. Govindan has joined the trial as a co-chair.

Amendment 4 and version date November 16, 2009, have been added.

Table of Contents

Page numbers were adjusted to match the current version.

Schema, Page 5

The Schema has been revised to:

- Define eligibility for Groups A and B (Stage IIIB with malignant pleural effusion or Stage IV, who are scheduled to undergo palliative chemotherapy) and Group C (Stages IIIA, IIIB or IV [therapy is not specified for this group]);
- Make the third FDG-PET/CT for Group B optional;
- Make all volumetric CT scans optional for all time points for all groups; however, two volumetric CT scans must be completed per participant for inclusion of these imaging data in the study analysis and, in Group B only, one of the two volumetric CT scans must be completed prior to treatment initiation; and
- Revise Inclusion/Exclusion Criteria for Groups A and B: including all cytotoxic chemotherapy regimens planned to be administered at 3-week intervals (these can be combined with bevacizumab or cetuximab), and excluding patients who have been treated with other targeted agents along (e.g., gefitinib or erlotinib) or who have failed first-line treatment with such agents.

Section 1.0, Abstract, Page 7

The Design portion of the Abstract has been revised to:

- Remove mention of the volumetric CT scans from the body of the 2nd paragraph;
- Describe the optional third FDG-PET/CT post-cycle 2 of chemotherapy for Group B; and
- Include a new NOTE as the 3rd paragraph describing the optional volumetric CT component.

Section 2.1, Introduction, Page 8

2nd paragraph, 4th sentence: has been updated to "more than 160,000 deaths occurring annually."

2nd paragraph, 5th sentence: "colorectal cancer" has been revised to "colon cancer".

Section 2.2, Lung Cancer: Challenges in Assessing Treatment Response, Page 8

2nd paragraph, former-5th sentence: has been deleted.

Section 2.3.1, Assessment of a Tumor Response after Several Cycles of Therapy, Pages 9–11

1st paragraph, final sentence: has been updated to describe "9" studies that have evaluated FDG-PET after completion of chemo- or chemoradiation "in a total of 455 patients with NSCLC" with accompanying new references.

Subsequent references have been updated throughout the protocol.

2nd paragraph, 1st sentence: has been deleted.

2nd paragraph, new-1st sentence: a period has been added after “et al.” for consistency.

2nd paragraph, final 4 sentences: have been deleted and replaced with new language related to the updated Table 1 below.

Table 1, “Response assessment on FDG-PET and survival of patients with NSCLC”: replaces the former Table 1 in a review of more-recent findings in the literature.

Paragraph between Tables 1 and 2, 1st sentence: references “(15-18)” have been deleted.

Table 2 has been updated with reference callouts (not previously included) for the articles cited, and to change footnotes from numbered sequence to lettered sequence.

Section 2.3.2, FDG-PET as an Early Predictor of Treatment Response and Survival, Page 12

Table 3, header: a colon has been replaced with a period for consistency.

Table 3, new-10th and 11th rows: two new references have been added under “Lung”—de Geus-Oei (2007) and Nahmias (2007). Subsequent references throughout have been updated.

Section 2.4.1, Volumetric Measures of Response, Page 14

Table 5, header: a colon has been replaced with a period for consistency.

Section 2.4.2, Reproducibility of 3D Measurements, Page 15

2nd paragraph, 1st sentence: “Although compelling, ...” is revised to “Compelling, ...”.

Section 2.5, Rational for Evaluating FDG-PET/CT in Patients with Advanced NSCLC Undergoing Palliative Chemotherapy, Page 16

1st paragraph, final sentence: hyphens have been replaced with em dashes in two locations.

4th paragraph, 5th sentence: “On the other hand,” has been deleted; “Malignant” is capitalized.

Section 2.5.1, Selection of Chemotherapy Regimens, Pages 17–18

1st paragraph: 3rd through 7th sentences have been added to provide background data on the efficacy, safety, and appropriate patient population for non-platinum-based doublet regimens.

With the inclusion of these new sentences, three new references have been added.

Subsequent references throughout the protocol have been updated to accommodate these new data.

1st paragraph, final sentence: the callout for “Section 8.7” has been updated to “Section 8.8”.

2nd paragraph, final two sentences: have been added in relation to gemcitabine.

