Supplement to:

15-11397 - Cognitive Decline with Whole Brain Radiotherapy after Radiosurgery for Metastases

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
   Notes: The original N0574 protocol is shown first, then all of the subsequent addendum and update summaries are shown, and then the final protocol is shown.

2. Original statistical analysis plan, final statistical analysis plan, summary of changes
   Note: All statistical analysis plans are specified in section 16 of the protocol.
North Central Cancer Treatment Group

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

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<table>
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NCI Version Date: June 14, 2006
## North Central Cancer Treatment Group (NCCTG)

### ADDRESS AND CONTACT INFORMATION

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| Patient eligibility, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion | Butch Kvittem  
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# CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

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<td>The CTSU Public Web site is located at: <a href="http://www.ctsu.org">www.ctsu.org</a> The CTSU Registered Member Web site is located at <a href="http://members.ctsu.org">http://members.ctsu.org</a> CTSU logistical information is found in Appendix II.</td>
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<tr>
<td>To submit site registration documents</td>
<td>CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone: 1-888-823-5923 Fax – 215-569-0206</td>
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</table>
| Patient Pre-Registration and Randomization *(for non-NCCTG only)* | CTSU Data Operations Center Voice Mail – 1-888-462-3009 Fax – 1-888-691-8039 [For randomization’s that must be completed within approximately one hour or other extenuating circumstances, call 301-704-2376. Please use the 1-888-462-3009 number for ALL other CTSU patient enrollments.]
| To Mail Forms or Data | Westat CTSU Data Operations Center 1441 W. Montgomery Avenue Rockville, MD 20850-2062 |
| Patient Eligibility or Treatment Related Questions | Contact the NCCTG Quality Control Specialist (listed under NCCTG Contacts below). The option remains to contact the CTSU Help Desk for assistance in obtaining a response from the Group. |
| All Other Questions | CTSU General Information Line – [1-888-823-5923](tel:+18888235923) or [ctsucontact@westat.com](mailto:ctsucontact@westat.com). All calls and correspondence will be triaged to the appropriate CTSU representative. |

CTSU logistics are located in Appendix II of the protocol.
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Pre-registration

Randomization

Arm A
Radiosurgery (SRS)

Arm B
Radiosurgery (SRS) + Whole Brain Radiation (WBRT)

Observation

Withdrawal or Refusal

Death

Event Monitoring
1.0 Background

1.1 Extra-cerebral metastases are the most common malignancy affecting the brain. There are an estimated 100,000 to 170,000 new patients with brain metastases in the United States each year [Johnson 1996]. As systemic therapy for malignancy improves, brain metastases will become an increasingly frequent management problem due to the impaired ability of chemotherapy to pass the blood-brain barrier. Survival for untreated patients with brain metastases is generally less than seven weeks. Standard palliative treatment, including glucocorticoids and whole brain radiation therapy (WBRT), extends median survival to three to six months by preventing or delaying neurologic progression [Posner 1992]. Radiation Therapy Oncology Group (RTOG) trials conducted during the 1970's demonstrated no difference in survival, or time to neurologic progression, among a wide range of WBRT regimens: 20 Gray (Gy) in 5 fractions, 30 Gy in 10 fractions, 30 Gy in 15 fractions, 40 Gy in 15 fractions, or 40 Gy in 20 fractions [Borgelt 1980]. About 40% of the patients in each treatment arm suffered neurologic progression. A follow-up RTOG trial found that favorable patients with controlled primary tumors fared no better with an escalated WBRT dose (50 Gy in 20 fractions) versus a dose of 30 Gy in 10 fractions. On that basis, 30 Gy in 10 fractions became the de facto regimen in the United States. Patients who received WBRT usually experienced mild acute toxicity, such as alopecia, skin reaction, and headache. More importantly, in long-term survivors, there are neurocognitive sequelae that may take months to years to manifest. A long-term study from the Memorial Sloan Kettering Cancer Center found a 11% risk of dementia in patients at one year following treatment with 3.0 Gy fraction sizes or greater [DeAngelis 1989]. Therefore, many institutions have adopted the 2.5 Gy fraction size as the standard protocol for patients with a good prognosis.

1.2 Resection of Brain Metastases Followed by Whole Brain Radiation Therapy

Although most patients with brain metastases succumb to systemic cancer progression, there is a select subgroup of patients with good performance status and limited systemic disease who are likely to die of neurological progression if treated by WBRT alone. Aggressive surgical resection provides better local control of brain metastases in these patients and can markedly prolong survival. Patchell et al. demonstrated, in a randomized trial of patients with a single brain metastasis, that surgery and WBRT resulted in survival of 40 weeks versus 15 weeks with WBRT alone [Patchell 1990]. Vecht et al. reported similar results [Vecht 1993]. The necessity of administering WBRT following surgical resection of metastases is controversial. After complete surgical resection of a single metastasis (confirmed by post-operative magnetic resonance imaging (MRI)), Patchell et al. demonstrated in a second prospective randomized trial that the addition of WBRT markedly decreased the incidence of local recurrence (46% versus 10%), distant brain recurrence (37% versus 14%), and death from a neurologic cause (44% versus 14%) [Patchell 1998]. There was no effect on overall survival or duration of functional independence, presumably due to successful salvage measures in the surgery alone group (delayed WBRT), or detrimental neurocognitive effects from WBRT. Surgery cannot be offered to all patients because many are poor medical candidates or have lesions in locations not amenable to resection. In addition, patients with multiple lesions have rarely been offered surgery because the morbidity was felt to be excessive [Kondziolka 1999].
1.3 Radiosurgery With or Without Whole Brain Radiation Therapy

Stereotactic radiosurgery (SRS) is less invasive than conventional surgery and has become an increasingly accepted method of treating brain metastases due to the high rate of local control. SRS delivers high-dose radiation in a single session, to a stereotactically defined target volume, and minimizes the dose to surrounding normal tissue. Brain metastases are ideal targets for SRS because most lesions are small, pseudo-spherical and well demarcated from the surrounding brain tissue. Rates of local control in large series have averaged 80% to 90% [Flickinger 1994]. Although there are no randomized trials directly comparing SRS to surgery, the preponderance of retrospective data supports the equivalence of the modalities for small, single lesions. For instance, a retrospective, matched comparison analysis of 108 patients concluded that survival for patients with a single metastasis was similar whether they received SRS alone or surgery and WBRT [Muacevic 1999].

A subgroup of patients who have multiple metastases may benefit from the addition of SRS to WBRT. A randomized trial from the University of Pittsburgh, of patients with two to four metastases, found a non-significant survival advantage for patients who received SRS + WBRT (11 months) versus for patients who received WBRT alone (7.5 months). Local control at one year was 100% for patients who received SRS + WBRT versus 8% for those who received WBRT alone [Kondziolka 1999]. The results of the RTOG 9508 trial have been presented in abstract form. In the study, patients with one to three brain metastases were randomized to WBRT + SRS boost or to WBRT alone. A statistically significant survival advantage was demonstrated for the patients in the WBRT + SRS arm that had a solitary brain metastasis, RPA class I, age <50 years, or non-small cell lung cancer or any squamous cell cancer [Sperduto 2002]. At one year, local control was significantly better for the WBRT + SRS boost arm.

As with excisional surgery, SRS is a focused treatment that would not be expected to address the risk of distant brain progression. Based on Patchell's randomized data, WBRT would be expected to decrease the risk of distant brain progression [Patchell 1990]. Nevertheless, the role of WBRT + SRS remains undefined. Retrospective data from the University of California at San Francisco and the Memorial Sloan Kettering Cancer Center have demonstrated that freedom from progression of brain metastases was significantly worse for patients who received SRS alone versus those who received SRS + WBRT, (28% vs. 69% at 1 year). However, overall survival was similar due to successful salvage measures [Sneed 1999]. Similar data have been reported from the University of Pittsburgh [Flickinger 1994] and from the Karolinska Institute in Stockholm [Kihlstrom 1991]. These studies are subject to retrospective biases, such as differences in selection criteria for WBRT and type of salvage treatment given. At the current time, it is unclear whether the addition of conventional WBRT results in either survival advantage or decreased risk of neurological death. Even if there is no survival advantage, quality of life may be improved and treatment may be cost effective, due to avoiding the psychological distress of brain recurrence and the future need for subsequent salvage therapy. On the other hand, the potential side effects of WBRT, including fatigue, alopecia, cognitive decline, and diminished hearing, may result in a decreased quality of life for the patient.
1.4 Quality of Life

Given the poor survival prognosis of patients in this study, quality of life (QOL) will be an important secondary endpoint. The primary QOL objective is to ascertain whether patients in Arm 1 (SRS) have better QOL than patients in Arm 2 (SRS + WBRT). Kondziolka reported no neurologic or systemic morbidity for patients who had two to four brain metastases treated with SRS. Similar patients treated with WBRT developed mild scalp erythema and hair loss [Kondziolka 1999]. If the addition of WBRT does not give significant survival gain, yet additional side effects, SRS alone might be preferred. Hence, one-sided null hypotheses for improvement on Arm 1 (SRS) will be used.

The focus of the QOL and neurocognitive assessments will be at three months post-treatment. The three month time point is proposed as being late enough to capture major treatment effects, but early enough to avoid a substantial difference between-arm morbidity and mortality. Patient self-reported QOL, using the FACT-BR questionnaire [Weitzner 1995], objective assessments of changes in cognitive signs and symptoms (e.g., speech impairment), and physician-assessed toxicities (e.g., nausea) will be collected.

The FACT-BR is a validated QOL instrument, comprising a general component (FACT-G, with five subscales (number of questions in parentheses): physical (8), social (8), emotional (3), functional (6), and relationship with doctor (3) [Cella 1993], and a disease-specific subscale (BR) of 20 questions [Weitzner 1995]. In the Weitzner study, only 14% of the patients (17/118) were unable to complete the questionnaire themselves, but the remainder completed multiple forms over time [Weitzner 1995]. Meyers reported a similar finding: 12/80 patients (15%) were unable to complete a baseline form [Meyers 2000]. What, if any, help that is necessary for patients to complete testing for this study will be included in the analyses.

The results will be combined with survival data in a ‘quality-adjusted survival analysis’ (QAS) [Murray 1995].

1.5 Functional Independence

The assessment of ‘function’ typically refers to the assessment of disability, as measured by the ability of the patient to perform activities of daily living (ADLs). Given the changes in ADLs that occur in patients with malignant brain tumors (e.g., the inability to work and care for themselves), functional independence will be an important measure of outcome. Functional independence has previously been equated with QOL [Patchell 1990], but recent studies suggest it is distinct from both QOL and cognitive function [Meyers 1995, 1997].
The Barthel ADL Index is a well-validated, reliable tool measuring patient ability to perform ADLs and is easily administered by a nurse or physician [Wade 1992, Meyers 2000]. No special training is necessary to complete the test and its utility is recognized in the medical outcomes literature [Sabers 1999]. The Barthel ADL Index has been shown to be sensitive to change and reflective of the degree of functional impairment in a study of patients with high-grade glioma, where it correlated with the Karnofsky Performance Status (KPS), $r = 0.872$. It also was reliable when administered verbally, as in cases when patients were unable to complete it in writing [Brazil 1997].

A Barthel score of 20 implies complete independence. Any lower score suggests that the patient requires some supervision. The bowel, bladder, toileting, feeding, dressing, and stairs categories are scored 0-2; grooming and bathing 0-1; transfer and mobility 0-3. Decreases of greater than or equal to 4 points are considered meaningful [Wade 1992].

We propose to include the Eastern Cooperative Oncology Group (ECOG) 0-4 performance status scale in this study as a secondary measure of ADL that will allow for comparison to other cancer trials. The ECOG rating is a numeric representation of an individual’s ability to perform normal activity, to do active work, and of their need for assistance.

1.6 Neurocognitive Status

Neurocognitive evaluation of patients with malignant brain tumors has established that they can experience measurable cognitive deficits [Anderson 1990, Milner 1963]. A wide range of mechanisms resulting in cognitive dysfunction have been identified, including destruction of brain tissue, displacement of surrounding brain structure, increasing intracranial pressure, seizures, edema of adjacent brain tissue, and alterations of endocrine pattern and/or brain biochemistry. Specific cognitive effects may occur due to anatomic location, tumor size, growth rate, and developmental age at the time of onset. Virtually all types and patterns of neurocognitive dysfunction have been demonstrated secondary to brain tumors, including deficits in attention, concentration, memory, pure language or visuospatial abilities, logical reasoning, motor or sensory impulse, coordination, balance or gait disturbance, and emotional/behavioral disorders such as depression, abulia, agitation, hallucinations, delusions, and paranoia [Lezak 1995].

More recently, neuropsychological studies have examined the following effects: specific tumor histology [Kramer 1997], patient response to treatment relative to the operative approach to the tumor [Hutter 1997, Villiani 1997], cranial radiation therapy [Armstrong 1995, Armstrong 2000, Crossen 1994], and chemotherapy [McAllister 2000] on patient outcome. Some studies have examined the success of medical treatment (methylphenidate) for cognitive and mood dysfunction of patients with brain tumors [Meyers 1998] and cognitive function in long-term survivors [Archibald 1994; Giovagnoli & Boiardi 1994]. These studies have demonstrated that as the evaluation, treatment, and survival of patients with malignant brain tumors becomes increasingly more sophisticated and successful, neurocognitive status is helpful in documenting patient outcome and QOL.
The neurocognitive tests to be used in this study were chosen on the basis of accepted standardization and psychometric principles, published normative data relative to routine demographics, relevance to general neurocognitive status, and brevity of the overall battery. The tasks selected have either low associated practice effect or include multiple equivalent formats (e.g., memory test, fluency test). Lezak reports that patients with brain tumors can tolerate this degree of cognitive testing without difficulty [Lezak 1995].

