TO: ALL PRINCIPAL INVESTIGATORS/NURSES/DATA MANAGERS

Please Note: Only sites which submitted Revision #5 to GOG-0262/ACRIN 6695 are required to submit this revision to their IRB. Sites which entered patients prior to 02/08/2012 and are not participating in the imaging component can continue to use the 12/22/2012 version which includes Revisions #1-4.

FROM: MEG COLAHAN
PROTOCOL SECTION

DATE: OCTOBER 22, 2012

RE: PROTOCOL GOG-0262/ACRIN 6695- REVISION #6

Protocol Title: GOG-0262: A PHASE III TRIAL OF EVERY-3-WEEKS PACLITAXEL VERSUS DOSE DENSE WEEKLY PACLITAXEL IN COMBINATION WITH CARBOPLATIN WITH OR WITHOUT CONCURRENT AND CONSOLIDATION BEVACIZUMAB (NSC#704865, IND #113912) IN THE TREATMENT OF PRIMARY STAGE II, III OR IV EPITHELIAL OVARIAN, PERITONEAL OR FALLOPIAN TUBE CANCER and ACRIN 6695: PERFUSION CT IMAGING TO EVALUATE TREATMENT RESPONSE IN PATIENTS PARTICIPATING IN GOG-0262” NCI Version Date: 09/26/2012

Study Chair: John K. Chan, MD; (415) 885-7561; chanjohn@obgyn.ucsf.edu

IRB Review Recommendation:
( ) No review required
(X) Expedited review; however, site IRB requirements take precedence
( ) Full board review recommended because there have been changes to the eligibility criteria and consent.

Please direct questions about the recommended level of IRB review to your local IRB. The local IRB is responsible for making this determination. If your local IRB does not agree with the GOG’s recommended level of review, please document the IRB’s decision, and the rationale for the decision, in your study files.

The following changes have been made for clarity and to include elements applicable to the ACRIN 6695 imaging sub-study and become effective October 22, 2012:

- Title Pages - NCI Version Date is now 09/26/2012.
- Includes Revisions #1-6.
To reflect date of revision

- Under Target Population, a typo in “neoadjuvant” has been corrected.
- “and must agree to participate in the ACRIN 6695 imaging component” has been added.

ACRIN 6695 Schema
- Headers have been added to the two Schemata to distinguish the two cohorts.
- The ACRIN 6695 Schemata have been revised to reflect the optional status of bevacizumab, changes in baseline T0 timeline around GOG registration, the need to confirm target lesion in baseline T0 and pre-treatment scans for RECIST measurement before the participant undergoes the intermediate T1 scan, and to ensure the Schemata accurately reflect the content of section 4.6 in the protocol.

Table of Contents
- Page numbers have been updated.
- Appendix VII’s title has been updated.
- Appendix IX’s title has been updated.

Sections 1.4 and 1.5
- Imaging Objectives have been revised to ensure consistency of language between sections (in comparison with section 11.8 language), to consistently clarify the “baseline” T0, “intermediate” T1, and “early-therapy” T2 perfusion CT scans (a revision made throughout the protocol), to clean up repetitive language and use of acronyms, and to ensure clarity of time point comparisons for each aim.

Section 2.8
- In the fifth paragraph, “affects” has been corrected to “effects.”

Section 2.9
- The background section has been extensively revised for flow, use of acronyms, and clarity. The content has not been changed.

Section 3.1
- “… at ACRIN-qualified institutions” has been added to ensure sites know study perfusion CT should not be conducted on participants in the GOG-0262 trial until the site has completed ACRIN’s qualification procedures.

Section 3.11
- Additional information on eligibility requirements for disease verification among patients after primary surgery has been introduced as follows: “For primary surgery patients, if no radiographic evidence of measurable disease is obtained prior to registration this can be based on surgical findings; imaging then would need to be completed in the 14 days between GOG registration and chemotherapy initiation.”
- A paragraph has been added to describe procedures after GOG registration and baseline imaging that will confirm target lesion parameters for the ACRIN 6695 sub-study. The paragraph reads: “After
GOG registration, the American College of Radiology [ACR] Imaging Core Laboratory will confirm target lesion as required per protocol. The GOG-eligibility (RECIST) scan and baseline T0 perfusion CT scans will be reviewed prior to the intermediate T1 perfusion CT time point.”