3rd paragraph, 3rd sentence: has been corrected for the first author’s last name—“de” Geuss-Oei.

6th paragraph, 1st sentence: has been revised to begin—“Given the large variety of chemotherapy regimens used for treatment of advanced NSCLC, limiting ...”; “also” has been deleted; and “..., since many different chemotherapy regimens are used in patients with NSCLC” has been removed from the end of the sentence.

Section 2.6, Rationale for Assessing the Test-Retest Reproducibility of FDG-PET, Page 18

1st paragraph, former-4th sentence: has been deleted.

1st paragraph, final sentence: a typo has been corrected “test-rest” has been replaced with “test-retest”.

Table 6, Studies evaluating the test-retest reproducibility of FDG-PET or PET/CT scans in various tumor types: has been added.

Final 2 paragraphs of this section: have been extensively revised; the new text follows—

“Four single-center studies (71, 72, 74, 75) have evaluated the test-retest reproducibility of FDG-PET or PET/CT scans in various tumor types (Table 6). In addition, there is a small two-center study and a larger multicenter study including patients with advanced gastrointestinal cancers (73, 76). Although different measurements of test-retest reproducibility have been used in these studies, FDG-PET has been found to be highly reproducible in single-center studies. The coefficient of variation for relative SUV changes and the SUV difference were 10% and 0.27 SUV, respectively. Larger variability has been reported by Kamibayashi et al. (75). However, in this study the two PET scans were performed on two different camera systems (a PET/CT and PET). This likely explains the higher coefficient of variation observed. In the current protocol, we are therefore requesting that the baseline and the follow-up PET/CT studies be performed on the same PET/CT system.

Velasquez et al. have recently published the results of a multicenter trial evaluating the test-retest reproducibility of FDG-PET in patients with metastatic GI cancers (76). They found a higher coefficient of variation (16%) than in the previous single-center studies. This variability was explained partly by inconsistent scan protocols (e.g., differences in the uptake period between the baseline and the follow-up scan). When only scans passing a strict quality control procedure were analyzed, the coefficient of variation decreased to 11%. Similar data from multicenter studies are missing in lung cancer. Furthermore, the test-retest reproducibility that can be achieved prospectively in a multicenter protocol with strict criteria for acquisition and analysis of PET scans needs to be determined.”

Section 3.2, Secondary Endpoints, Page 23

Former Section 3.2.3: has been deleted and moved to new-Section 3.3.1 as an Exploratory aim with the optional status of the third FDG-PET/CT in Group B.

The subsequent section has been updated.

Section 3.3, Exploratory Data Analysis, Page 23

Section 3.3.1: has been added (as mentioned above) with revised language reflecting an Exploratory analysis instead of a Secondary Endpoint.

Subsequent numbers have been updated.

Section 4.0, Study Overview, Pages 23–24

Headers: have been added and this section has been re-written to reduce repetition, introduce the same changes made to the protocol throughout (e.g., the optional status of all volumetric CT scans and now-optional status of Image B3 in Group B), and clarify the overall goals of the study.

Section 4.5: has been added to describe per case reimbursement dependent on the number of scans completed.

Section 5.1, Inclusion Criteria, Page 25

Section 5.1.2.1 has been updated to distinguish disease staging status for Groups A and B (“newly diagnosed Stage IIIB [with malignant pleural effusion] or Stage IV”) with those for Group C (“newly diagnosed Stage IIIA, IIIB, or IV”).

Section 5.1.3 has been updated to include “a cytotoxic chemotherapy regimen planned to be administered at 3-week intervals; this regimen can be combined with bevacizumab OR cetuximab **(Groups A and B ONLY)**”

Section 5.1.10: the semicolon at the end of the criterion has been changed to a period.

Section 5.2, Exclusion Criteria, Page 26

Section 5.2.10 has been revised to read: “Treatment planned with any targeted or biologic therapy alone, such as gefitinib and erlotinib, or failure of first-line treatment with such agents **(Groups A and B ONLY)**.”

Section 5.2.11 has been deleted with the update to Section 5.1.3 listed above.

Section 8.0.1, Scanner Technical Specifications, Page 29

1st paragraph, 1st sentence: “Appendix” is now “Appendices”.