1.7 Summary

This study is designed to test the hypothesis that in patients with one to three brain metastases, WBRT adds no additional benefit to SRS. Patient entry will be stratified in order to achieve well-balanced groups with regard to the extent of systemic disease. As SRS will presumably control the detected metastatic lesions, the WBRT dose needs to be sufficient only to control metastatic aggregates below the detection threshold of contrasted MRI brain scans. A WBRT dose of 24 Gy in 8 fractions was studied in France, in a randomized prophylactic cranial irradiation (PCI) trial for patients with small cell lung cancer, and in a recent German randomized PCI trial that used 25 Gy in 10 fractions for patients with non-small cell lung cancer [Stuschke 1999]. In both of these studies, the PCI dose controlled sub-clinical brain metastases. Arm 2 will therefore test a WBRT dose of 30 Gy in 12 fractions. Salvage treatment guidelines will be defined in order to assure uniformity of treatment between Arm 1 and Arm 2. If patients in Arm 1 suffer a limited local recurrence or a distant brain recurrence, they will be directed to undergo repeat SRS without WBRT. Common Toxicity Criteria (CTC) scoring, QOL questionnaires, functional independence measurements, neurocognitive testing, and post-treatment adverse events will be obtained at serial follow-up visits in order to ascertain any differences in long-term outcome.

2.0 Goals

2.1 Primary Objective

2.11 To ascertain in patients with one to three brain metastases whether there is equal (or better) overall survival in patients who receive SRS alone (Arm A) compared to patients who receive SRS combined with WBRT (Arm B).

2.2 Secondary Objectives

2.21 To ascertain in patients with one to three brain metastases whether there is equal (or greater) time to central nervous system (CNS) failure (brain) in patients who receive SRS alone (Arm A) compared to patients who receive SRS combined with WBRT (Arm B).

2.22 To ascertain in patients with one to three brain metastases whether there is improved QOL in patients who receive SRS alone (Arm A) compared to patients who receive SRS combined with WBRT (Arm B).
2.23 To ascertain in patients with one to three brain metastases whether there is longer duration of functional independence in patients who receive SRS alone (Arm A) compared to patients who receive SRS combined with WBRT (Arm B).

2.24 To ascertain in patients with one to three brain metastases whether there is better long-term neurocognitive status in patients who receive SRS alone (Arm A) compared to patients who receive SRS combined with WBRT (Arm B).

2.25 To tabulate and descriptively compare the post-treatment adverse events associated with the interventions.

3.0 Patient Eligibility

3.1 Pre-Registration (Step 1)

3.11 Required Characteristics

3.111 One to three presumed brain metastases from a histologically confirmed extracerebral tumor site (e.g. lung, breast, prostate, etc.). The histologic confirmation may have been from the primary tumor site, from another metastatic site (e.g. an osseous metastasis, adrenal metastasis, etc.), or from the metastatic brain lesion(s).

**NOTE:** Each lesion must measure <3.0 cm in maximal extent on the contrasted pretreatment MRI brain scan obtained ≤21 days prior to randomization (see Magnetic Resonance Imaging (MRI) Guidelines section 11.2).

3.112 All standard tumor-staging procedures necessary to define baseline extracranial disease status completed ≤42 days prior to pre-registration.

3.113 Ability to be treated with either a gamma knife or a linear accelerator-based radiosurgery system. Note: A treating center must have completed stereotactic radiosurgery credentialing (see section 6.1).

3.114 ≥18 years of age.

3.115 Ability to complete questionnaire(s) by themselves or with assistance.

3.116 ECOG performance status 0, 1, or 2. For reference see https://ncctg.mayo.edu/ncctg/formsNonProtocolSpecificForms/

3.117 Grooved peg board available for Neurocognitive Testing (See Section 6.29 for further details). Note: The examiner must have credentialing confirming completion of the neurocognitive testing training (see section 6.1)
3.12 Pre-Registration Contraindications

3.121 Any of the following:
   • Pregnant women
   • Men or women of childbearing potential who are unwilling to employ adequate contraception

3.122 Pacemaker or other MRI non-compatible metal in the body.

3.123 Known allergy to gadolinium.

3.124 Prior resection of cerebral metastasis.

3.125 A lesion that is located ≤5 mm of the optic chiasm or within the brainstem.

3.126 Prior chemotherapy ≤7 days prior to pre-registration.

3.127 Prior cranial radiation therapy.

3.128 Primary germ cell tumor, small cell carcinoma, or lymphoma.

3.129a Leptomeningeal metastasis.

3.129b Clinical or radiographical evidence of systemic progression (other than the study lesion(s), i.e. other than the brain metastases) within one month prior to randomization.

3.13 Randomization Required Characteristics (Step 2)

3.131 Planning MRI confirmed one to three lesions. Each lesion must measure < 3.0 cm in maximal extent on the contrasted planning MRI brain scan.

3.132 Negative urine or serum pregnancy test done ≤7 days prior to randomization, for women of child bearing potential only.
## 4.0 Test Schedule

Refer to Section 18.0 for a list of forms to electronically enter (NCCTG sites) or submit at each visit (CTSU sites).

### PHYSICAL

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1. Patient, if female of childbearing potential, must have a negative urine or serum pregnancy test result ≤ 7 days prior to randomization.
2. Pre-registration contrasted MRI brain scans must be obtained ≤ 21 days prior to randomization.
3. Report ALL AEs that have occurred since the previous visit this includes late effects of radiation.
4. Randomization is ≤ 14 days after pre-registration (with planning MRI scan obtained the same day as randomization). For the vast majority of patients treatment will be delivered the same day as the planning scan and randomization. Follow-up will be based on the date the SRS treatment is completed.
5. Patients will continue to be followed per test schedule (even in the event of PROG) until withdrawal, refusal, death or 5 years from randomization.
6. After informed consent and prior to randomization.
7. All standard tumor-staging procedures necessary to define baseline extracranial disease status (as deemed appropriate by the investigator) completed ≤ 42 days prior to pre-registration.
5.0 **Stratification Factors (collected at randomization):**

5.1 Age (years): 18 to 59 vs. ≥60.

5.2 Extracranial disease controlled (months): ≤3 vs. >3.

5.3 Number of Brain Metastases: 1 vs. 2 vs. 3.

6.0 **Randomization Procedures (NCCTG members)**

**Note:** CTSU sites should refer to the CTSU appendix (Appendix II) for site registration instructions and patient pre-registration/randomization instructions.

6.1 Site registration and completion of the below Credentialing is required **Prior** to the Pre Registration/Randomization of patients:

- IRB approval(s) is required for each treating site. A signed Cancer Trials Support Unit (CTSU) IRB Certification Form is to be on file at the CTSU Regulatory Office (fax 215-569-0206). This form can be found at the following Web site: www.ctsu.org/rss2_page.asp. Guidelines can be found under Quick Fact Sheets.

- Radiological Physical Center (RPC) Questionnaire for Stereotactic Radiosurgery (SRS) with Gamma Knife or with Linear Accelerator or successful irradiation of the RPC SRS phantom.

The questionnaire or phantom information is available on the RPC web site, [http://rpc.mdanderson.org](http://rpc.mdanderson.org), under “Credentialing.” Complete this form and submit electronically on the RPC website.

RPC will notify the NCCTG Operations Office of your approved credentialing by emailing the following address: N0574credentialing@mayo.edu. The operations office will then forward this information to the CTSU Central Regulatory Office (CCRO) at ctsuregoffice@ecogchair.org. The CTSU CCRO will enter this information in the CTSU Regulatory Support System (RSS) so that the status of your site’s credentialing review will be reflected in the RSS Site Registration Status screen at [http://members.ctsu.org/rss/](http://members.ctsu.org/rss/).

- The Neurocognitive Testing Verification Form

Examiners must complete the Neurocognitive Testing training online, produced by Elana Farace, Ph.D. This training is found on the NCCTG website, at [https://ncctg.mayo.edu/ncctg/group/](https://ncctg.mayo.edu/ncctg/group/) under “Disciplines,” then under the “CRA page.” Once the video has been viewed, practice the testing with another colleague (NOT a patient) to ensure accurate results. Contact Dr. Farace with any questions. Once the practice testing is completed, fax the practice forms found in Appendix IX to Dr. Farace at (717) 531-0748. In addition, download the N0574 Neurocognitive Testing Verification Form and complete it as necessary. Keep a copy of this form at the site and fax a copy to Elana Farace, Ph.D. at (717) 531-0748.

Dr. Farace will notify the NCCTG Operations Office of your approved credentialing by emailing the following address: N0574credentialing@mayo.edu. The operations office will then forward this information to the CTSU Central Regulatory Office (CCRO) at ctsuregoffice@ecogchair.org. The CTSU CCRO will enter this information in the CTSU Regulatory Support System (RSS) so that the status of your site’s credentialing review will be reflected in the RSS Site Registration Status screen at [http://members.ctsu.org/rss/](http://members.ctsu.org/rss/).
6.2 Pre-registration (Step 1)

6.21 Prior to performing the planning MRI, call (507/284-4130) or fax (507/284-0885) a completed NCI Cooperative Group Pre-registration Eligibility Checklist to the NCCTG Randomization Center between 8 a.m. and 4:30 p.m. central time Monday through Friday. At the time of pre-registration the patient will receive an NCCTG patient identification number.

6.23 Prior to accepting the pre-registration, the Random Center personnel will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information (U.S.A. institutions only)

6.24 Pre-registration tests/procedures must be completed within the guidelines specified on the test schedule (see Section 4.0).

6.25 All required baseline symptoms (see Section 10.3) must be documented and graded.

6.26 A radiation oncologist has seen the patient and confirms the patient is a suitable candidate for this study.

6.27 Patient questionnaire booklet availability checked. Note: copies of the Appendices are not acceptable for this submission.

6.28 Site booklets ({1}QOL: FACT-BR Booklet, {2}Neurocognitive Patient Completed Booklet and {3}Neurocognitive Examiners Booklets) are available.

6.29 Grooved peg board available for Neurocognitive testing. (These peg boards can be purchased for approximately $105.00 at the following web address: http://www.ausmed.com/medecat/rs/ecatalog/details.asp?productid=10225A)

6.3 Randomization (Step 2)

6.31 After performing the planning MRI, call (507/284-4130) or fax (507/284-0885) a completed NCI Cooperative Group Randomization Eligibility Checklist to the NCCTG Randomization Center between 8 a.m. and 4:30 p.m. central time Monday through Friday.

6.32 Treatment on this protocol must commence at the accruing membership under the supervision of an NCCTG member physician.

6.33 Upon completion of the patient’s planning MRI, the treating location will randomize the patient to the study as instructed by the NCCTG Randomization Center.

6.34 Treatment cannot begin prior to randomization and must begin \( \leq 7 \) days after randomization.
6.35 After the patient has been randomized into the study, the values of the stratification factors (Section 5.0) will be recorded, and the patient will be randomly assigned to one of the following treatment groups:

- SRS
- SRS + WBRT

6.36 Tests/procedures must be completed prior to randomization within the guidelines specified on the test schedule (see Section 4.0 for further details).

7.0 Protocol Treatment

7.1 Treatment considerations

7.11 Prior to Treatment: After informed consent is obtained from the patient and prior to randomization, baseline QOL, functional independence, and neurocognitive tests must be completed. Patients must undergo radiosurgery treatment \(\leq 7\) days after randomization.

The radiosurgery can be delivered at a different site than the site pre-registering the patient as long as treatment guidelines are followed and the site delivering the SRS has been credentialed for SRS by the Radiological Physics Center (RPC).

7.12 The SRS dose has been selected in order to provide a high rate of local control with minimum risk of radionecrosis. Due to the additive biological effect of WBRT to the target lesion and surrounding normal tissue, the SRS dose has been decreased slightly when WBRT is given. The SRS dose is decreased modestly for larger lesions in order to account for the volume effect on complication rates.

7.2 Radiosurgery (SRS) Guidelines

If all lesions cannot be treated on the same day, all lesions MUST be treated \(\leq 7\) days of treatment of the first lesion. The radiosurgery can be delivered at a different site than the site pre-registering the patient (see section 7.11).

7.21 Medications

7.211 Patients may be given an intravenous bolus dose of 8 to 16 mg of dexamethasone or 40 to 80 mg of SoluMedrol at the time of SRS, at the discretion of the treating physician.

7.22 Equipment

7.221 Modality: Gamma knife or X-rays with nominal energy of 4 megavoltage (MV) or greater for accelerator-based treatments, including mini-multi-leaf technology.

7.222 Calibration: The calibration of linear accelerators used in this study shall be verified by the Radiological Physics Center (RPC).
7.23 Target Volume Definitions

7.231 The volumes shall be defined by a planning MRI brain scan, with the patient in the treatment position. ICRU-50 nomenclature target volumes are defined as follows:

7.232 Gross Tumor Volume (GTV): This is defined as the contrast enhanced tumor seen on planning MRI. The maximal cross-sectional diameter must be < 3.0 cm.

7.233 Clinical Target Volume (CTV): This is defined as the GTV for this study.

7.24 Target Dose:

7.241 Prescription Specification: The dose should be prescribed to the highest isodose line encompassing the CTV, which can range from 50% to 80% of the maximum dose.

7.242 Dose Definition: Dose is specified in Gray (Gy) to muscle.

7.243 Prescription Dose: The total prescribed dose is determined by treatment arm and tumor size.

<table>
<thead>
<tr>
<th>Arm A (SRS only):</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRS:</td>
</tr>
<tr>
<td>Lesions &lt; 2.0 cm receive 24 Gy</td>
</tr>
<tr>
<td>Lesions 2 – 2.9 cm receive 20 Gy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm B (SRS and WBRT):</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRS:</td>
</tr>
<tr>
<td>Lesions &lt; 2.0 cm receive 22 Gy</td>
</tr>
<tr>
<td>Lesions 2 – 2.9 cm receive 18 Gy</td>
</tr>
<tr>
<td>WBRT:</td>
</tr>
<tr>
<td>Refer to prescribed dose and fractionation in Whole Brain Radiation Therapy (WBRT) Guidelines section.</td>
</tr>
</tbody>
</table>

7.244 Dose Uniformity: It is acknowledged that isodose coverage varies with the equipment used. Efforts should be made to cover the GTV with as uniform a dose as possible.

7.245 Dose Conformity: The ratio of the prescription isodose volume to the target volume (GTV) should be between 1.0 and 2.0. It is understood that this ratio may be difficult to achieve with some very small lesions. For lesions less than 5 mm in size, a ratio up to 3.0 is acceptable.
7.25 Treatment Technique

7.251 An immobilization/patient localization system is mandatory for this study. Multiple isocenter techniques are permitted.

