

North Central Cancer Treatment Group

N0574: Phase III Randomized Trial of the Role of Whole Brain Radiation Therapy in Addition to Radiosurgery in Patients with One to Three Cerebral Metastases

Addendum 2 – November 30, 2007

Summary

- Changes requested by CTSU for transition from forms tracking to basic service.
- NCI recommendations which were made upon approval of Addendum 1 have been incorporated into Addendum 2.
- Statistical sections 16.23 and 16.3 have been revised.
- Other administrative and editorial changes.

A replacement protocol is provided. Please replace the current copy with the one attached. Please keep this addendum with your protocol

Title page Reflects the addition of Addendum 2 and revised NCI version date.

Instructions to CTSU sites have been revised as follows due to conversion to basic service:

CTSU sites (Non-NCCTG members): Patient enrollments from institutions that are not aligned with NCCTG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data from these institutions should be sent to ~~CTSU Data~~ **NCCTG Operations Office** unless otherwise specified in the CTSU logistical appendix.

North Central Cancer Treatment Group (NCCTG) ADDRESS AND CONTACT INFORMATION

Page 3: The contact information has been updated as follows:

Neurocognitive Testing	Elana Farace, Ph.D. Associate Professor of Neurosurgery and Public Health Evaluation Sciences Phone: 717-531- 4152 7386 Fax: 717-531-0748 Email: farace@psu.edu efarace@hmc.psu.edu
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Cancer Trials Support Unit (CTSU) Address and Contact Information

Page 4: The contact information has been updated as follows as requested by CTSU:

<p>To Mail Forms or Data</p>	<p>Westat CTSU Data Operations Center 1441 W. Montgomery Avenue Rockville, MD 20850-2062 NCCTG Operations Office Northwest Clinic, 3rd Floor Mayo Clinic 200 First St SW Rochester MN 55905</p> <p>Please do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions</p>
<p>All Other Questions For questions unrelated to patient eligibility, treatment, or data submission:</p>	<p>CTSU General Information Line – 1-888-823-5923 or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</p>

Page 5: The following was added as requested by CTSU for transition from forms tracking to basic service.

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Institutions not aligned with NCCTG will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix.

- **The study protocol and all related forms and documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at <https://members.ctsuo.org>**
- **Send completed site registration documents to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.**
- **Patient enrollments will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.**
- **Data management will be performed by the NCCTG Operations Office. Case report forms (with the exception of patient enrollment forms), clinical reports, and transmittals must be sent to the NCCTG Operations Office unless otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations.**
- **Data query and delinquency reports will be sent directly to the enrolling site by the NCCTG Operations Office. Please send query responses and delinquent data to the NCCTG and do not copy the CTSU Data Operations.**
- **Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the NCCTG Operations Office.**

NOTE: Repagination has occurred throughout remainder of protocol.

4.0 Test Schedule

Page 15 Footnote 6 of Test Schedule revised as follows for clarification:

6. After informed consent and prior to randomization. **Note: If FACT-BR, the Barthel, and/or the neurocognitive assessments were completed prior to randomization for clinical reasons within the time allowed, and comply with the standards of the testing outlined in the protocol, these results will be allowed (as per protocol, proper documentation is required and booklets need to be forwarded) and do not need to be repeated immediately after randomization.**

Section 8.0 Neurocognitive/Quality of Life Assessment and Treatment / Follow up Decision

Page 22: Section 8.2 has been revised as follows for clarification:

Prior to intervention and at the beginning of each scheduled study visit, the treating physician or his/her authorized designee will rate the patient's functional independence (**in consultation with the patient and/or caregiver**) on the Barthel ADL Index ordinal scale....

Page 23 The following editorial changes have been made to Section 8.32:

- 8.32 Mail completed Neurocognitive Examiners Booklet and Neurocognitive Patient Completed Booklet (and keeping a copy at the treating institution) to:

Elana Farace, PhD
Associate Professor of Neurosurgery and Public Health Sciences
 Director of Clinical Research
 Department of Neurosurgery
 Penn State Milton S. Hershey Medical Center
 500 University Drive, PO Box 850 MC: HS86 600 Centerview
Drive, Suite 5400
 Hershey, PA 17033

Page 23: The following information has been added to the second paragraph of Section 8.33 for clarification:

The tests will be scored centrally at Penn State by Elana Farace, Ph.D. to reduce inter-rater subjectivity in scoring. **After scoring the booklets, Dr. Farace's office will forward all of the booklets to the following address: NCCTG Operations Office, RO_FF_03_24-CC/NW Clinic, 200 First Street SW, Rochester, MN 55905**

Section 16.0

Page 32: The following changes have been made to Section 16.23 in response to NCI reviewer comments:

Three formal interim analyses will be performed at the time at which 25%, 50%, and 75% of the projected total number of events have occurred using a **two-sided** O'Brien-Fleming type stopping boundary (O'Brien, 1979), ~~truncated at 3.5~~. This will allow for early reporting of results if SRS is found to be inferior to SRS + WBRT **as well as if SRS is found superior to SRS + WBRT**. The interim analyses cutoff values (**z-scale**), boundary probabilities and cumulative Type I error for the log-rank statistics at the four analyses times (three interim and final) are in the table below.