Section 8.0.2, Baseline FDG-PET/CT Scan, Page 30

4th paragraph, 1st sentence: “still need to” and “per the protocol guidelines” have been deleted.

4th paragraph, new-2nd through 5th sentences have been added, replacing previous content (former-2nd and 3rd sentences and former-5th sentence). The new sentences describe the optional status of all volumetric CT scans, as well as that two volumetric CT scans will be necessary for data analysis and that one of the two volumetric CT scans in Group B would have to occur prior to treatment initiation. Timing of the test-retest volumetric CT scans is also described.

Section 8.0.3, Number and Timing of FDG-PET/CT Scans, Pages 30–31

1st paragraph, 2nd sentence: has been added, “Eligible participants for Group C will be recruited regardless of intended therapy.”

1st paragraph, now-3rd sentence: has been revised to describe the optional status of the third FDG-PET/CT scan in Group B as introduced in this amendment.

3rd paragraph, Participants in Group B: paragraph has been revised to describe the optional third FDG-PET/CT scan post-cycle 2 of chemotherapy.

5th paragraph, Participants in Group C: the first four words have been underlined for consistency.

Section 8.0.4, CT Scans, Page 31

1st paragraph, 3rd sentence: has been added to describe that two volumetric CT scans will be necessary for imaging data to be included in the study analysis.

1st paragraph, now-4th sentence: has been combined with the former-5th sentence to reduce repetition.

1st paragraph, former-6th sentence: has been deleted as it related to the optional status of specific volumetric CT scans introduced in Amendment 3—now transitioned to optional status in all volumetric CT scans in Amendment 4.

1st paragraph, final sentence: “in Section 8.0.2” has been added to specify the location of the note.

2nd paragraph, 1st sentence: has been revised in relation to the collection and potential repetition of the baseline diagnostic CT scan for RECIST; the following language has been added “... collected if performed within 28 days prior to treatment initiation and otherwise will need to be repeated; diagnostic CTs will be ...”

Section 8.0.5, Timing Scenario Guidance for Test-Retest FDG-PET/CT and Optional Volumetric CT Scans (Groups A and C Only), Page 32

The header has been revised to reflect the optional status of all volumetric CT scans.

1st paragraph, final 2 sentences: have been added in relation to the optional volumetric CT scans.

2nd paragraph, Guidance A: “optional” has been added in relation to the volumetric CT scans.

Section 8.0.6, Submission of Images to ACRIN, Page 32

Reference to Section 10.0 has been deleted.

Section 8.1, Registration Visit, Page 33

New-9th bullet: has been added in relation to the collection and timing of the baseline diagnostic CT scan, as follows—“Collect CT scan for baseline RECIST (Groups A and B only; standard clinical practice—must have been completed within 28 days prior to treatment initiation);”

Section 8.2, Group A Participants, Pages 33–34

1st paragraph, 3rd sentence: has been revised to accommodate the optional status of all volumetric CT scans.

1st paragraph, 4th sentence: has been added to specify two volumetric CT scans are needed per participant for study analysis.

Section 8.2.1, 1st paragraph, 2nd sentence: Section 8.7 has been updated to Section 8.8.

Section 8.2.1, 1st paragraph, 3rd sentence: has been revised from Amendment 3 to describe all volumetric CT scans as optional.

2nd bullet: “mandatory” has been revised to “optional” in relation to the volumetric CT scan.

2nd paragraph: has been moved up from Imaging Visit A2 and revised to describe timing of FDG-PET/CT, volumetric CT, and RECIST only in cases when the diagnostic RECIST CT scan needs to be repeated because no baseline scan can be collected (e.g., the previous RECIST CT scan may have been completed outside of the 28-day time window prior to treatment initiation described in Section 8.1).

3rd paragraph, *NOTE, 2nd sentence: has been revised to describe the optional status of the volumetric CT component.

Section 8.2.2, 1st paragraph, 2nd sentence: reference to the volumetric CT scan has been deleted.

1st paragraph, 3rd sentence: has been revised to describe the optional status of the volumetric CT scans.

Former-4th bullet: has been deleted as the CT scan for baseline RECIST needs to be collected if it has been completed within 28 days prior to treatment initiation, or repeated if images are not available within that time window (see Section 8.2.1 for timing description for the latter scenario).