7.26 Normal Tissue/Critical Structures

7.261 The treatment parameters should be modified to optimize the fit of the prescription volume to the target volume while minimizing dose to critical structures. The dose to the optic chiasm should be less than 8 Gy.

7.27 Dose Calculation and Reporting

7.271 Treatment Time: The monitor units or time required to deliver the prescribed dose shall be calculated and submitted.

7.272 Dose Uniformity: The maximum and minimum doses in the CTV shall be calculated and reported. These may be extracted from isodose distributions, calculated separately or derived from Dose Volume Histograms (DVHs).

7.273 Conformity Index: The PITV, defined as the ratio of the prescription isodose volume to the target volume, shall be calculated and reported. If the prescription isodose volume is calculated from a DVH, that DVH shall be submitted (see QA Documentation).

7.274 Prescription Isodose Line: The total dose delivered to the prescription isodose line shall be calculated and reported.

7.275 Normal Tissue and Critical Organ Dose Points: Documentation of the highest point dose to the optic chiasm or a DVH of the optic chiasm shall be submitted (see QA Documentation).

7.276 Isodose Distribution: A hard copy of the isodose distribution for each target must be submitted. Isodose distributions should be displayed on three orthogonal planes or, if not possible, on multiple transverse slices through each target.

7.3 Whole Brain Radiation Therapy (WBRT) Guidelines: For ARM B Only

Note: For patients randomized to Arm B: SRS and WBRT, the initiation of WBRT is ≤14 days following SRS.

7.31 Equipment

7.311 Modality: X-ray beams with a nominal energy between 4 and 6 MV.

7.312 Calibration: The calibration of therapy machines to deliver WBRT used in this study shall be verified by the RPC.
7.32 Target Volume

7.321 The target volume consists of the entire brain and meninges, including the frontal lobe as well as the posterior halves of the globes of the eyes, with the optic disk and nerve, superior to the vertex, and posterior to the occiput. The caudal border shall be below the skull base at the top of the C2 vertebral level.

7.322 Localization: The planning target volume shall be defined by means of a simulator.

7.33 Target Dose

7.331 Prescription Point: The prescription point in the cranial volume is at or near the center. For multi-convergent beams, the prescription point is usually at the intersection of the beam axes. NOTE: Regardless of the location of the central axis, the dose should be prescribed at the center on the cranial volume (midway between the maximum separation).

7.332 Dose Definition: The absorbed dose is specified below in Gy to muscle.

7.333 Tissue heterogeneity: No corrections for bone attenuation shall be made.

7.334 Prescribed dose and fractionation: The total dose to the prescription point is 30 Gy. This dose is delivered in 12 fractions of 2.5 Gy. All radiation fields shall be treated once each day. The treatment shall be given 5 days a week.

7.335 Dose Uniformity: The dose variations in the target volume shall be within +7% (-5% of the prescription-point dose).

7.336 Treatment Interruptions: No corrections shall be made for treatment interruptions less than seven days. For interruptions greater than seven days, please contact Dr. Paul Brown (See title page).

7.34 Treatment Technique

7.341 Patient Position: It is recommended that the patient be treated supine.

7.342 Beam Configuration: The cranial volume is treated with two lateral, equally weighted photon beams. The fields shall extend at least 1 cm beyond the periphery of the scalp. “Compensating beams” that block hot spots (these hot spots are typically present along the midline due to less tissue present in these regions compared to mid-brain) are allowed to achieve better dose homogeneity.

7.343 Field Shaping shall be done with blocks that are at least 5 half-value layers (HVL) thick. Multi-leaf collimation is allowed.

Note: Chemotherapy is not allowed during the SRS and WBRT.
8.0 Neurocognitive/Quality of Life Assessment and Treatment / Follow up Decision

8.1 Quality of Life Booklet – FACT-BR

Please note it is necessary that sites have booklets on hand prior to putting any patients on study. Sites cannot use Appendix IV in place of the QOL Booklet. See Appendix VII to order booklets.

Prior to randomization (baseline) and at the beginning of each scheduled study visit the patient is to complete the Quality of Life (QOL) Booklet. The patient’s self-reported QOL booklet may take 10 to 15 minutes to complete. Since the patient may experience cognitive deterioration during treatment, a ‘significant other’ (e.g., a spouse) may help the patient complete the questionnaire, if necessary. The responder, identified in consultation with the patient and his/her physician, will be recorded on the forms. As further measures of possible cognitive decline during treatment, physician-assessed ratings will be made of neurological signs and symptoms and treatment adverse events (See Appendix III).

Mail completed booklet to (and keeping a copy at the treating institution):

NCCTG Neuro Quality Control Specialist
Cancer Center Statistics
NW Clinic
200 First Street SW
Rochester, MN  55905

8.2 Functional Independence

Prior to intervention and at the beginning of each scheduled study visit, the study doctor or his/her authorized designee will rate the patient’s functional independence on the Barthel ADL Index ordinal scale. The administration of the Barthel ADL Index will take approximately five minutes.

Mail completed form to (and keeping a copy at the treating institution):

NCCTG Neuro Quality Control Specialist
Cancer Center Statistics
NW Clinic
200 First Street SW
Rochester, MN  55905
8.3 Neurocognitive Status

8.31 Tests and Battery Format

The tests and battery format that will be done includes the following and will take approximately 20 to 30 minutes to complete:

- **Memory** (4.5 minutes): Hopkins Verbal Learning Test (HVLT) [Brandt 1991].
- **Fine Motor Control** (5 minutes): Grooved Pegboard Test [Matthews 1964].
- **Fluency** (3.5 minutes): Controlled Oral Word Association Test from the Multilingual Aphasia Examination (COWAT) [Benton 1978].
- **General Mental Ability** (5 minutes): Trail Making Test A and B [Reitan 1958].
- **Delayed Memory** (1.5 minutes): Recall and Recognition of Word List encoded from the HVLT [Brandt 1991].

**NOTE**: The HVLT consists of six forms. Only one HVLT form is to be used at each visit. Although selection of the form is at the discretion of the investigator, it is recommended for convenience and consistency Form 1 is used at baseline, Form 2 at second assessment (i.e. 6 weeks), Form 3 at third assessment (i.e. 3 months), et. Most importantly, the patient should get all 6 forms once before getting a form for the second time (i.e. repeating the cycle). The clinical site should obtain all necessary booklets before pre-registering patients.

In addition if the examiner has questions or is unsure about a patient's ability to complete the forms (Neurocognitive or the FACT-Br) then they should contact Dr. Farace as adjustments may be made depending on the patient's situation.

8.32 Mail completed Neurocognitive Examiners Booklet and Neurocognitive Patient Completed Booklet (and keeping a copy at the treating institution) to:
Elana Farace
Director of Clinical Research
Department of Neurosurgery
Penn State Milton S. Hershey Medical Center
500 University Drive, PO Box 850 MC: HS86
Hershey, PA 17033

8.33 Fax the Neurocognitive Evaluations Submission Form to Elana Farace at (717)531-0748.

The tests will be scored centrally at Penn State by Elana Farace, Ph.D. to reduce inter-rater subjectivity in scoring.
9.0 Ancillary Treatment

9.1 Concomitant Medications

Patients may be currently receiving hormonal agents, steroids, and/or anticonvulsants.

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 for adverse event monitoring and reporting. The CTCAE v3.0 can be accessed from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE v3.0.

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE. Next, determine whether the event is expected or unexpected (see Section 10.12) and if the adverse event is related to the medical treatment or procedure (see Section 10.13). With this information, determine whether an adverse event should be reported as an expedited report (see Section 10.12). Important: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.3 and 18.0).

Expedited adverse event reporting requires submission of an Adverse Event Expedited Reporting System (AdEERS) report(s). Other expedited reporting requirements and systems may also apply. Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.2 and 10.3. All expedited AE reports must also be sent to the local Institutional Review Board (IRB) according to local IRB’s policies and procedures.

10.12 Expected vs. Unexpected

- The determination of whether an AE is expected is based on information/data in available sources, including the protocol (including the model consent form).
- Unexpected AEs are those not listed in the available sources, including the protocol (including the model consent form).

10.13 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event is clearly related to the agent(s).
Probable - The adverse event is likely related to the agent(s).
Possible - The adverse event may be related to the agent(s).
Unlikely - The adverse event is doubtfully related to the agent(s).
Unrelated - The adverse event is clearly NOT related to the agent(s).
10.2 Expedited Adverse Event Reporting Requirements

10.21 Standard Expedited Reporting for Commercial Agents

<table>
<thead>
<tr>
<th>Grade 4 or 5 Unexpected with Attribution of Possible, Probable, or Definite</th>
<th>Increased Incidence of an Expected AE¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submit a full expedited commercial report via AdEERS within 7 working days²</td>
<td>X</td>
</tr>
</tbody>
</table>

1. Any increased incidence of a known AE (as reported in the package insert or the literature), including adverse events resulting from a drug overdose.
2. In the rare event when Internet connectivity is disrupted, a report may be prepared using the Adverse Event Expedited Report – Single Agent or Multiple Agents paper template (accessible from the CTEP Home Page at [http://ctep.cancer.gov](http://ctep.cancer.gov)). Contact the NCCTG SAE Coordinator (as identified on the NCCTG Protocol Resources page) for back-up submission instructions.

10.22 Other Required Expedited Reporting

<table>
<thead>
<tr>
<th>EVENT TYPE</th>
<th>REPORTING PROCEDURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary AML/MDS</td>
<td>Reporting for this event required during and after completion of study treatment. Submit the NCI/CTEP Secondary AML/MDS Report form within 15 days via fax or mail to the NCCTG SAE Coordinator, NCCTG Operations Office, 200 First Street SW, Rochester, MN 55905, Fax (507)284-9628. The Operations Office will submit to NCI.</td>
</tr>
<tr>
<td>Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report</td>
<td><strong>NCCTG Institutions Only:</strong> Complete a Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form within 5 working days. If an AdEERS report has been submitted, this form does not need to be submitted. Fax or mail to the NCCTG SAE Coordinator, NCCTG Operations Office, 200 First Street SW, Rochester, MN 55905, Fax (507)284-9628.</td>
</tr>
</tbody>
</table>
10.3  Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per Common Terminology Criteria for Adverse Events (CTCAE) v3.0 grading unless otherwise stated:

<table>
<thead>
<tr>
<th>CTCAE Category</th>
<th>Adverse Events/Symptoms</th>
<th>Baseline</th>
<th>Each Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatology/Skin</td>
<td>Hair loss/Alopecia (scalp or body)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Rash: dermatitis associated with radiation - radiation</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Neurology</td>
<td>Cognitive disturbance</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Neuropathy – motor</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>CNS necrosis</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Ocular/Visual</td>
<td>Retinopathy</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Auditory/Ear</td>
<td>Hearing, patients without baseline audiogram and not enrolled in a monitoring program</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Otitis, external ear</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

1.  Hypersensitivity to the local anesthetic.

10.31  Submit to the NCCTG Research Base via the Nadir/AE Log the following AEs experienced by a patient and not specified in Section 10.3:

10.311  Grade 2 AEs deemed possibly, probably, or definitely related to the study treatment or procedure.

10.312  Grade 3 and 4 AEs regardless of attribution to the study treatment

10.313  Grade 5 AEs (Deaths)

10.3131  Any death within 30 days of the patient’s last study treatment or procedure.

10.3132  Any death more than 30 days from the patient’s last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.32  Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).
11.0 **Treatment Evaluation/Imaging Guidelines**

11.1 **Response criteria:**

The response score will be rated as one of the following (follow-up MRI brain scans will be compared to the planning MRI brain scan):

**Complete response**  Radiographic disappearance of brain metastasis (es)

**Partial response**  Greater than 50% reduction in the size of each lesion radiographically, using perpendicular diameters

**Stable disease**  0 to 50% reduction in the size of each lesion radiographically, using perpendicular diameters

**Disease progression**  increase of > 25% in the size of any lesion or a new, non-contiguous lesion (in the brain)

NOTE: Tumor progression of the treated SRS lesions will be evaluated independently of the development of new lesions. Radionecrosis will not be considered tumor progression.

11.2 **Magnetic Resonance Imaging (MRI) Guidelines**

The diagnostic MRI brain scan will fall into one of three categories: pre-registration, planning and follow-up. The planning MRI brain scan will be used to determine final eligibility and used for treatment planning of the SRS treatment. The pre-registration MRI brain scan will be used to determine preliminary patient eligibility. The pre-registration MRI brain scan is without parameters since it is performed prior to study entry.

The minimum parameters for the planning MRI brain scan and the follow-up MRI brain scans are:

- Sagittal T1 pre-contrast images
- Coronal and axial post-contrast images
- 5mm or less slice thickness
- Scanner should be at least a 1.5 Tesla magnet

NOTE: The same technique must be used for each of the diagnostic MRI brain scans at follow-up.

11.3 **Patients will be monitored for clinical evidence of progression of neurological symptoms and treatment failure.** Patients will be assessed with a physical and neurological examination and contrasted MRI brain scan at baseline (prior to randomization), at week 6, week 12, month 6, month 9, month 12, month 16, month 24, month 36, 48 and at month 60. Follow-up is required +/- 14 days for visits week 6 and 12, +/- 1 month for visits month 6, 9, 12 and 16, and +/- 4 month for visits month 24, 36, 48, and 60. At each scheduled study visit, a QOL (FACT-BR) questionnaire, functional independence (Barthel ADL Index and ECOG performance status), and neurocognitive status tests will be completed.
11.4 Patients will be monitored for local recurrence, distant brain recurrence and progression until death or 5 years from study entry. Patients also will be monitored, whenever possible, for additional primaries and regional recurrence, with histological confirmation.

11.5 Response Rate

The follow-up MRI brain scans will be compared to the planning MRI brain scan and will be used to score a response rate for each lesion and to detect distant brain recurrence. Every effort will be made to distinguish between disease progression and radionecrosis including, as indicated, MRI, SPECT (single photon emission computed tomography), PET (positron emission tomography), or surgical resection.

11.6 Time to CNS Failure

Time to CNS failure will be measured from the date the patient is randomized on this study to the date of diagnosis of disease progression.