Below Section 3.110 - “Patients enrolled after February 8, 2012 must participate in the ACRIN 6695 component. (04/30/2012)” has been deleted to reduce repetition.

Section 3.29 - “Bevacizumab” has been capitalized at the beginning of a sentence.

Section 3.2112 - Above this section, language has been added to describe that the following content applies only to the ACRIN 6695 imaging portion of the trial and to describe procedures related to the target lesion confirmation of ACRIN 6695 eligibility (and trial conduct in cases when the target lesion is not confirmed).
- A header has been added: “ACRIN 6695 Eligible Patients”.
- Section 3.2112 has been added to describe the confirmation of eligibility parameters for target lesion assessment between baseline T0 and intermediate T1 imaging time points for the ACRIN 6695 sub-study.

Section 3.2113 - A header has been added above this section: “ACRIN 6695 Ineligible Patients”.
- This section has been renumbered.

Section 3.2114 - This section has been renumbered.
- “of” has been revised to “before” for clarity of timing.

Section 4.6 - This section has been extensively revised to clarify procedures related to the target lesion confirmation between baseline T0 and intermediate T1 time points and scanner qualification requirements.
- Reference to a 7-day submission timeline has been added. Sites are required to deliver baseline T0 scans (perfusion CT and standard care RECIST scans) and receive confirmation of receipt from the ACR Imaging Core Lab within 7 days after the acquisition of the baseline T0 perfusion CT for the ACRIN 6695 sub-study. This requirement will allow for target lesion assessment per protocol prior to the intermediate T1 perfusion CT time point so participants without confirmed target lesion will not continue will additional study-related imaging.

Section 4.61 - The header has been updated to specify the section describes the perfusion CT scans’ timelines and analysis.
- Sub-sections have been renumbered.
Sections 4.611 and 4.612 - These sections have been revised to clarify the two cohorts (primary surgery versus neoadjuvant chemotherapy), clarify timeline distinctions for the baseline T0 perfusion CT scan, and explain the reasoning behind the timing parameters.

- Figures 1 and 2 have been added to visually display the timing distinctions between the two cohorts for baseline T0.

Section 4.613 - This section has been revised to identify the “intermediate” T1 time point, for consistency of language, to allow for scan timing adjustments should Cycle 1’s completion be delayed for any reason, and to clearly explain the reproducibility T1 perfusion CT scan is to be completed at the intermediate T1 time point in a subset of 15 participants (after a site has received clearance from the ACR Core Lab to perform reproducibility T1 scans).

Section 4.614 - This section has been revised to identify the “early-therapy” T2 time point, for consistency of language, and to identify the optional status of bevacizumab during Cycle 2 chemotherapy.

Section 4.615 - The contents of this section have been moved up from Section 4.62, but have not been changed.

Section 4.62 - The header has been revised because the section applies to the “Perfusion CT Scanning Procedures”.

- A paragraph has been added as follows: “At each time point, every patient will have an abdominal strap put on with gentle pressure over the area of the perfusion scan to decrease the breathing motion of the abdomen or pelvis during the perfusion scan. Additional information about the perfusion CT scan parameters is available in Appendix VII of the protocol and in the ACRIN 6695 / GOG-0262 Imaging Manual available online at www.acrin.org/6695_protocol.aspx under Imaging Materials.”

Section 4.621 - The baseline T0 perfusion CT scan protocol section has been renumbered and extensively revised. These revisions include, for clarification purposes only in consideration of participant convenience and institutional standard practices, same-day scanning details for the baseline T0 perfusion CT scan and the CT scan required for GOG eligibility assessment within 28 days prior to chemotherapy initiation and changes to the scan parameters.
Section 4.622 - The intermediate T1 perfusion CT scan protocol section (including details about the reproducibility T1 perfusion CT scan) has been revised for clarity and consistency per previous revisions and to clarify that the target lesion needs to be included in the scan coverage; a pre-scan review of creatinine, or blood draw if not assessed within the 28 days prior to the scheduled scan, has been added to check kidney sufficiency prior to contrast agent administration.

Section 4.623 - The early-therapy T2 perfusion CT scan protocol section has been revised for clarity and consistency per previous revisions and to clarify that the target lesion needs to be included in the scan coverage; a pre-scan review of creatinine, or blood draw if not assessed within the 28 days prior to the scheduled scan, has been added to check kidney sufficiency prior to contrast agent administration.