Former 3rd-paragraph, “NOTE” related to timing of the RECIST, FDG-PET/CT, and volumetric CT scans: has been deleted and moved up to Section 8.2.1.

3rd paragraph, “* NOTE”, 1st sentence: “Test-“ is now “Optional test-“.

Section 8.2.3, 2nd bullet: “optional” has been added in relation to the volumetric CT scan.

Section 8.3, Group B Participants, Pages 34–36

1st paragraph, 2nd sentence: has been revised to reflect the optional status of all volumetric CT scans.

1st paragraph, 3rd and 4th sentences: have been added to explain additional requirements for Group B participants undergoing the optional volumetric CT scans, as follows—“Two (2) optional volumetric CT scans will need to be completed for inclusion of these imaging data in the study analysis. At least one (1) of these optional volumetric CT scans must be obtained before treatment.”

1st paragraph, 5th sentence: “maximum” has been added in two places.

Section 8.3.1, 1st paragraph, 2nd sentence: “Appendix” is now “Appendices”.

Section 8.3.1, 2nd bullet: “optional” has been added.

Former-4th bullet, performing CT scan for baseline RECIST: has been deleted; the 3rd bullet therefore ends in a period instead of a semicolon.

2nd paragraph: has been moved up from the 4th paragraph and revised to describe timing of FDG-PET/CT, volumetric CT, and RECIST only in cases when the diagnostic RECIST CT scan needs to be repeated because no baseline scan can be collected (e.g., the previous RECIST CT scan may have been completed outside of the 28-day time window prior to treatment initiation described in Section 8.1).

3rd paragraph, “* NOTE”, 2nd sentence: has been revised to describe the optional volumetric CT scans.

Former-4th paragraph: has been deleted/moved up as described above.

Section 8.3.2, 2nd bullet: “optional” has been added.

Section 8.3.3, header: “OPTIONAL” has been added in relation to the post-cycle 2 of chemotherapy imaging visit for Group B. Both the FDG-PET/CT and the volumetric CT scans at this time point are optional.

1st paragraph, 1st sentence: “Optional” has been added.

1st paragraph, 2nd sentence: “Each participant ...” has been revised to “Participants ...”.

2nd bullet: “optional” has been added.

2nd paragraph, “NOTE”: has been deleted.

Section 8.5, Group C Participants, Pages 36–37

1st paragraph, 3rd sentence: “also” has been moved.

Section 8.5.1, 2nd bullet: “optional” has been added in relation to the volumetric CT scans.

2nd paragraph, “* NOTE”, 2nd sentence: language has been revised to adjust to the optional status of the volumetric CT scans.

2nd paragraph, “* NOTE”, new-3rd sentence: has been added to describe the need for both volumetric CT scans to be completed for participants in Group C to be included in the study analysis.

2nd paragraph, “* NOTE”, now-4th sentence: “Test-“ has been revised to “Optional test-“.

New-final paragraph: has been added to describe timing of FDG-PET/CT, volumetric CT, and RECIST only in cases when the diagnostic RECIST CT scan needs to be repeated because no baseline scan results can be collected (e.g., the previous RECIST CT scan may have been completed outside of the 28-day time window prior to treatment initiation described in Section 8.1).

Final sentence, callout for Section 8.0.2: has been deleted as it does not relate to the test-retest portion of the trial.

Section 8.5.2, 2nd paragraph, 2nd bullet: “optional” has been added in relation to the volumetric CT scan.

4th paragraph, “* NOTE”, final sentence: has been added as follows—“Both optional volumetric CT scans will need to be completed for inclusion of these imaging data in the study analysis.”

Section 8.8, Chemotherapy Regimens (Groups A and B Only), Pages 38–39

Section 8.8.1.1, 1st paragraph, 3rd through 5th sentences: have been added to describe the trends in Table 5’s review of the literature (3rd and 4th sentences) and to describe newer data in support of third-generation non-platinum-based doublets now included in the trial (5th sentence).

Table 5 has been deleted.

3rd paragraph, 3rd sentence: has been added in support of the inclusion of non-platinum-based doublet regimens, as follows—“On the other hand, since a variety of regimens are in common use clinically, inclusion of newer options—non-platinum-based doublets in particular—will allow us to obtain results more generalizable to current clinical practice.”