11.7 Survival

Survival time will be measured from the date the patient is randomized on this study to death, due to any cause. Death will be scored either as due to neurological cause (any CNS event such as an intracranial mass, hemorrhage, or hydrocephalus) or non-neurological cause. A copy of the death certificate should be submitted. Autopsy reports should be obtained, whenever possible, and sent by fax NCCTG Operations Office at 507/266-7240.

11.9 Response Review

Radiologic Images: All radiologic images must be free of marks that might obscure the lesions or bias the evaluation of the reviewer(s). The following MRI brain scans are to be submitted ≤1 week of completion (Note: this applies to ALL NCCTG and CTSU sites):

- Pre-registration and planning
- Completion of therapy (six weeks after SRS)
- Best response (These images may be submitted once best response has been radiographically established.)
- Disease progression
- The MRI brain scans performed at Month 12 should be submitted, in the absence of any change post-completion of therapy. These studies will be reviewed by the NCCTG PIs for final classification of disease progression versus radionecrosis.
Submit all materials to (images on CDs are preferred to film but must be DICOM compatible):

NCCTG Neuro Quality Control Specialist
Cancer Center Statistics
NW Clinic
200 First Street SW
Rochester, MN  55905

In the absence of any change post-completion of therapy, the MRI brain scans performed at Month 12 should be submitted. These studies will be reviewed by the NCCTG PIs for final classification of disease progression versus radionecrosis.

Note: Reimbursement will not be given for any cost incurred for submitting these materials.

12.0 Descriptive Factors: None.

13.0 Treatment in the Event of Recurrent Cerebral Metastases

13.1 Directions for the treatment of recurrence are important in order to assure the comparability of patient outcomes between treatment arms. Clinical judgment in the management of palliative patients is paramount. At the discretion of the local investigator, the N0574 Study Chair should be contacted for guidance.

13.2 Retreatment guidelines

13.21 Patients who develop recurrence to the brain following study treatment should be retreated with SRS alone if one to three NEW lesions are present in the absence of rapidly progressive systemic disease (please note it is NOT recommended that a brain metastases previously treated with SRS be retreated with SRS). WBRT should be withheld unless more than three lesions recur in a rapid fashion or the patient refuses SRS.

13.22 For more than three metastases, WBRT alone should be given, reserving SRS for salvage. WBRT should be considered (especially in those patients not previously treated with WBRT) in patients with progressive metastases that have received SRS to these (specific) lesions.

13.221 The salvage WBRT dose guidelines are as follows:

Arm A: Initial WBRT of 30 Gy in 10 fractions.
If needed repeat WBRT of 25 Gy in 10 fractions.

Arm B: Repeat WBRT 25 Gy in 10 fractions.

13.23 An abbreviated course of treatment for the patient may be more appropriate, depending on systemic disease progression. Palliative surgery is recommended for patients with a symptomatic lesion not responsive to high-dose steroids when there is no evidence of rapidly progressive systemic disease. Chemotherapy is administered at the discretion of the treating physician.
13.24 All patients should be instructed to communicate with their study doctor (i.e. treating physician) prior to accepting any additional therapy.

13.3 Treatment / Follow up Decision

13.31 Patients who have progressed will continue with evaluation as outlined under observation in Section 4.0. However it is recommended to treat patients per Section 13.2.

13.32 If a patient does not complete treatment, they will go to observation.

13.33 Patients who refuse continued observation (i.e. withdraw from the study) will go to event-monitoring.

13.34 If a patient refuses a treatment assignment (and is classified as a cancel), it is necessary to provide follow-up information. The patient will go directly to the observation phase of the study. On-study material is to be submitted.

14.0 Translational/Pharmacologic Studies: None.

15.0 Nursing Guidelines

15.1 Stereotactic Radiosurgery

15.11 Nursing guidelines

15.111 Instruct patient regarding possible localized hair loss and redness and dryness of the scalp.

15.112 Corticosteroid use not required per protocol.

15.113 Report any neurologic changes to physician.

15.2 Whole brain radiation

15.21 Nursing guidelines

15.211 Advise patient of probable hair loss, redness and dryness of the scalp.

15.212 Instruct patient in corticosteroid use per MD order.

15.213 Observe for signs and symptoms of neurology changes. Report any changes to physician immediately.

15.214 Advise patient of probable taste changes. Suggest hard candy to minimize dry mouth and taste changes.

15.215 Observe patient for possible skin reaction to external ear, inner canal inflammation. Report changes to the physician.

15.216 Assess for increased fatigue; instruct patient in energy-saving life-style.
16.0 Statistical Considerations

16.1 Introduction

This protocol is meant to be a continuation of the ACOSOG trial Z0300, which was closed by ACOSOG leadership as a result of the ACOSOG leadership restructuring following their Type 2 review in 2004. Since this is a continuation of the previous study, we have tried to make very few changes to the original protocol so that we can include the 70 patients who have already been accrued by Z0300. Most of the changes are the result of switching from ACOSOG forms and formats to NCCTG forms and formats—no substantial changes have been made to the original study design and analysis plans.

The primary study objective is to assess whether patients randomized to receive SRS (Arm A) will experience equal (or better) survival than patients randomized to receive SRS + WBRT (Arm B).

16.2 Primary Endpoint

The putative six-month survival for patients receiving SRS + WBRT is approximately 60%. The annual hazard rate associated with this outcome is 1.022 (based on exponential distribution assumptions). If it is demonstrated that patients receiving SRS alone experience six-month survival lower than that of patients receiving SRS + WBRT by 10 points or more on the percent scale (that is, six-month survival of 50% or less), then the modalities will not be considered equivalent with respect to survival. This lower bound for six-month survival among patients receiving SRS alone implies a test criterion hazard ratio (SRS divided by SRS + WBRT) of 1.33. Specifically, the study hypotheses are as follows: Let $\lambda_1$ designate the hazard rate for patients receiving SRS + WBRT, and let $\lambda_2$ designate the hazard rate for patients receiving SRS. We will test

$$H_0: \frac{\lambda_2}{\lambda_1} \geq 1.33$$
versus the alternative hypothesis

$$H_a: \frac{\lambda_2}{\lambda_1} < 1.33$$

The primary analysis for survival (the primary outcome) will be by randomized arm using the stratified logrank test. The stratification factors to be used will be those used in implementing the randomization scheme.

16.21 Power

A type I error probability of 0.05 (one-sided) and desired power $\geq 90\%$ is specified. Study size computations are based on the randomization to the arms with equal probability, the assumed baseline (SRS + WBRT) hazard rate given, the clinically consequential difference specified, and an assumed accrual rate of approximately 96 eligible patients per year. A waiting period of 0.5 years following the completion of accrual and the final analysis is specified.

Using these assumptions, it is computed that an accrual period of five years is necessary [Rubinstein 1981]. The number of eligible patients required is 480.

16.22 Accrual and Sample Size

It is our intent to include the 70 patients that have been accrued by Z0300 in our analysis. This protocol requires a total of 480 eligible patients randomized equally between the two study arms (SRS versus SRS + WBRT). We plan on an
overaccrual of 10%, i.e. 48 patients, to account for ineligible patients found on eligibility review, patient cancellations (patients who are registered but then withdraw prior to initiation of assigned treatment), and major protocol violations (violations that result in a drastically different treatment regimen than that proscribed by the protocol). This results in a total target enrollment sample size of $480 + 48 = 528$ patients. This is expected to yield the necessary 480 eligible patients. Since 70 patients have already been accrued through Z0300, this protocol anticipates enrolling a total of $528 - 70 = 458$ patients. Assuming 96 accrual per year, it is anticipated that the accrual period will be completed in under 5 years and final analysis will begin 5.5 years after this protocol is first opened for accrual.

16.23 Interim Analyses

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 an O’Brien-Fleming type stopping boundary (ref), truncated at −3.5. This will allow for early reporting of results if SRS is found to be inferior to SRS + WBRT. The interim analyses cutoff values, 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.

<table>
<thead>
<tr>
<th>Time (proportion of expected events)</th>
<th>stopping boundary</th>
<th>nominal boundary probability</th>
<th>cumulative type I error</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>−3.50</td>
<td>0.00023</td>
<td>0.00023</td>
</tr>
<tr>
<td>0.50</td>
<td>−2.54</td>
<td>0.0055</td>
<td>0.0056</td>
</tr>
<tr>
<td>0.75</td>
<td>−2.02</td>
<td>0.022</td>
<td>0.024</td>
</tr>
<tr>
<td>1.00</td>
<td>−1.72</td>
<td>0.043</td>
<td>0.050</td>
</tr>
</tbody>
</table>

16.3 Secondary Endpoints and Analysis

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 with respect to survival is established, then treatment preference may be determined by these other factors.

A low incidence of local failure has been achieved with the use of SRS + WBRT relative to WBRT alone or WBRT alone relative to surgery only [Kondziolka 1999]. Analyses will be performed to determine if CNS failure is unacceptably high for patients receiving SRS alone.

Finally, we will also conduct an analysis of the primary endpoint using Cox proportional hazards models that incorporate the stratification factors and adjust for other important prognostic factors such as location of primary tumor (e.g. lung, breast, etc.).

16.4 Quality of Life

The primary QOL objective is to ascertain at 3 months post-treatment whether patients assigned to Arm 1 (SRS) have better QOL than patients on Arm 2 (SRS + WBRT). The potential side effects of the additional WBRT treatment (e.g., fatigue, alopecia, cognitive decline, and diminished hearing) suggest the combination Arm 2 has worse QOL. Furthermore, a recent study [Kondziolka 1999] found there was no neurologic or systemic morbidity related to SRS. Hence, one-sided null hypotheses for improvement
on Arm 1 (SRS) will be used. The 3 month time point is proposed as being late enough to capture major treatment effects, but early enough to avoid a substantial difference between-arm morbidity and mortality.

The QOL will be assessed at baseline (prior to randomization), at week 6, week 12, month 6, month 9, month 12, month 16, month 24, month 36, month 48 and at month 60 (essentially QOL will be obtained out to 5 years after the completion of the SRS treatment). The three specific QOL endpoints of primary interest proposed are: brain subscale (using the BR subscale total score) and physical and emotional functioning (using the respective subscale totals of the FACT-BR). The primary analysis will be based on the corresponding change scores from baseline to month 3, using two-sample t-tests and associated confidence intervals. The Bonferroni adjustment will be used to adjust the $\alpha$ level (Type I error) for the 3 endpoints to 0.05/3, and hence 0.016 will be the 1-sided significance level for each of the 3 treatment comparisons.

The relationship of the existence of missing data at specific time points to both baseline assessment data and data from the immediate prior assessment, both using disease status and scores, will provide a basis of assessing the degree to which missing data may be informative (non-random). The existence of a significant amount of non-random missing data will trigger attempts to impute missing data. In addition, the instances of surrogate responders will be treated as both missing and non-missing data in order to assess the degree to which the analyses are robust to assumptions about the nature of missing or surrogate responder data.

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. Various methods of handling missing data will be used, and the robustness of the analyses to various assumptions about missing data will be investigated. Also, the data will be analyzed according to whether the patient completed the instruments, both with respect to assessing the consistency of scoring and detecting differences between arms.

The QAS analysis will adjust each patient’s time on study, by weighting neurological signs and symptoms (a variety of weighting schemes will be explored); the resultant weighted sum is defined as the patient’s QTIME. Subtracting the impact of Aes and retreatment gives the QAS subtracting QAS value for each patient [Murray 1995]. The QAS values will be compared between treatment arms by the two-sample t-test.

Functional Independence

The duration of functional independence, where Barthel ADL Index score is maintained above baseline level, will be compared between treatments by the logrank test. A patient whose Barthel ADL Index score has not decreased from baseline will be censored at the last valid Barthel ADL Index assessment time. Kaplan-Meier plots of functional independence will be presented, by treatment and estimates of the corresponding median durations will be obtained. Similar, exploratory analyses will be performed based on a decrease of ≥4 Barthel points, and for decrease to 3 or 4 in ECOG/Zubrod scores.

16.5 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.

16.6 Other Analyses

Additional supporting and exploratory statistical analyses will be conducted using proportional hazard regression and logistic regression. These additional analyses will focus on host and tumor features that might provide prognostic information for patients with multiple brain metastases, though statistical power will be limited.

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Sex/Gender</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>156</td>
<td>366</td>
</tr>
<tr>
<td><strong>Ethnic Category: Total of all subjects</strong></td>
<td><strong>158</strong></td>
<td><strong>370</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Racial Category</th>
<th>Sex/Gender</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian or Alaskan Native</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Asian</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Black or African American</td>
<td>17</td>
<td>34</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>White</td>
<td>138</td>
<td>327</td>
</tr>
<tr>
<td><strong>Racial Category: Total of all subjects</strong></td>
<td><strong>159</strong></td>
<td><strong>369</strong></td>
</tr>
</tbody>
</table>

Ethnic Categories: Hispanic or Latino – a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term “Spanish origin” can also be used in addition to “Hispanic or Latino.”

Not Hispanic or Latino

Racial Categories: American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American.”

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations for Quality Control: None.
### 18.0 Records and Data Collection Procedures

#### 18.1 Submission Timetable

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

<table>
<thead>
<tr>
<th>Forms</th>
<th>Active-Monitoring Phase (Compliance with Test Schedule)</th>
<th>Event-Monitoring (Completion of Active-Monitoring Phase)</th>
<th>At Each Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial Material</td>
<td>Follow-up material</td>
<td>At each evaluation</td>
</tr>
<tr>
<td>On-Study Form</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Screening Failure Form'</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Adverse Events/Symptoms</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OP and Path Reports</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurement Form</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT material'</td>
<td></td>
<td>X'</td>
<td></td>
</tr>
<tr>
<td>Response review material'</td>
<td>X'</td>
<td>X'</td>
<td></td>
</tr>
<tr>
<td>Event-Monitoring Form</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluation/Treatment Form</td>
<td>X'</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluation/ Observation Form</td>
<td>X'</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Event Form</td>
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</tr>
<tr>
<td>End of Active Treatment Form</td>
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<td></td>
</tr>
<tr>
<td>ADR/AER (See Section 10.0)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Secondary AML/MDS Report Form</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional Independence'</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of Life Booklet: FACT-BR'</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Patient FACT-BR Booklet Compliance Form</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Neurocognitive Testing Booklet Compliance Form</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Neurocognitive Booklets'</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Neurocognitive Evaluations</td>
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<td></td>
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<tr>
<td>Submission Fax Form</td>
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<td></td>
</tr>
<tr>
<td>Autopsy Reports</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death Certificate</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

See footnotes on next page.
Both NCCTG and CTSU Sites submit the following to NCCTG Operations Office: For patients who do not receive any scheduled radiation therapy, submit the radiation therapy reporting form with the reason radiation was not given at the address given at the end of this paragraph. For patients who receive partial or complete radiation therapy, submit the following materials ≤14 days after the last day of radiation to Radiation Coordinator, Cancer Center Statistics, NW Clinic, 200 First Street SW, Rochester, MN 55905.

a. RT reporting form. (Arm B Only)
b. SRS reporting form.
c. Daily treatment records.
d. Dosimetry calculations, monitor unit calculations, DVHs, and isodose curves.
e. Copies of representative simulation films of all treated fields.
f. Copies of representative port films of all treated fields.
g. Copies of pre-registration and planning contrasted MRI brain scans

If a patient is still alive 5 years after randomization, no further follow-up is required.