Section 4.63 - Has been added to identify the need for sites to report imaging AEs and SAEs reported within 24 hours after each perfusion CT scan.

Former-Section 4.64 - The expected risks description has been moved to appear in the expanded imaging-related AEs and SAEs content added as section 10.3.

Section 5.3 - The header has been revised to remove reference to a “treatment” plan.
- This section (and subsections 5.31-5.33) has been extensively revised to reflect changes to content from previous sections.
- The image submission guidelines in section 5.33 have been updated to reflect current ACRIN procedures.

Section 6.314 - Subsection numbering has been corrected.

Section 7.1 - § footnote: “Kidney sufficiency will need to be assessed prior to ACRIN 6695 intermediate T1 and early-therapy T2 perfusion CT scans to review kidney health prior to administration of contrast. If creatinine has not been measured within 28 days prior to the perfusion CT scans, sites will need to measure creatinine prior to imaging. If creatinine is not \( \leq 1.5 \times \) institutional upper limit normal, then the participant will not continue with ACRIN 6695 imaging but will continue with the GOG therapeutic trial.” has been added.
- #11 footnote: Has been revised to more accurately detail the timeline of the initial CT or MRI of the abdomen and pelvis required to establish post-surgical baseline for extent of residual disease and the potential to complete this scan after GOG registration and at the same time as the baseline T0 perfusion CT scan. “11” has been added to the pre-treatment column’s cell immediately to the right of the perfusion CT scan row in the procedures table (final row, 2nd cell).
- # 21 footnote: Has been corrected for consistency of language and clarify of timeline parameters at each perfusion CT imaging time point.
Section 7.5 - Reference to a 7-day submission timeline has been added. Sites are required to deliver baseline T0 scans (perfusion CT and standard care RECIST scans—the standard care scan should be available as required for GOG eligibility, either post-surgically or to define disease in the neoadjuvant cohort) to the ACR Imaging Core Lab. After the core lab reviews the images, sites will receive confirmation of receipt. The 7-days after acquisition requirement will allow for target lesion assessment per protocol prior to the intermediate T1 perfusion CT time point so participants without confirmed target lesion will not continue with additional study-related imaging. 
- Clarification on the submission of forms with the images to the core lab has been added throughout section 7.5. 
- Additional revisions have been made for consistency and to incorporate changes made in previous sections.

Section 8.2 - In the “Perfusion CT” section, reference to assessment of “non-target” lesions has been deleted and ROIs will be recorded in the ACR Imaging Core Lab, not on the evaluation forms previously identified.

Section 8.34 - Changes have been made to remove reference to “non-target” tumor assessment and for language consistency.

Section 10.2 - Reference to the “ACRIN Clinical Rationale for Imaging Declination Form” has been removed since all participants on the GOG-0262/ACRIN 6695 trial will be consenting to participate in the ACRIN 6695 sub-study at the time joining the GOG-0262 therapeutic trial. 
- Corresponding note § has been deleted.

Section 10.3 and subsections - Expected risks associated with the perfusion CT scan for the ACRIN 6695 trial have been moved to Section 10.3. 
- Reporting requirements for imaging-related AEs and SAEs occurring within 24 hours of the study-related perfusion CT scans and contrast agent administration have been added to this section, including the reporting requirements table created by NCI (version May 5, 2011).

Section 11.7 - A typo has been corrected.

Section 11.8 - Changes to the language in the Statistical Considerations for the Imaging Study reflect the language in the imaging objectives as described in sections 1.4 and 1.5. 
- Additional changes are for consistency and style. 
- Neither the overall objectives nor the analysis procedures have been changed with this amendment.
- Reference to a potential delay in ACRIN accrual has been removed from section 11.831.

Bibliography
- The references have been revised to reflect the reorganization of section 2.9’s background description for the imaging component of the trial.