3rd paragraph, now-4th sentence: “However, all ...” has been revised to “All ...”.

Section 8.8.1.2, 1st paragraph, 1st sentence: “cytotoxic” has been added, as well as “..., which can be combined with bevacizumab or cetuximab,” in relation to therapeutic options for Groups A and B.

1st paragraph, former-2nd sentence: has been deleted.

1st paragraph, now-3rd sentence: begins “Most of ...” as opposed to “Furthermore, most of ...”.

Section 8.9, Overview of the Study Procedures, Pages 41–46

Pages 41 and 42, Section 8.9.1, Group A: Changes to the procedures description and table are to make all volumetric CT scans optional (deleting “mandatory” language).

In the table, the collection of the initial diagnostic CT (RECIST) has been altered to become part of the Registration Visit instead of falling under “Imaging Visit A2”.

Footnotes 6 and 7 have been revised in relation to the optional volumetric CT scans and the need for two to be completed for each participant.

Footnote 8 has been added to reaffirm the need to complete the optional volumetric CT scan post-cycle 1 of chemotherapy if one of the pre-treatment volumetric CT scans has been completed.

Page 43 and 44, Section 8.9.2, Group B: Changes to the procedures description and table are to make all volumetric CT scans optional (adding “optional” and deleting “mandatory” language) and to introduce the optional status of the FDG-PET/CT scan to be completed post-cycle 2 of chemotherapy (the B3 scan).

In the table, the collection of the initial diagnostic CT (RECIST) has been altered to become part of the Registration Visit.

Footnote 5 has been updated to describe the optional volumetric CT scans and that two must be completed to be included in the data analysis.

Footnote 7 has been added in relation to the timing of the optional volumetric CT scans for Group B participants.

Pages 45 and 46, Section 8.9.3, Group C: 4th column, 2nd row, “(before start of treatment)” has been added.

1st column, 10th row: has been revised to read “Collection of Diagnostic CT Results”.

2nd column, 10th row: “(Standard of Care)” has been added.

Footnote 6 has been updated to describe that both of the optional volumetric CT scans for Group C must be completed for inclusion of these data in the study analysis.

Section 10.1, Overview of PET and CT Data Acquisition, Page 50

1st paragraph, 4th sentence: has revised to read” ... participants will be asked to undergo optional CT scans ...”.

Section 10.2.3, Measurement of Tumor Volume, Pages 50–51

1st paragraph, 1st and 2nd sentences: “optional” has been added to both sentences in relation to the volumetric CT scans.

Section 10.3, FDA Preliminary Public Health Notification for CT Scans, Page 51

Header: “Scans” is capitalized.

Section 10.4, Radiation Dose to the Participant, Pages 51–52

2nd paragraph, 4th through 7th sentences: have been revised/added to describe the optional status of the volumetric CT scans for Group A and the need for completed scan images for at least two time points.

3rd paragraph, 1st sentence: “a maximum of” has been added.

3rd paragraph, 2nd sentence: “an optional” has been added in relation to the post-cycle 2 of chemotherapy FDG-PET/CT.

3rd paragraph, 3rd through 6th sentences: have been revised/added to describe the optional status of the volumetric CT scans for Group B, that two of these optional scans must be completed for inclusion into the data analysis, and that one of the two optional volumetric CT scans for this group must be completed prior to treatment.

4th paragraph, 3rd sentence: “are” has been added, “are the first and second FDG-PET/CT scans” has been deleted, “both” has been added, and “such treatment is” has been added.

4th paragraph, 4th sentence: “also” has been moved to before “may”.

New-5th paragraph: has been added to introduce the need to repeat the FDG-PET/CT at baseline if the timing or technical parameters do not meet study criteria, as follow—

“Additionally, note that if the baseline FDG-PET/CT scan obtained clinically before participant consent and registration does meet the technical parameters required for this protocol, this can be repeated as a research-related examination. The radiation exposure in such a case will be further increased (since the participant will have three research-related FDG-PET/CT scans).”