Both NCCTG and CTSU Sites submit the following to NCCTG Operations Office:
Submit the reports AND the following radiographic images free of marks that may obscure the lesions or bias the evaluation of the independent reviewer(s). Images on CDs are preferred to film but must be DICOM compatible. The radiographic images must be identified with the NCCTG study number of N0574 and the assigned patient identification number. The radiographic images must be identified with the date the image was performed and the corresponding time point in the study (i.e. W-6, W-12, M-9 or M-24). See Section 11.9 for additional details.

a. Pre-registration and planning MRIs and reports (reports may not be available with planning scans but if available should be submitted)
b. Completion of therapy MRI (six weeks after SRS) and report
c. Best response MRI and report
d. Disease progression MRI and report
e. The MRI brain scans performed at Month 12 and the report should be submitted, in the absence of any change post-completion of therapy. These studies will be reviewed by the NCCTG PIs for final classification of disease progression versus radionecrosis.

Complete at each evaluation during Observation (see Section 4.0).

Both NCCTG and CTSU sites submit the following to Dr. Farace: The Neurocognitive Examiners Booklet and the Neurocognitive Patient Completed Booklet should be mailed per Section 8.32. The Neurocog Booklet Submission Form should be faxed to Elana Farace, Ph.D. per Section 8.33.

Submit if available.
Submit if applicable.
Cycle 1 only.
NCCTG Sites submit the following to NCCTG Operations Office: 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).

This form must be completed only if the QOL FACT-BR Booklet was not completed.

**19.0 Budget:** None.
## 20.0 References

<table>
<thead>
<tr>
<th>Reference and Medline Universal Indicator #(UI)</th>
</tr>
</thead>
</table>
Matthews, CG, Klove, H. Instruction manual for the Adult Neuropsychology Test Battery, Madison WI, University of Wisconsin Medical School, 1964.


Appendix I

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

WHO IS CONDUCTING THIS STUDY?
This study is a clinical trial conducted by the North Central Cancer Treatment Group (NCCTG). Clinical trials are research studies designed to find better ways to treat diseases like cancer.

You are being asked to take part in this research study because you have cancer somewhere else in your body that has metastasized (spread) to your brain. You have one to three metastases in your brain. It is up to you to decide whether or not to take part in this study.

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please read this consent form carefully and take your time making your decision. We encourage you to talk with your doctor, family and friends before you decide to take part in this research study.

WHY IS THIS STUDY BEING DONE?

• The purpose of this research study is to compare overall survival and to compare the effects (good and bad) of radiosurgery (SRS) to radiosurgery plus whole brain radiation therapy (WBRT) on you and your brain metastases.
• There may be microscopic tumor deposits that are not yet visible on imaging (the MRI scan) that may appear at some point in the future. This research study is being done to find out if adding WBRT to SRS will offer any additional benefit to receiving SRS alone in treating these possible microscopic tumor deposits in the brain since it is not known whether more treatment will be better or worse.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY
About 528 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

As part of the evaluation of your eligibility to take part in this research study, your study doctor will do a MRI that needs to be done within 3 weeks prior to signing up for the study. To be eligible, the results of the MRI must show that you have at least one but no more than three brain metastases and that none are more than approximately one inch in size (a little larger than a quarter). Your study doctor must also verify that you meet other study requirements, such as not being pregnant and not having uncontrolled growth of cancer that is outside of your brain. If you are eligible and agree to participate, you will be randomized into one of the two treatment groups. The two treatment groups are described by the procedures that will be tested in this study: (Arm A) radiosurgery and (Arm B) radiosurgery plus whole brain radiation therapy. Everyone is this research study will have radiosurgery.
Randomization means that you are put into a group by chance. It is like flipping a coin. Neither you nor your study doctor will choose what group you will be in. The group you are put in is chosen by a computer. You will have a 50-50 chance of being in one of the two treatment groups (Arm A or Arm B).

If there are more than three brain metastases or if any of the brain metastases are larger than approximately one inch in size on your pre-treatment/planning MRI, you will not be eligible for this research study.

There are procedures that are part of regular cancer care that may be done even if you do not join the study. If you participate in this research study, some of these tests may be done more frequently than if you were not taking part in this research study.

**Radiosurgery (SRS)**
Radiosurgery utilizes immobilization (a head frame) to allow very precise targeting of tumors. Radiosurgery is a single treatment and will be done as an outpatient procedure in most cases. A high dose of radiation will be delivered to a small, focused area of your brain. One technique, called the 'gamma knife,' uses gamma rays. Other systems use a specially designed x-ray machine called a linear accelerator. This machine works much like a regular x-ray machine, but the x-ray dose is much higher and the machine will target the tumor. Either a gamma knife or a linear accelerator can be used in this research study.

You will be given a local anesthesia to numb your skin and make it easier to position a special head frame. The head frame must be fixed in place with pins partially extending into your skull. The head frame holds your head to prevent it from moving and to focus the gamma rays or x-rays and aim them at the tumor(s) in your brain. To plan the procedure, a MRI is done while you are wearing the head frame. You will be given a steroid medicine through a needle into a vein in your arm before the radiosurgery to prevent swelling. For most patients, the actual time on the radiosurgery treatment machine is in the range of 30 to 90 minutes. The head frame will be removed after the treatment and the frame attachment sites on your head will be cleaned.

**Whole Brain Radiation Therapy (WBRT)**
Whole brain radiation therapy will be given to you as an outpatient for 5 days a week for approximately 2 ½ weeks (about 12 treatments). The treatments will deliver small doses of radiation to the whole brain each treatment day. The treatments typically last anywhere from 10 to 20 minutes (and part of this time includes making adjustments to accurately target the whole brain). The treatment will use a specially designed x-ray machine called a linear accelerator. This machine works much like a regular x-ray machine, but the targeting is more specific and the x-ray dosage is much higher. The linear accelerator will deliver the radiation with x-ray beams on each side of your head. The treatment is painless and bloodless, and there is no danger of infection (no head frame is used for whole brain radiotherapy although a soft plastic mask that helps hold the head in place during treatment may be utilized).
**Follow-up Visits**

Regardless of which treatment group you are in (Arm A or Arm B), you will be asked to visit your study doctor for follow-up visits after your radiosurgery treatment is completed. These follow-up visits will be at 6 weeks, 12 weeks, 6 months, 9 months, 12 months, 16 months, 24 months and then every year until it has been 5 years since you started the study. During these visits your study doctor or a member of the research team will talk with you about your symptoms, give you a physical and neurological examination and you will have a MRI scan. You will be asked questions to determine your ability to think and remember, and you will be asked questions about your daily living activities. These questions will take approximately 20 to 30 minutes to complete.

In addition to the questions that your study doctor will ask you, you will be asked to complete a questionnaire that will take an additional 10-15 minutes before your treatment and at each follow-up visit after your treatment. The questionnaire asks how you feel physically, socially, emotionally and functionally.

**HOW LONG WILL I BE IN THE STUDY?**

We would like to keep track of your medical condition as long as you are alive or for a maximum of five years after you begin this study to look for any long-term effects of the treatment in this study.

Your study doctor may decide to take you off this study if your medical condition changes, or if NCCTG finds it must limit or stop the study. You may stop participating at any time. However, if you decide to stop taking part in the study, we encourage you to talk to the study doctor or your own doctor first.

**WHAT ARE THE RISKS OF THE STUDY?**

While on the study, you are at risk for these side effects. You should discuss these with your study doctor. There also may be other side effects that we cannot predict. Your study doctor may be able to offer medical treatment to decrease your side effects and make you more comfortable. Some side effects go away after the treatment, but in some cases side effects can be serious, long lasting, or permanent.

Risks and Side Effects of Radiosurgery:

<table>
<thead>
<tr>
<th>Very Likely</th>
<th>Less Likely</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Temporary pain associated with the head frame placement</td>
<td></td>
</tr>
<tr>
<td>• Headache</td>
<td>• Nausea</td>
</tr>
<tr>
<td></td>
<td>• Vomiting</td>
</tr>
<tr>
<td></td>
<td>• Allergic reaction to the local anesthesia (rash, itching, nausea, or difficulty breathing)</td>
</tr>
<tr>
<td></td>
<td>• Bleeding and/ or infection around the head frame</td>
</tr>
</tbody>
</table>
Risks and Side Effects of Whole Brain Radiation:

<table>
<thead>
<tr>
<th>Very Likely</th>
<th>Less Likely</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hair loss</td>
<td>• Nausea</td>
</tr>
<tr>
<td>• Temporary scalp redness and drying</td>
<td>• Decreased mental capacity</td>
</tr>
<tr>
<td>• Fatigue (tiredness)</td>
<td>• Decreased motor function (coordination/movement)</td>
</tr>
<tr>
<td></td>
<td>• Cataract formation</td>
</tr>
</tbody>
</table>

Expected Long-Term Serious Side Effects of SRS and WBRT Include:

<table>
<thead>
<tr>
<th>Less Likely</th>
<th>Rare, but serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nausea</td>
<td>• Vomiting</td>
</tr>
<tr>
<td>• Permanent hair loss</td>
<td>• Seizures</td>
</tr>
<tr>
<td></td>
<td>• Weakness, paralysis, loss of sensation</td>
</tr>
<tr>
<td></td>
<td>• Loss of vision or hearing</td>
</tr>
<tr>
<td></td>
<td>• Difficulty with speech</td>
</tr>
<tr>
<td></td>
<td>• Decreased mental abilities</td>
</tr>
<tr>
<td></td>
<td>• Radiation necrosis (brain tissue death which may require surgery or steroid therapy)</td>
</tr>
<tr>
<td></td>
<td>• Death</td>
</tr>
</tbody>
</table>

The above listed long-term side effects can occur with either treatment (SRS or WBRT) and the risks may be increased if the patient receives both SRS and WBRT (i.e. patients on Arm B).

Reproductive risks: Being a part of this study while pregnant may expose the unborn child to significant risks. Therefore, pregnant women may not participate in the study. If you are a woman who can become pregnant, a urine or blood pregnancy test will be done within 7 days prior to radiosurgery (using 1 teaspoon of blood drawn from a vein by needle-stick). The pregnancy test must be negative before you can enter this study. If you are sexually active, you must agree to use birth control measures for the duration of the radiation treatment (SRS Arm A or Arm B WBRT + SRS).

The treatment used in this study could affect your sperm and could potentially harm a child that you may father while on this study. If you are sexually active, you must agree to use birth control measures for the duration of the radiation treatment (Arm A SRS or Arm B SRS + WBRT) and for three months following the completion of the radiation treatment.

Medically acceptable birth control includes: (1) surgical sterilization, (2) approved hormonal contraceptives (such as birth control pills, Depo-Provera, or Lupron Depot), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). If you do become pregnant during this study, you must inform your study doctor immediately (or your institution’s standard language on acceptable methods of birth control).

For more information about risks and side effects, ask the study doctor (NAME) ____________________________ at ____________________________ or contact (NAME) ____________________________ at ____________________________.
ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
If you agree to take part in this study, there may or may not be a direct medical benefit to you. The treatments in this study have been given before to people with brain metastases, but it is not known which of these treatments works the best. We hope that information learned from this study will help people who have brain metastases in the future.

WHAT OTHER OPTIONS ARE THERE?
Instead of being in this study, some of the following options may be available to you:

- Whole brain radiation therapy
- Radiosurgery
- Radiosurgery + Whole brain radiation therapy
- Surgery
- Surgery + Whole brain radiation therapy
- Surgery + Radiosurgery
- Steroids
- Chemotherapy
- Biological response modifier therapy or immunotherapy
- No therapy at this time, but care that will help you feel more comfortable

You may get radiosurgery and/or whole brain radiation therapy even if you do not take part in the study.

Please talk to your doctor about these and other options.

In addition, if after treatment, brain metastases recur or new brain metastases develop, all of the above treatment options may be available for you. Please talk to your doctor about these and other options and your doctor will help you decide what is best for your situation.

WHAT ABOUT CONFIDENTIALITY?
Your medical records and study records are confidential but they may be disclosed if required by law.

If the study results are published, no personal information will be identified. This is to ensure that no one will be able to tell that you took part. Records of your progress on the study will be kept in a confidential form at this institution and also in a computer file at the North Central Cancer Treatment Center (NCCTG). The confidentiality of the central computer record is carefully guarded. Your research records will include your medical history, results of your exams, reports from your treatment, and reports of your office visits. Some of the information collected as part of the research also may be included in your medical records.
Organizations that may look at and/or copy your research records for quality assurance and data analysis include:

- North Central Cancer Treatment Group (NCCTG);
- the Radiological Physics Center (RPC);
- the local Institutional Review Board (IRB), a group of people who review the research study to protect your rights; and
- government agencies including the Office for Human Research Protections (OHRP) and the National Cancer Institute (NCI).
- the Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials.

These agencies may look to see that the study is being done safely and correctly.

WHAT ARE THE COSTS?
You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute’s Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the “Clinical Trials and Insurance Coverage” information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

WHAT ARE MY RIGHTS AS A PARTICIPANT?
Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

A Data Monitoring Committee, an independent group of experts, will be reviewing the data from this research throughout the study. In addition, a qualified representative of the FDA may inspect your study records.

We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.
WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor ______________ [name(s)] at ______________ [telephone number].