Time (proportion of expected events)	stopping boundary ies	nominal boundary probability ies	cumulative type I/II error
0.25	-3.50 3.75/-1.56	0.000231/ 0.94	0.0002309/ 0.0010
0.50	- 2.54/ 0.11	0.0055/ 0.46	0.0056/ 0.020
0.75	2.02/ 1.02	0.022/ 0.15	0.024/ 0.057
1.00	- 1.72/ 1.72	0.043/ 0.43	0.050/ 0.10

The following changes have been made to the first paragraph of Section 16.3 to in response to NCI reviewer comments:

Secondary endpoints to be examined include time to CNS failure and various QOL and related endpoints described in this protocol. If ~~equivalence between the interventions~~ **non-inferiority of SRS compared to SRS + WBRT** with respect to survival is established, then treatment preference may be determined by these other factors.

Page 34: The following changes have been made to Section 16.5 to clarify the statistical analysis of the Neurocognitive status:

~~The scores and change in scores from the neurocognitive status assessments will be compared between the arms.~~

~~Post Treatment Adverse Events~~

~~Physician-assessed ratings of neurological signs and symptoms and treatment adverse events will be tabulated, descriptively, by treatment arm.~~

The scores and change in scores from the neurocognitive status assessments will be compared between the arms, similar to the analyses described above. Specifically, exploratory Generalized Estimating Equations (GEE) analysis [Horton 1999] will be used to investigate the effect of treatment over time, incorporating baseline and follow-up visits to 12 months, as well as the correlations within a patient's data over time.

Once 60 evaluable patients have been accrued in each arm (total of 120 patients) and have completed the baseline and follow-up visits to 12 months, we will perform an interim analysis on the neurocognitive status. The intent is to determine whether one treatment has a clinically significant adverse effect on neurocognitive status. If the results indicate that one arm has clinically, significantly worse neurocognitive status, the study team in consultation with the DSMB will determine appropriate actions. The study team will request of the DSMB that the results of this interim analysis be released.

Section 18.0 Records and Data Collection Procedures

Page 36: The following changes were made for CTSU's transition from forms tracking to basic service:

18.1 Submission Timetable

Note: NCCTG members will enter data into the NCCTG RDE system. Sites participating through the CTSU will **submit the following** ~~assess completed case report forms to CTSU Data Operations for tracking unless otherwise specified in the CTSU~~ logistics (Appendix II).

Page 37: Footnote 1 parts d, e & f have been revised as follows for clarification:

- d. Dosimetry calculations (**Arm B only**), monitor unit calculations (**Arm B only**), DVHs (**as applicable**), and isodose curves.
- e. Copies of representative simulation films of all treated fields (**Arm B only**).
- f. Copies of representative port films of all treated fields (**Arm B only**).

Page 37: Footnote 9 has been revised as follows:
NCCTG and CTSU Sites: ~~sSubmit the following~~ to NCCTG Operations Office, **Neuro Quality Control Specialist, RO_FF_03_24-CC/NW Clinic, 200 First Street SW, Rochester, MN 55905.** ~~See Section 8.1. CTSU sites submit Quality of Life FACT-BR hard copy booklets to CTSU Data Operations Center as outlined in the CTSU logistics (Appendix II).~~

Appendix I **Consent Form**

Page 6: As requested by NCI the following has been added to the list of organizations that may look at and/or copy research records:

- **Food and Drug Administration (FDA)**

As requested by NCI the following changes have been made under the heading “What are my rights....”

1st sentence of 1st paragraph:

Taking part in this study is your choice **and does not take away any of your rights.**

3rd paragraph:

In the case of injury, **you will need to report them to your study doctor and you will be treated as needed.** ~~resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.~~

Page 7: As requested by NCI the following change has been made to the first paragraph, under the heading “Whom do I call if I have questions....”

You can talk to your study doctor about any **study-related injury,** questions or concerns you have about this study.

Appendix II

Pages 1-7: Appendix II has been replaced in its entirety as requested by CTSU.

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