Section 16.0, Institutional Monitoring and Audits, Page 59

2nd paragraph, 1st sentence: has been deleted; a new paragraph has been introduced as follows—*“All participating institutions that enroll participants will be audited. The timing of the initial on-site audit will depend upon several factors, including the rate of accrual (both study-wide and site-specific), the number of evaluable participants enrolled at an individual site, the status of the protocol and pending amendments, and monitoring status. Generally, audits will be conducted after the number of evaluable participants reaches 20% of targeted accrual, either study-wide and/or site-specific. Audits are typically scheduled to occur at least 3 months after an institution has been monitored, providing that monitoring did not identify issues that mandate immediate auditing. This schedule may be altered in the event of pending protocol amendments. Closure of the study to accrual will trigger auditing of all participating institutions not yet audited. Additionally, site-specific circumstances may prompt an audit at any time.”*

Section 17.1, Study Design and Endpoints, Page 60

1st paragraph, 2nd sentence: reference to former-Secondary Endpoint (iii), which is now an exploratory aim, has been deleted.

2nd paragraph, including new-sentences 5 and 6: has been revised extensively to focus the paragraph on the FDG-PET/CT study components, add “FDG-“ to “FDG-PET/CT” in four locations, make the third FDG-PET/CT optional in Group B, and introduce the optional volumetric CT scans for each time point and explain directives and distinctions (new sentences 5 and 6).

Section 17.2.2, Analysis of Secondary Endpoints, Page 62

Former-Secondary endpoint (iii) has been deleted (see below).

Section 17.2.3, Exploratory Analysis, Page 63

Language from former-Secondary Endpoint (iii) has been reorganized as an Exploratory Aim; it now appears as the 2nd paragraph of Section 17.2.3.

Section 17.4.1, Power and Precision Calculations, Page 65

1st paragraph, 3rd and 4th sentences: have been rewritten as follows—*“In addition, 57 participants are needed in Groups A and C in order to provide adequate statistical precision to assess reproducibility (secondary endpoint iii). Thus, in the extreme case of no accrual in Group A, the total accrual to all groups could be as high as 285 (228 in Group B plus 57 in Group C).”*

2nd paragraph: has been added to describe how the different groups will be closed to enrollment based on accrual targets being reached, as follows—

“Closing enrollment to protocol cohorts will depend on the status of complete images for participants in all three groups:

- *If the sample size in Groups A + B < 228, but the sample size in Groups A + C =57, enrollment to Groups A and C will be closed and recruitment to Group B will continue until the sample size in Groups A + B = 228.*
- *If the sample size in Groups A + B =228, but the sample size in Groups A + C < 57, accrual to Group B will be closed and accrual will continue in Groups A and C until the sample size in Groups A + C = 57.*
- *If the sample size in Groups A + B < 228 and the sample size in Groups A + C < 57, accrual will continue in all groups.”*

Section 17.4.3, Sample Size Calculation for the Secondary Endpoints, Page 67

Former-“For secondary endpoint iii” section has been deleted.

Former-“For secondary endpoint iv” has been renumbered.

References, Pages 68–75

The references list has been extensively updated for consistency and to accommodate the protocol revisions described above.

Appendix I: Informed Consent Form Templates for Groups A, B, and C, Pages 74–98

The Informed Consent Form Templates have been revised for clarity and consistency, as well as to explain that potential participants may not receive all of the imaging scans that they consent to by signing the form (depending on what the participant and his/her clinicians decide is best in regards to health and timing of the optional scans).

The following specific changes have been made:

Page 76, 1st paragraph, 2nd sentence: “obtained” has been deleted, “or” replaces “and”, and “is” has been added.

2nd paragraph, 1st sentence: “utilize in creating” has been revised to “to create”; “to address” has been revised to “for patients”; and hyphens have been added to “standard-of-care”.

GROUP A

Page 78, 2nd paragraph, “*Taking Part in Clinical Trials: What Cancer Patients Need to Know*“ has been updated to “*Taking Part in Cancer Treatment Research Studies*” per an update to the NCI ICF Template.

Page 79, under “What Will Happen if I Take Part in This Research Study?”, bulleted list under “Standard medical procedures that are part of regular cancer care ...”: new 4th bullet has been added as follows—“Clinical labs related to your treatment (within 4 weeks of registration to the trial)”

Under “What Will Happen if I Take Part in This Research Study?” 5th paragraph, 3rd sentence: “... one (1) of the two (2) pre-treatment ...” has been revised to “... one pre-treatment FDG-PET/CT scan or the ...”.