For questions about your rights while taking part in this study, call the ______________ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at ______________ (telephone number).

You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only).

WHERE CAN I GET MORE INFORMATION?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI’s clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI’s general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.
Signature

I have been given a copy of all _____ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Printed Participant Name: ________________________________

Participant Signature: _________________________________

Date: ______________________________________

Printed name of person obtaining informed consent:

__________________________________________

Signature of person obtaining informed consent:

___________________________________________

Date ______________________________

Local IRB changes to this document are allowed. Sections “What are the risks of the research study” or “What other choices do I have if I don’t take part in this research study?” should always be used in their entirety if possible. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the North Central Cancer Treatment Group Operations Office for approval before a patient may be randomized to this study.

Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This information should be specific for each institution.
APPENDIX II

CANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES

REGISTRATION/RANDOMIZATION

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member Web site or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. All forms and documents associated with this study can be downloaded from the N0574 Web page on the CTSU registered member Web site (http://members.ctsu.org) unless otherwise indicated below. Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and all pertinent forms and documents are approved and on file with the CTSU.

Requirements for N0574 site registration:

- CTSU IRB Certification
- IRB/Regulatory Approval Transmittal Sheet
- Radiation Therapy Facility Inventory Form

NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Radiological Physics Center (RPC) monitoring program. For sites enrolling through the CTSU a Radiation Facilities Inventory Form must be on file with CTSU. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility.

- The Radiological Physics Center (RPC) Questionnaire for Stereotactic Radiosurgery (SRS) with Gamma Knife or with Linear Accelerator, as appropriate, or phantom irradiation, must be completed and submitted to the RPC. RPC will notify the NCCTG Operations Office if the site is compliant. NCCTG will then notify the CTSU Central Regulatory Office (CCRO) and the regulatory office will enter this information in the CTSU Regulatory Support System (RSS). The status of the credentialing review will be reflected on the RSS Site Registration Status screen http://members.ctsu.org/rss/ of the CTSU Member Web site.
NOTES:
The questionnaire is available on the RPC web site, under Credentialing, at http://RPC.mdanderson.org. Institutions previously approved for the ACOSOG Z0300 study will not need to be re-credentialed.

- Neurocognitive Skills Review: Examiners must complete the Neurocognitive Testing on-line training produced by Elana Farace, Ph.D. Once the video has been viewed, sites are to practice/rehearse the testing with a colleague (NOT a patient) and fax the completed forms found in Appendix IX to Dr. Farace at the number below. In addition, the Neurocognitive Testing Verification Form must be completed by the site, then faxed to and approved by Dr. Farace (Fax # 717-531-0748).

Dr. Farace will notify the NCCTG Operations Office via email once the site has complied with this requirement. NCCTG will then contact the Central Regulatory Office and the CCRO will enter this information in the CTSU Regulatory Support System (RSS). The status of the neurocognitive skills review will be reflected on the RSS Site Registration Status screen http://members.ctsu.org/rss/ of the CTSU Member Web site.

NOTES:
A link to the on-line training video to be used by the neurocognitive testing examiners is available as a link under the Site Registration documents section of the N0574 page of the CTSU Member Web site.

Sites must have an adequate supply of N0574 Neurocognitive Examiners Booklets and the Neurocognitive Patient Completed Booklets on hand before attempting to pre-register patients. These booklets contain the neurocognitive test and battery forms and the scoring instructions to be used in this study. To order booklets, complete the CTSU Supply Request form located on the N0574 documents page under ‘site registration documents’ and fax it to the CTSU.

A grooved peg board must be available for neurocognitive testing. These peg boards can be purchased for approximately $105.00 at the following web address:
http://www.ausmed.com/medecat/rs/ecatalog/details.asp?productid=10225A

- Quality of Life (QOL): Sites must have an adequate supply of N0574 Quality of Life – FACT BR booklets on hand before attempting to pre-register patients. To order, complete the CTSU Supply Request form located on the N0574 documents page under ‘site registration documents’ and fax it to the CTSU.
Prestudy requirements for patient pre-registration on N0574

- Patient must meet all pre-registration inclusion criteria, and no exclusion criteria should apply.
- Patient has signed and dated all applicable consents and authorization forms.
- All applicable baseline laboratory tests and prestudy evaluations performed.
- Baseline N0574 Quality of Life – FACT BR and the Functional Independence: Barthel ADL Index must be completed after informed consent and prior to randomization.
- Baseline neurocognitive testing must be completed after informed consent and prior to randomization.

**CTSU Procedures for Patient Pre-Registration (Step 1)**

Contact the CTSU Patient Registration Office by calling 1-888-462-3009 and leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, i.e. within one hour, call the registrar cell phone at 1-301-704-2376. Complete the following forms:

- CTSU Patient Enrollment Transmittal Form
- NCI Cooperative Group Pre-registration Eligibility Checklist

Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 7:00 p.m., Mon-Fri, Eastern Time (excluding holidays). The CTSU registrar will check the investigator and site information provided to ensure that all regulatory and special credentialing requirements have been met. The registrar will also check the forms for completeness and will follow-up with the site to resolve any discrepancies. Once investigator eligibility is confirmed and enrollment documents deemed complete, the CTSU registrar will contact the NCCTG Randomization Center within the confines of their office hours to obtain assignment of a unique NCCTG patient identification number. This number is to be used on all future forms and correspondence. The CTSU registrar will relay the patient identification number to the enrolling site and follow up with a pre-registration confirmation via e-mail or fax.

Randomization must take place within 14 days of patient pre-registration.

**CTSU Procedures for Patient Randomization (Step 2)**

After performing the planning MRI, call the CTSU Patient Registrar cell phone at 1-301-704-2376 to randomize the patient. Be prepared to give your contact information and the patient’s identification number assigned at pre-registration.

**IMPORTANT:** Note that the CTSU Patient Registrar can only randomize patients during NCCTG’s Randomization Office hours (8:00 a.m. to 4:30 p.m. Central Time).

Complete the following forms:

- CTSU Patient Enrollment Transmittal Form (include patient identification number assigned at pre-registration)
- NCI Cooperative Group Randomization Eligibility Checklist
Fax these forms to the CTSU Patient Registrar at 1-888-691-8039. The CTSU registrar will check these forms for completeness and follow-up with the site to resolve any discrepancies. Once randomization forms are deemed complete, the CTSU registrar will contact the NCCTG Randomization Center within the confines of their office hours to obtain a randomization assignment. The CTSU registrar will then relay the treatment assignment to the randomizing site and follow up with a randomization confirmation via e-mail or fax.

Treatment must begin within ≤ 7 days of patient randomization, but may begin on the same day as patient randomization. (For the vast majority of patients, treatment will be delivered the same day as the planning MRI and randomization.)

DATA SUBMISSION

All case report forms (CRFs) and other documents associated with this study must be downloaded from the N0574 Web page located on the CTSU registered member Web site (http://members.ctsu.org). CTSU investigators must use the current version of the protocol-specific N0574 forms and adhere to the N0574 schedule for data submission per protocol Section 18.0. CRFs and associated reports must be submitted in the following manner:

- Patient pre-registration and randomization forms should be faxed to the CTSU according to the instructions outlined above.

- RT materials and radiographic images listed in Section 18.0 must be submitted to NCCTG Data Operations and not to the CTSU. Please copy the CTSU on relevant transmittals when forwarding these materials to NCCTG.

- Refer to the ‘Special Materials or Substudies’ section below for instructions on special submission of the Neurocognitive Examiners hard copy booklets and the Neurocognitive Patient Completed hard copy booklets.

6 Original and amended CRFs (including the N0574 Quality of Life – FACT BR hard copy booklets) reports, and responses to query and delinquency letters must be mailed directly to the CTSU Data Operations Center accompanied by a properly completed CTSU Data Transmittal Form; the CTSU will forward all data submissions to the NCCTG.

- Copies of clinical reports submitted to the CTSU must include the Patient ID and protocol number on all pages of the report. The patient’s name must be redacted.
A CTSU Data Transmittal Form must accompany all post-enrollment data submissions. Data submitted with an improperly completed CTSU Data Transmittal Form or without a CTSU Data Transmittal Form will be returned to the site for corrective action without being processed. The CTSU Data Transmittal Form may only be used when mailing post-enrollment case report forms and reports. Do not use this form when faxing site registration or patient enrollment documentation.

Mail original and amended post-enrollment CRFs, reports, and responses to query and delinquency letters to:
Westat
CTSU Data Operations Center
1441 W. Montgomery Avenue
Rockville, MD  20850-2062

SPECIAL MATERIALS OR SUBSTUDIES

Quality of Life and Functional Independence Assessments

- Patient self-reported quality of life data will be collected in the N0574 Quality of Life – FACT BR hard copy booklets and submitted to CTSU Data Operations accompanied by a completed CTSU Data Transmittal. Clinical sites must have Patient Questionnaire booklets on hand prior to enrolling patients on this trial (see the Site Registration section of this appendix).

- The Functional Independence: Barthel ADL Index and the ECOG PS scales are available from the case report forms section of the N0574 protocol Web page. Submit completed forms to CTSU Data Operations along with a completed CTSU Data Transmittal.

Neurocognitive Assessments

Assessment data will be collected in the Neurocognitive Examiners hard copy booklets and the Neurocognitive Patient Completed Booklets. Clinical sites must have these booklets on hand prior to enrolling patients on this trial (see the Site Registration section of this appendix). Submit hard copy booklets directly to Elana Farace, Ph.D. at the address provided in the protocol and fax the Neurocognitive Evaluations Submission Form to Elana Farace at 717-531-0748. Do not send neurocognitive booklets to the CTSU or copy CTSU on the submission form.
Adverse Event (AE) Reporting

Assessing and submitting expedited reports

This study will utilize the CTCAE version 3.0 for toxicity and Adverse Event (AE) reporting. A link to the CTCAE guidelines is available on the CTSU registered member Web site. CTSU investigators should assess adverse events according to the instructions and tables in section 10.0 of the protocol. All reporting should be conducted within the time frames specified in section 10.0 of the protocol.

Events must be reported electronically using the CTEP AdEERS application. A link to the AdEERS application can be found on both the CTSU member homepage and the N0574 Web page on the CTSU member site.

Please do not copy the CTSU on expedited serious adverse event reports.

CTSU sites must comply with the expectations of their local Institutional Review Board (IRB) regarding submission of documentation of adverse events. Local IRBs must be informed of all reportable serious adverse events.

Secondary AML/MDS/ALL reporting:

CTSU investigators will submit the NCI Secondary AML/MDS/ALL Report Form and supporting documentation to the CTSU. Once received, the CTSU will send this information to NCCTG where it will be forwarded on to the NCI.

Drug Procurement:

Not applicable.

REGULATORY AND MONITORING

Study Audit

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site’s primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.
Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTSU Operations Manual located on the CTSU Member Web site.

**Health Insurance Portability and Accountability Act of 1996 (HIPAA)**

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the informed consent section of this protocol document; however, authorization for the release of Protected Health Information is considered separate and distinct from the Informed Consent process for participation in this clinical trial.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

**Clinical Data Update System (CDUS) Monitoring**

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDUS data collected from the study-specific case report forms.
Appendix III

Administration of FACT-BR Questionnaire

Instructions for Study Staff

The instructions given below are intended to serve as a guide for the administration of the FACT-BR Quality of Life (QOL) questionnaire. The FACT-BR should be self-administered by the patient.

1. Following patient’s check-in at clinic, the patient should be taken to a quiet area where he/she may complete the questionnaire without interruption. Adequate time should be provided to the patient so that the questionnaire can be completed at the beginning of the clinic visit.

2. The patient will be given the questionnaire PRIOR to being seen by the physician or nursing staff or having any tests/procedures done at the clinic visit, as indicated in the protocol.

3. The patient should be instructed to read the brief directions at the top of the page. After the patient’s correct understanding has been confirmed, he/she should be encouraged to complete every item in order. Some patients may feel that a given question is not applicable to them and will therefore skip the item altogether. **Patients should be encouraged to check the response that is most applicable.** If, for example, a patient is not currently receiving any treatment, the patient should check "not at all" to the question "I am bothered by side effects of treatment."

4. The FACT-BR must be completed by the patient alone, without coaching or suggestions as to the "correct" answer by health care personnel, relatives, or anyone else.

**OR**

If the patient has experienced cognitive deterioration during treatment, a ‘significant other’ (e.g., a spouse) should complete the FACT-BR on behalf of the patient, without coaching or suggestions as to the “correct” answer by health care personnel, other relatives, or anyone else. The respondent must sign the back of the questionnaire.

5. The study staff may provide clarification but should not rephrase questions, suggest answers, or discuss answers.

6. The study staff will collect the questionnaire as soon as it has been completed, check to see that each question has been answered, and remind the patient/respondent to answer any questions that may have been missed. If the patient/respondent declines to answer some or any of the questions, the study staff should enter an explanatory comment on the questionnaire.

7. The questionnaire must be completed in the clinic, at the beginning of the visit. The questionnaire may not be taken home nor may it be completed at a later time.

**NOTE:** Varying the environment in which the questionnaire is completed by allowing completion at other times than the time of the clinic visit introduces unnecessary variables into the study.

8. The information provided by the patient in the completed questionnaire is confidential and should not be discussed with, or shown to, anyone who is not a member of the study team.
Appendix IV
FACT-BR Questionnaire

PLACE HOLDER
Welcome to the NCCTG trial on the effect of whole-brain radiation following radiosurgery in patients with 1-3 brain metastases. I am Dr. Elana Farace, neuropsychologist from the Department of Neurosurgery at the University of Virginia. I am here to teach you what you need to know about the neurocognitive measures in the N0574 protocol.

Rationale:
The primary outcome measure chosen for the study is survival, but we are particularly interested in neurocognition, functional status, and quality of life in these patients. These additional measures will allow us to better understand the impact of treatments on all aspects of a patient with brain metastases.