Informed Consent
- NCI Version Date is now 09/26/2012.
  - Under “Why is this Study Being Done?:”
    - Reference to “conventional” CT or MRI scans has been revised to “the standard of care” to reduce the reading level.
    - Grammatical and clarifying changes have been made.
  - Under “What Will Happen if I Take Part in this Study?, Before you Begin the Study:”
    - Reference to the timing of the standard of care CT scan and the review of the first perfusion CT scan for continued eligibility on the ACRIN 6695 trial has been revised to read: “If you have not had a post-surgery CT scan before you join the trial, a CT scan may be performed the same day as the perfusion CT scan.”
    - The timeline of the first perfusion CT scan has been revised from 28 days before chemotherapy begins to 14 days to coincide with GOG timeline from registration to chemotherapy.
    - Reference to “conventional” CT or MRI scans has been revised to “standard of care” to reduce the reading level.
    - In the last paragraph, “small” has been removed before “dose of a contrast agent.”
  - Under “What Will Happen if I Take Part in this Study?, During the Study:”
    - The first paragraph has been revised for clarity.
    - The bullets have been revised to clarify CT timing, and include information on checking kidney health.
    - “You will receive a small dose of the x-ray dye according to your body weight” has been changed to “You will receive a dose of a contrast agent according to your body weight.”
- Under the Study Chart, Cycle 1:
  - The perfusion CT scan has been moved to the “within 14 days before starting treatment” column.
  - Under Between Days 18 and 21:
    - “get your kidney health checked if it has not been done recently” has been added.
- Under the Study Chart, Cycles 2-6 (for patients who had primary surgery):
  - Under Between Days 8 and 10:
    - “get your kidney health checked if it has not been done recently” has been added.
- Under Cycle 2 (for patients who will have interval cytoreductive surgery):
  - Under Between Days 8 and 10:
    - “get your kidney health checked if it has not been done recently” has been added.
- Under The Study Plan:
  - The timing of the perfusion CT scans has been corrected for both Groups.
- Under “How Long Will I Be in the Study?:”
  - The first paragraph now reads: “The perfusion CT scanning portion of the study will last approximately eight to ten weeks. You will complete the imaging portion of the study (perfusion CT scans) before the start of your third cycle of chemotherapy.”
- Under “What Side Effects or Risks Can I Expect from Being in the Study?:”
  - Under “Risks and Side Effects Related to the Perfusion CT”:
    - Section now reads: “Two different types of risks are associated with the perfusion CT scans in the study: radiation from the X-ray used in the perfusion CT and possible reactions to the contrast agent, also known as X-Ray dye.”
    - Headings have been changed from “Risks Associated with X-Ray dye” to “Risks Associated with the Contrast Agent or X-Ray Dye.”

Appendix VII
- A “Perfusion” and a serial comma have been added to the title of the appendix.
- An extensive Note has been added as an introduction to the appendix. The Note describes interscan delay parameters and other procedures associated with the perfusion CT scan (e.g., breath hold and use of abdominal strap for each participant).
- Throughout the detailed descriptions of scanner type differentials, the contrast dose now consistently reads: “0.7 to 0.8 ml•kg⁻¹”; and the injection rate now reads: “0 to 5 s before scanning starts”.
- The two paragraphs above the Dosage table have been revised for accuracy and clarity.
- The Dosage table reflecting effective and skin doses associated with the perfusion CT for the ACRIN 6695 sub-study has been revised (in language only, not in dosage information) to reflect the consistency and language clarification changes from the protocol.
- Reference to “normal” has been deleted from the paragraph below the Dosage table.
- The second paragraph below the Dosage table has been revised to clarify “standard institutional care” instead of “normal care”, to correct typos, apply style consistently, and remove a sentence referencing content of the Dosage table that was not included in the previously submitted content.
- The reference #1 for this appendix has been added.

Appendix VIII - This appendix has been extensively revised to reflect the current protocol content for ACRIN eligibility requirements.
- The flow chart has been updated to more accurately reflect the process for determining target lesion before intermediate T1 imaging, including the 7-day timeline for ACR Imaging Core Lab receipt and confirmation of baseline T0 and RECIST criteria (images related to GOG eligibility that need to come to ACRIN for target lesion confirmation).

Appendix IX - This appendix has been extensively revised to provide content for the ACRIN site research staff for imaging-related adverse events reporting.
- The content is in support of revisions to the AE/SAE reporting requirements for imaging studies section of the protocol (section 10.3).

Appendix X - This appendix has been revised to reflect current data management requirements, explain sites’ ability to revise data from their locations, describe data to be provided to ACRIN from the GOG database, and alter language for clarity and consistency.

Please update all copies of the protocol at your institution with these changes. Do not discard the old version. Please retain a copy of earlier versions of the protocol in your regulatory binder as historical documentation.