Under “What Will Happen if I Take Part in This Research Study?” 6th paragraph, 4th sentence: “regular” has been added to identify the doctor.

Page 80, 1st paragraph below “Time Required”: 5th sentence—“will” has been replaced with “are consenting to”; new-6th and 7th sentences have been added—“However, the other CT scans are optional. You may not undergo all of these scans, depending on what you and your study and regular doctors decide is in your best interest.”; and, final sentence, now begins with “The scans ...” instead of “This ...”.

Page 81, Study Chart, 2nd row, 2nd column, 3rd bullet: has been revised to read “(may not be on ...)”.

Study Chart, 2nd row, 2nd column, 4th bullet: a dagger footnote symbol has been added.

Study Chart, 3rd row, 2nd column, 3rd bullet: has been revised to read “(may not be on ...)”.

Study Chart, 3rd row, 2nd column, 4th bullet: a dagger footnote symbol has been added.

Study Chart, 4th row, 2nd column, 3rd bullet: “(may not on the same day as the FDG-PET/CT—ask your study doctor about what works best for you)*” has been added.

Study Chart, 4th row, 2nd column, 4th bullet: a dagger footnote symbol has been added.

Study Chart, 5th row, 2nd column: revised bullet as follows—“Have a diagnostic CT scan at time intervals based on the recommendation and standard practice of your regular doctor.”

2nd paragraph under Study Chart: the “*” footnote has been revised to read as follows—
 “* *Even if you agree to the other CT scans, you may not receive them if your study and regular doctors decide it is in your best interest or if time becomes an issue.*

† *It is important to the study to make sure you have completed the first two FDG-PET/CT scans before you start any treatment and the third FDG-PET/CT scan after your first cycle of chemotherapy.*”

Page 82, under Risks Associated with Radiation Exposure from FDG-PET/CT and CT scans, 2nd paragraph, 1st sentence: “a maximum” has been added.

GROUP B

Page 86, 2nd paragraph, “*Taking Part in Clinical Trials: What Cancer Patients Need to Know*” has been updated to “*Taking Part in Cancer Treatment Research Studies*” per an update to the NCI ICF Template.

Page 87, under “What Will Happen if I Take Part in This Research Study?”, bulleted list under “Standard medical procedures that are part of regular cancer care ...”: new 4th bullet has been added as follows—
 “Clinical labs related to your treatment (within 4 weeks of registration to the trial)”

Under “What Will Happen if I Take Part in This Research Study?” 4th paragraph: has been revised to introduce the volumetric CT scans at each time point, and two new sentences have been added as follows—
 “*You may not receive all of these scans if you and your study and treating doctors decide it is in your best interest or if time becomes an issue. Your study doctor will try to take imaging scans on the same day as possible, or on days when you are already scheduled to be at the facility for care.*”

Page 88, 1st paragraph below “Time Required”: 5th sentence—“will” has been replaced with “are consenting to”; “and one (1) other CT” has been added; and “FDG-PET/CT and one (1) other CT scans” has been added in two locations for clarification.

1st paragraph under “Time Required”: new-6th and 7th sentences have been added—
 “*One of the FDG-PET/CT scans and all of the other CT scans are optional. You may not undergo all of these scans, depending on what you and your study and treating doctors decide is in your best interest.*”

1st paragraph under “Time Required”: final sentence, now begins with “The scans ...” instead of “This ...”.

Page 89, Study Chart, 2nd row, 2nd column, 3rd bullet: has been revised to read “(may not be on ...)”.

Study Chart, 2nd row, 2nd column, 4th bullet: a dagger footnote symbol has been added.

Study Chart, 3rd row, 2nd column, 3rd bullet: has been revised to read “(may not be on ...)”.

Study Chart, 3rd row, 2nd column, 4th bullet: a dagger footnote symbol has been added.

Study Chart, 4th row, 2nd column, 3rd bullet: “(may not on the same day as the FDG-PET/CT—ask your study doctor about what works best for you)*” has been added.

Study Chart, 4th row, 2nd column, 4th bullet: a dagger footnote symbol has been added.

Study Chart, 5th row, 2nd column: revised bullet as follows—“Have a diagnostic CT scan at time intervals based on the recommendation and standard practice of your regular doctor.”