Neurocognitive testing battery selected for this study

The tests in this battery are:
- Brief
- Repeatable
- Inexpensive
- Sensitive to change in patient function
- Simple enough that most patients can complete them
- Able to be given across sites
- Published measures
- Standardized, with known reliability and validity

The tests to be given are the:
- Hopkins Verbal Learning Test (HVLT) a test of verbal memory
- Trailmaking Tests A&B
  - Trails A is a test of visual scanning and visual perception
  - Trails B is a test of divided attention
- Controlled Oral Word Association Test (COWA) a test of verbal fluency
- Grooved Pegboard, a test of fine motor control

Timing of test battery:

No test takes more than five minutes to give. Each has a “discontinue rule” that if it is taking longer than five minutes to give that you can stop the test.
Test Schedule:

The neurocognitive and QOL tests in the protocol will be administered on this schedule. As you can see, we monitor patients more closely at the beginning of the study, but it is important to follow them over time to determine the longer-term effects of treatments.

<table>
<thead>
<tr>
<th>Pre-intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 6</td>
</tr>
<tr>
<td>Month 3</td>
</tr>
<tr>
<td>Month 6</td>
</tr>
<tr>
<td>Month 9</td>
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<tr>
<td>Month 12 (Year 1)</td>
</tr>
<tr>
<td>Month 16</td>
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<tr>
<td>Month 24 (Year 2)</td>
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<tr>
<td>Month 36 (Year 3)</td>
</tr>
<tr>
<td>Month 48 (Year 4)</td>
</tr>
<tr>
<td>Month 60 (Year 5)</td>
</tr>
</tbody>
</table>

Test forms:

For the neurocognitive testing, the examiner should use the Neurocognitive Examiners Booklet, the Neurocognitive Patient Completed Booklet, as well as, the Administration of Neurocognitive Evaluations Instructions. The examiners complete the Neurocognitive Examiners Booklet. They also use the Administration of Neurocognitive Evaluations Instructions to conduct the tests. Patient responses are recorded directly onto the Neurocognitive Examiners Booklet.

It is very important that the person administering the neurocognitive tests fax in a completed Neurocognitive Booklet Checklist Form indicating who administered the tests with the appropriate contact information.
Setting up for Neuropsychological Testing

Set up of testing situation:

- Private room
- Door that closes
- Quiet
- Alone with just the patient—No family members
- May want to hang a sign that says “do not disturb”
- Some tests are timed—it is very important not to be interrupted during these
- Desk for you both to write on (clipboard works in a pinch)
- Stopwatch or other second timer
- Black ink pens (one for you and one for the patient)

Testing tips

- Do not indicate to the patient how well they are doing
- Hide your writing from the patient so they cannot get feedback on how they are performing
- However, it is OK to be generically encouraging (make sure you make the same response whether patient is performing well or not)
- Please do not assist them in any way if they struggle with a task; we need an accurate view of what they can do themselves.
Hopkins Verbal Learning Test

**Purpose:**
- The HVLT is a great memory test that gives a wealth of information about memory and takes less than 5 minutes to administer.
- The test consists of 12 nouns in 3 semantic categories that are read aloud (with a one-second interval between each word) for three consecutive trials, each trial followed by a free-recall test.
- Keep the order of the words the same across trials.
- Repeat instructions before each trial to minimize forgetting.
- After all 3 trials are given, there is a 20-30 minute delay during which other neurocognitive tests are administered.
- After the 20-30 minute delay, you will ask the patient to recall words from the list again to test delayed recall.
- Finally, you will test recognition memory for words in the list. A longer list of 24 items containing the 12 words on the list and other distracter words will be read aloud and the patient will respond “yes” if the word was on the original list, and “no” if not.

**Alternate forms:**
- You have six alternate forms of this test.
- You only complete ONE test at each visit in the study.
- This is important so that you are testing new memory, not old learning from a previous version of the test, or what we call a “practice effect.”
- Do not ever repeat the same form of a test on two successive visits.

**Materials needed:**
- HVLT Administration Sheet

**Administration:**
- For Trial 1, say this:
  “I am going to read a list of words. Listen carefully, for when I stop, you are to say back to me as many of the words as you can remember. It doesn’t matter in what order you repeat them. Just try to remember as many as you can.”
- Read the list of words, with a one-second interval between each of the 12 words.

“What words were on the list?”
- Mark an X in the YES box if the word the patient states was on the list.
- Mark an X in the NO box if the patient does not say the word.
- If the patient repeats a word, you can ignore it.
- If the patient gives you another word, you can ignore it.
- To be correct, the word has to be the exact word.
- Make sure to speak loudly and clearly.
- When the subject indicates that he or she can recall no more words, the examiner rereads the list after giving a second set of instructions.
“Now I am going to read the same list of words again, and once again when I stop, I want you to tell me as many words as you can remember, including words you said the first time. It doesn’t matter in what order you say them. Try to remember and say as many as you can, whether or not you said them before. “

“What words were on the list?”

- Repeat same instructions for Trial 3
- Note: Use a post it to remind yourself to go back to this test so you can test delayed memory and recognition in 20-30 minutes.
- Proceed to the Trail Making Tests

**HVL T Delay**

- After a 20-30 minute delay, during which the subject would be engaged in the other neurocognitive tests required in Study N0574
- Ask the subject to recall the words for the list.

  “Remember that list of words I had you repeat back to me earlier? I want you to say as many of those words as you can remember now.”

- Mark an X in the YES box if the word the patient states was on the list
- Mark an X in the NO box if the patient does not say the word
- Then test recognition. For the recognition trial say:

  “Now I am going to read you a list of words. You tell me if the word I read was included in the list of words you were learning. Just say “yes” or “no”.”

- **Mark an X in the correct box corresponding to whether the patient says Yes or NO to whether the word was in the original list.**

- Sign and date the form and you are done!
Trail Making Tests A & B

**Purpose:**
- Trails A is a test of visual scanning and visual perception.
- Trails B is a test of divided attention
- Both tests take less than 5 minutes to administer
- The tests consist of numbers in Trails A, and numbers and letters in Trails B, arranged on a page.
- The patient is asked to draw a line in a “connect the dots” test so this is a test where the patient themselves draws on the form, which is found in the patient completed booklet

**Materials needed:**
- Stopwatch
- A black pen for the patient to use
- Trails A and B sample (Patient completed booklet)

**Administration:**

**Sample Test A:**

Place the Sample Test A in front of the patient and say this and point to the numbers you are pointing out:

"On this page (point) are some numbers. Begin at number 1 (point to "1") and draw a line from one to two (point to "2"), two to three (point to "3"), three to four (point to "4"), and so on, in order until you reach the end (point to the circle marked "end"). Draw the lines as fast as you can. Do not lift your pencil from the paper and do not try to erase. Ready? Begin."

- Start timing with stopwatch
- If the subject makes a mistake on Sample A, point it out and explain it. The following explanations of mistakes are acceptable:
  - "You started with the wrong circle. This is where you start."
  - "You skipped this circle (point to the one omitted). You should go from number one (point) to two (point), two to three (point) and so on until you reach the circle marked "END".
  - “You need to cross into the circles as you draw like this.”
  - “Please don’t lift your pencil off the paper.”

After the mistake has been explained, the examiner marks out the wrong part with a has line and says:

"Please keep the pencil on the paper and continue on to the next circle. Go on from here."

- Point to the last circle completed correctly in sequence
“Work as fast as you can. Ready? Begin.”

- If the subject succeeds this time, go on to PART A of the test. If not repeat the procedure until the subject does succeed or it becomes evident that he or she cannot do it.
- If the subject completes the sample item correctly, and in a manner that shows that he or she knows what to do, say:

"Good! Let's try the next one."

Turn the page and give PART A of the test.

**Trails A Test**

"On this page are numbers from 1 to 25. Do this the same way. Begin at number one (point) and draw a line from number one to two (point), two to three (point), three to four (point), and so on, in order until you reach the "end" (point). Remember work as fast as you can. Ready? Begin."

- Start timing now
- If the subject makes an error immediately call it to his or her attention and have the subject proceed from the point where the mistake occurred. Do not stop timing.
- When the subject completes Trails A Test, stop timing and remove the test sheet
- If the patient takes more than 5 minutes (300 seconds) to complete the test, discontinue the test and mark 300 seconds on the form
- Record the time in seconds
- Record the number of errors, that is the number of times you had to correct the patient.
- Proceed immediately to Part B

**Sample Test B**

"On this page are some numbers and letters. Begin at number one (point) and draw a line from one to A (point to "A"), A to two (point to "2"), two to B (point to "B"), B to three, (point to "3"), three to C (point to "C"), and so on until you reach the end (point to the circle marked "END"). Remember, first you have a number (point to "1"), then a letter (point to "A"), then a number (point to "2"), then a letter (point to "B"), and so on. Draw the lines as fast as you can. Ready? Begin."

- Start timing with stopwatch
- If the subject makes a mistake proceed as on Sample Test A
- If the patient succeeds, go on to Trails B Test

**Trails B Test**

"On this page are both numbers and letters. Do this the same way. Begin at number one (point to '1') and draw a line from one to A (point to 'A'), A to two (point to '2'), two to B (point to 'B'), B to three (point to '3'), three to C, and so on until you have reached the end (point to the circle marked "END"). Remember, first you have a number, then a letter and so on. Do not skip around, but go from one circle to the next in proper order. Draw the lines as fast as you can and don’t lift your pen off the paper. Ready? Begin."

- If the subject makes an error immediately call it to his or her attention and have the subject proceed from the point where the mistake occurred. Do not stop timing.
- When the subject completes the Trails B Test, stop timing and remove the test sheet
• Record the time in seconds
• Record the number of errors, that is the number of times you had to correct the patient
• Sign and date the form and proceed to the Controlled Oral Word Association Test

**Benton Controlled Oral Word Association Test**

**Purpose:**
- The Controlled Oral Word Association Test is a test of verbal fluency and is sensitive to patients’ changes in patients’ language skills
- The test takes less than 5 minutes to administer
- The patient is given a letter and asked to name all the words they can think of that begin with a that letter

**Materials needed:**
- Stopwatch
- COWAT answer sheets

**Alternate forms:**
- You have two alternate forms of this test.
- You only complete ONE test at each visit in the study
- Do not ever repeat the same form of a test from on two successive visits

**Administration:**

"I am going to say a letter of the alphabet and I want you to say as quickly as you can, all the words that you can think of which begin with that letter.

You may say any words at all, except proper names, such as the names of people or places.

So if the letter is “r” you would not say "Rochester" or "Robert".

Also, do not use the same word again with a different ending, such as "eat" and "eating".

For example, if i say "s", you could say "son", "sit", "shoe" or "slow". Can you think of other words beginning with the letter "s"?

• Wait for the patient to give a word. If they succeed, indicate to them that they are performing correctly, and move on to the test
• If the patient does not understand, repeat the directions.
• If the subject has succeeded in giving an appropriate word beginning with the demonstration letter, say:

"That is fine, now I am going to give you another letter and again you will say all the words beginning with that letter that you can think of. Remember, no names of people or places, just ordinary words. Also, if you should draw a blank, i want you to keep on trying until the time limit is up. You will have a minute for each one."
The first letter is C.” (or F).

- Start Timing NOW
- If the subject discontinues before the end of the time period, encourage them to find more words. If they are silent for 15 seconds, repeat the basic instructions and letter. No extension on the time limit is made in the event that the instruction is repeated in the course of the test.

- Make sure to continue through the full 60 seconds even if patient cannot name a word.
- Record every word the patient says. Write each word on a new line. If patient speaks quickly try to write at least first few letters. However, all incorrect responses should be recorded verbatim.
- If a word is wrong, draw a line through it as you go
- Spelling does not count against the patient (or the tester)
- Keep writing even if patients list more than 20 words for which there are blanks. We need to know how many words the patient can name in 60 seconds.
- If the patient produces a word which may or may not be a proper noun (e.g. frank/Frank) or is a word with two or more meanings (e.g., can; catch) the tester should query the patient after the timing has stopped. However, during the testing, the words should simply be recorded and the patient should not be interrupted. At the end of each one-minute test of a letter, the patient should be asked what they meant by the responses to clarify, and the response should be marked out if in error. Repetition of the word is acceptable if the subject definitely indicates the alternative meaning. Proper nouns are not accepted.
- Continue the test with the letters "F" and "L" (or “A” and “S”) allowing one minute for each
- Sign and date the form and proceed to the Grooved Pegboard
Grooved Pegboard

Purpose:
• The Grooved Pegboard Test is a test of fine motor coordination.
• The test is sensitive to left versus right hand motor impairment and overall motor slowing
• The test takes less than 5 minutes to administer
• The patient is asked to place pegs into a pegboard with their left and right hands.

Materials needed:
• Stopwatch
• Grooved pegboard with pegs
• Scoring sheet

Administration:

Handedness testing:
• Ask the patient if they are right or left handed and mark the corresponding box
• Ask the patient if they have always been right or left handed, or if anyone ever made them change handedness as they used to do in school and mark the corresponding box
• Ask the patient which hand they use for wiring, drawing, or throwing a ball
• Based on the answers to these questions, the patient’s dominant hand is their RIGHT hand if they have always been right-handed AND no one has ever made them change handedness AND are always or usually right-handed when writing, drawing, or throwing a ball. Otherwise, the patient is LEFT hand dominant

Pegboard Administration:
• Place the pegboard centered in front of the subject with the tray at the top of the board.
• Empty the pegs from the compartment into the tray

“This is a pegboard and these are the pegs.”
• Point out the board and the pegs. Pick up a peg. Show them the peg and say:

“All the pegs are the same. They have a groove, that is, a round side and a square side and so do the holes in the board. What you must do is match the groove of the peg with the groove of the board and put these pegs into the holes like this.”
• Demonstrate this by filling in the top row
• Allow the patient to practice with 3-4 pegs if they wish
• Remove the pegs, putting them back in the tray

“When I say go, begin here and put the pegs into the board as fast as you can, ONLY using your (their dominant) hand. Fill the top row completely from this side to this side (starting at the opposite side of their dominant hand.) Do not skip any holes, fill each row the same way you filled the top row. Any questions? Ready, as fast as you can. Go.”