1st paragraph below Study Chart: final two sentences have been added as follow—“*The FDG-PET/CT scan after your second cycle of chemotherapy (Visit B3) and the other CT scans are optional. You and your study and treating doctors will decide if it is in your best interest to undergo some or all of these scans during the trial.*”

2nd paragraph under Study Chart: the “*” footnote has been revised to read as follows—“* *Even if you agree to the other scans, you may not receive them if your study and treating doctors decide it is in your best interest or if time becomes an issue.*

† *It is important to the study to make sure you have completed the first two FDG-PET/CT scans—one before you start any treatment and the second after your first cycle of chemotherapy.*”

Page 90, under Risks Associated with Radiation Exposure from FDG-PET/CT and CT scans, 2nd paragraph, 1st sentence: “a maximum” has been added.

Under Risks Associated with Radiation Exposure from FDG-PET/CT and CT scans, 2nd paragraph, 2nd sentence: “will” has been revised to “may”.

Under Risks Associated with Radiation Exposure from FDG-PET/CT and CT scans, 2nd paragraph, 3rd sentence: a close-parenthesis has been deleted from the end of the sentence.

GROUP C

Page 94, 2nd paragraph, “*Taking Part in Clinical Trials: What Cancer Patients Need to Know*“ has been updated to “*Taking Part in Cancer Treatment Research Studies*” per an update to the NCI ICF Template.

Page 96, 1st paragraph below “Time Required”: 3rd sentence “..., if any” has been added in relation to treatment options for this group.

1st paragraph below “Time Required”: 4th sentence—“will have” has been replaced with “are consenting to”.

1st paragraph under “Time Required”: new-5th and 6th sentences have been added—“*However, the two (2) other CT scans are optional. You may not undergo all of these scans, depending on what you and your study and treating doctors decide is in your best interest.*”

1st paragraph under “Time Required”: final sentence, now begins with “The scans ...” instead of “This ...”.

Page 97, Study Chart, 2nd row, 2nd column, 3rd bullet: has been revised to read “(may not be on ...)”.

Study Chart, 2nd row, 2nd column, 4th bullet: a dagger footnote symbol has been added.

Study Chart, 3rd row, 2nd column, 3rd bullet: has been revised to read “(may not be on ...)”.

Study Chart, 3rd row, 2nd column, 4th bullet: a dagger footnote symbol has been added.

2nd paragraph under Study Chart: the “*” footnote has been revised to read as follows—“**Even if you agree to the CT scans, you may not receive them if your study and treating doctors decide it is in your best interest or if time becomes an issue.*

† *It is important to the study to make sure you have completed the two FDG-PET/CT scans before you start any treatment.*”

Page 98, under Risks Associated with Radiation Exposure from FDG-PET/CT and CT scans, 2nd paragraph, 1st sentence: “a maximum” has been added.

Under Risks Associated with Radiation Exposure from FDG-PET/CT and CT scans, 2nd paragraph, 3rd sentence: a close-parenthesis has been deleted from the end of the sentence.

Appendix VI, PET Imaging Acquisitions Parameters and Image Data Analysis, Pages 108–109

Section 7.2.2.1: “less than 10 min” has been revised to “10 min or less”.

Section 7.2.2.2: “but by less than 15 min” has been revised to “up to 15 min”.

Section 9: “Appendix VI” has been revised to “Section 5 above”.

Appendix VII, CT Acquisition Parameters and Image Data Analysis, Pages 112–119

Section 2, header: a colon has been added after “CT Volumetry” and “Optional (Participant May Not Undergo Volumetric CT Scans/Decision Left to Clinicians and Participants)” has been added as a subheader.

Section 2.1, 3rd paragraph, 1st sentence: “optional” has been added.

Section 2.1, 3rd paragraph, 3rd sentence: has been revised to read “may occur at both or either timepoint—post-cycle 1 or 2 of chemotherapy”.

Section 2.1, 3rd paragraph, 4th sentence: “optional” has been added.

Section 3.1, Table 2, 7th row, 2nd column: “3 mm” has been corrected to “5 mm”.

Section 4, header: “0” has been deleted for consistency of section numbering; 1st sentence, the page number for Appendix VII has been updated to “page 113”.