• Have the patient fill the board with their right hand from left to right as you would read a book. This keeps them from having already placed pegs get in their way and slow them down.
• With the left hand patients fill the board from right to left. Again this keeps them from having already placed pegs get in their way and slow them down.
• Begin timing when they start to place the pegs.
• Make sure to keep track of any pegs that are dropped inadvertently and tally them on the scoring sheet.
• Record, in seconds, the time it takes to finish putting all the pegs in.
• If a subject takes longer than five minutes the trial must be discontinued.
• Record the number of pegs placed at the end of the trial.
• Repeat this with the non-dominant hand starting from the opposite side of the board.
• Sign and date the form and proceed to HVLT delayed memory testing.
To: Elana Farace, Ph.D
(fax) 717-531-0748

From:

Date:

Re: Neurocognitive Booklet Submission Form

Attention:
The 2 Neurocognitive booklets have been sent to you via mail, as of _______________________________ (date).

Contact Information: ________________________________________________________________

Person administering test: __________________________________________________________

Name of site: _________________________________________________________________

Phone: ________________________________________________________________

Email: ________________________________________________________________
Attention OSU Clerk:

Booklets Order Form

Title: 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

<table>
<thead>
<tr>
<th>Booklets needed</th>
<th>Amount requested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fact BR Questionnaire</td>
<td></td>
</tr>
<tr>
<td>Neurocognitive Examiners Booklet</td>
<td></td>
</tr>
<tr>
<td>Neurocognitive Patient Completed Booklet</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total number of booklets needed:

Note to OSU clerk:

There are 3 different booklets for this study! Be sure to send the same amount of each booklet as requested by the site above.

Fax form to: 507-284-1902
Attention of NCCTG Operational Support Clerk

Requestor: _____________________________  Phone: _____________________________
Affiliate/Membership: _______________________/___________________________
Date: _____________________________
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 1 – July 6, 2007

Summary

Scientific Changes:
- Revisions made throughout protocol and the model consent form to allow for the use of pinless systems for Radiosurgery (SRS).
- Collection of additional baseline AEs added to Section 10.3.
- Information on the Data Monitoring Committees review of the protocol has been added to Section 16.0.
- Revisions to the Risks section of the model consent form.

Administrative/Editorial Changes:
- Personnel changes.
- Schema revised to comply with current NCCTG template standards.
- Editorial/administrative corrections to the following: CTSU Information, Index, Sections 4.0, 7.0, 8.0, 11.0, 15.0, 16.0, 18.0 and Appendix II and V.
- Revisions for clarification have been made to the following: Sections 6.0, 7.0, 8.0, 11.0, 13.0 and the model consent form.
- Corrections to web links were made to the following: Section 6.0.

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 1 and revised NCI version date.

The phone number for the NCCTG Study Chair has been updated as follows:

507/284-2511 3559

NCI Version Date has been updated.

A new page 2 title page has been added in order to reflect the Co-chairs and their respective cooperative groups who will be sponsoring this study on CTSU.

**ECOG**
Co-chair: Lawrence Kleinberg, M.D.

**RTOG**
Co-chair: Anthony L. Asher, M.D.
**Protocol Resource Page**

Page 3: Sara M. Braun replaces Lori K. Bratvold as the NCCTG Protocol Development Coordinator.

Email addresses have been added for the NCCTG Research Base Nurse and the NCCTG Member Nurse as follows:

Marcia Salayi  
NCCTG Research Base Nurse  
Phone: 507-284-2459  
Email: salayi.marcia@mayo.edu

Beverly L. Kowbel  
NCCTG Member Nurse  
Phone: 306-766-2681  
Email: bev.kowbel@scf.sk.ca

**Cancer Trials Support Unit (CTSU) Address and Contact Information**

Page 4: The first sentence under the section “Patient Eligibility or Treatment Related Questions” has been corrected as follows:

Contact the NCCTG Quality Control Specialist (listed under NCCTG Contacts below on page 3).

**Index Page**

Page 5: Title of Appendix VI revised as follows to match form:

Neurocognitive Evaluations Booklet Submission Fax Form

The following appendix is in the forms packet so it has been removed from the protocol appendices:

Appendix VII—Neurocognitive Booklet Order Form

Title of Appendix IX revised as follows to clarify that the appendix contains the Neurocognitive examiners booklets and the Patient completed booklets:

Neurocognitive Practice Forms (Neurocognitive Examiners and Patient Completed booklets)
The following revisions have been made to the schema in order to comply with our current templates:

**Schema**

*In the event of progressive brain metastases the patient remains in observation (see Section 13.31).*
**Section 3.0**  
**Patient Eligibility**

Page 12: Link corrected for Section 3.116 as follows:

https://ncctg.mayo.edu/ncctg/forms/NonProtocolSpecificForms/
https://ncctg.mayo.edu/ncctg/forms/NonProtocolSpecificForms/

Section 3.118 is newly added for clarification as follows:

SRS facility is RPC approved (see Section 6.1).

Page 13: New Section 3.127 has been added for clarification as follows and all remaining section have been renumbered:

Planned chemotherapy during the SRS and WBRT.

**Section 4.0**  
**Test Schedule**

Page 14: The following corrections have been made to the first row under “Physical:”

- The first column now reads “History and exam, weight, ECOG performance status.”
- Reference to footnote 7 has been moved from the first column to the column “≤21 days prior to pre-reg.”

The “Height” row has been deleted from the test schedule per Dr. Brown’s request.

Under the column “≤7 days prior to randomization” an X with a reference to footnote 4 has been added to the row for “MRI brain scans.”

Footnote #7 has been corrected as follows:

All standard tumor-staging procedures necessary to define baseline extracranial disease status (as deemed appropriate by the investigator treating oncology physician) completed ≤42 days prior to pre-registration.

**Section 6.0**  
**Randomization Procedures (NCCTG members)**

Page 15: The second sentence in the first paragraph of the third bullet in Section 6.1 has been corrected as follows:

This training is found on the NCCTG website, at https://ncctg.mayo.edu/ncctg/group/ under “Disciplines,” then under the “CRA page.”
Page 16: The following note has been added to the end of Section 6.1 to insure clarity of the certification requirements for Neurocognitive testing:

Notes:

- An individual certification does not certify an entire institution. If more than one individual wants to administer the Neurocognitive test, each individual must be certified.

- The individual registering the patient does not have to complete the neurocognitive credentialing component unless they intend to be an examiner HOWEVER patients cannot be registered to the study until at minimum one person from the institution is approved for credentialing.

Page 16: Section 6.29 has been revised as follows to delete reference to the price of the peg boards and to add a statement that if a site has a psychology department, they are allowed to use their peg boards:

Grooved peg board available for Neurocognitive testing.

(These peg boards can be purchased for approximately $105.00 at the following web addresses:

http://www.ausmed.com/medecat/rs/ecatalog/details.asp?productid=10225A
http://www.rehaboutlet.com/dexterity_hand_eye_coordination_tests.htm)

NOTE: If site has a psychology department, they may use their peg boards and not have to purchase them.

Page 17: Section 6.33 has been deleted as follows and remaining sections renumbered as this statement is already located in Section 6.31:

Upon completion of the patient’s planning MRI, the treating location will randomize the patient to the study as instructed by the NCCTG Randomization Center.

Section 7.0 Protocol Treatment
Page 17: The note at the end of section 7.3 has been deleted and the information is now in Section 7.13:

7.13 Chemotherapy is not allowed during the SRS and WBRT.

The following opening statement has been added to Section 7.2 to clarify which facilities may be used for radiosurgery:

Radiosurgery for patients on this protocol can only be performed at RPC approved facilities. See protocol section 6.1 for details.
Page 18: The following new statement has been added to Section 7.221 to clarify that pinless systems may now be included in this protocol:

Modality: Gamma knife or X-rays with nominal energy of 4 megavoltage (MV) or greater for accelerator-based treatments, including mini-multi-leaf technology or linear accelerators mounted on robotic arms utilizing skull tracking software.

Page 20: The following opening statement has been added to Section 7.3 to clarify which facilities may be used for radiation therapy:

*Radiation therapy for patients on this protocol can only be delivered at facilities which are approved by your cooperative group.*

Page 20: A typographical error has been corrected in the “Note” statement in Section 7.3 as follows:

*Note: For patients randomized to Arm B: SRS and WBRT, the initiation of WBRT is ≤14 days following SRS.*

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

Page 21: The opening statement and first paragraph of Section 8.1 has been revised for clarification as follows:

8.1 Quality of Life (QOL) Booklet – FACT-BR

Please note it is necessary that sites have booklets on hand prior to putting any patients on study. Sites cannot use copies of Appendix IV in place of the QOL Booklet. See Appendix VII the forms packet for booklet order form to order booklets.

The contact information in Section 8.1 has been updated as follows:

**NCCTG Operations Office**
NCCTG Neuro Quality Control Specialist
Cancer Center Statistics
RO_FF_03_24-CC/NW Clinic
200 First Street SW
Rochester, MN  55905

The first sentence of Section 8.2 has been revised for clarification as follows:

Prior to intervention and at the beginning of each scheduled study visit, the study doctor *treating physician* or his/her authorized designee…
Page 22: The contact information in Section 8.2 has been updated as follows:

**NCCTG Operations Office**
NCCTG Neuro Quality Control Specialist
**Cancer Center Statistics**
**RO_FF_03_24-CC/NW Clinic**
200 First Street SW
Rochester, MN 55905

The opening statement of Section 8.3 has been revised for clarification as follows:

8.3 Neurocognitive Status **Tests**

Page 22: The second sentence in the “Note” paragraph in Section 8.31 has been revised for clarification as follows:

Although selection of the form is at the discretion of the investigator treating physician, it is recommended for convenience and consistency that Form 1 is used at baseline, Form 2 at second assessment (i.e. 6 weeks), Form 3 at third assessment (i.e. 3 months), etc.

Section 10.0 **Adverse Event (AE) Reporting and Monitoring**

Page 25: To allow for collection of additional baseline AEs, the table in Section 10.3 has been revised to add Xs under the “Baseline” column for Rash, Nausea, and Vomiting.

Footnote 1 located below the table in Section 10.3 has been deleted as follows as this does not apply to this study:

1. Hypersensitivity to the local anesthetic.

Section 11.0 **Treatment Evaluation/Imaging Guidelines**

Page 26: The second sentence in the first paragraph of Section 11.2 has been revised for clarification as follows:

The planning MRI brain scan will be used to determine final eligibility and used for planning the SRS treatment.

Section 11.3 has been revised for clarification as follows:

Patients will be monitored for clinical evidence of progression of neurological symptoms and treatment failure. Patients will be assessed with a physical and neurological examination and contrasted MRI brain scan at baseline (prior to randomization) and post-treatment at weeks 6, week and 12, months 6, month 9, month 12, month 16, month 24, month 36, 48, and at month 60. Follow-up is visits required +/- 14 days for visits weeks 6 and 12, +/- 1 month for visits months 6, 9, 12, and 16, and +/- 4 month for visits months 24, 36, 48, and 60. At each scheduled study visit, a QOL (FACT-BR) questionnaire, functional independence (Barthel ADL Index and ECOG performance status), and neurocognitive status tests will be completed.
Page 28: The contact information in Section 11.9 has been updated as follows:

NCCTG Operations Office
NCCTG Neuro Quality Control Specialist
Cancer Center Statistics
RO_FF_03_24-CC/NW Clinic
200 First Street SW
Rochester, MN  55905

The second sentence in the second to the last paragraph of Section 11.9 has been revised for clarification as follows:

These studies will be reviewed by the NCCTG PIs study chairs for final classification of disease progression versus radionecrosis.

Section 13.0 Treatment in the Event of Recurrent Cerebral Metastases
Page 28: The last sentence in Section 13.1 has been revised for clarification as follows:

At the discretion of the local investigator treating physician, the N0574 Study Chair should be contacted for guidance.

Section 15.0 Nursing Guidelines
Page 29: Section 15.111 has been revised as follows as this is also stated in Section 15.211:

Instruct patient regarding possible localized hair loss and redness and dryness of the scalp.

Section 15.114 has been added as a reminder for study nurses:

15.114 Remind all patients of the need to use adequate contraception throughout the study and for male patients for 3 months beyond study treatment.

Section 16.0 Statistical Considerations
Page 31: Typographical errors were corrected in the third sentence of Section 16.22 as follows:

We plan on an over accrual of 10%, i.e. 48 patients, to account for ineligible patients found on eligibility review, patient cancellations (patients who are registered but then withdraw prior to initiation of assigned treatment), and major protocol violations (violations that result in a drastically different treatment regimen than that prescribed by the protocol).

Page 31: Correct reference added to Section 16.23 as follows:

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 O'Brien-Fleming type stopping boundary (O'Brien, 1979 ref), truncated at –3.5.
Page 32: The first and second sentences in the first paragraph of Section 16.4 have been revised as follows:

The primary QOL objective is to ascertain at 3 months (12 weeks) post-treatment whether patients assigned to Arm 1 (SRS) have better QOL than patients on Arm 2 (SRS + WBRT).

The potential side effects of the additional WBRT treatment (e.g., fatigue, alopecia, cognitive decline, and diminished hearing) suggest the combination Arm 2 has worse will have reduced QOL.

Page 32: Editorial changes to Section 16.4, second, fourth, fifth and sixth paragraphs as follows:

The QOL will be assessed at baseline (prior to randomization), at weeks 6, 12, and at months 6, 9, 12, 16, 24, 36, 48, and 60 (essentially QOL will be obtained out to 5 years after the completion of the SRS treatment).

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.

The Quality-Adjusted Survival (QAS) analysis will adjust each patient’s time on study, by weighting neurological signs and symptoms (a variety of weighting schemes will be explored); the resultant weighted sum is defined as the patient’s QTIME. Subtracting the impact of AEs and re-treatment gives the QAS subtracting QAS value for each patient [Murray 1995]. The QAS values will be compared between treatment arms by the two-sample t-test.

Functional Independence: The duration of functional independence, where Barthel ADL Index score is maintained at or above baseline level, will be compared between treatment arms by the logrank test.

Page 33: Section 16.5. Editorial revision for clarification as follows:

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

A new Section 16.7 has been added in accordance with the requirements of the Data Monitoring Committee (DMC) as follows:

In accordance with NCI’s current DMC policy, the NCCTG External Data Monitoring Committee will meet every 6 months in conjunction with the NCCTG semi-annual group meetings to review the progress of this protocol.

A new section heading has been added before the ethnic table as follows:

16.8 Inclusion of Women and Minorities
Section 18.0 Records and Data Collection Procedures

Page 34: Section 18.1, a typographical correction has been made to the note above the table:
NCCTG RDC system has been changed to NCCTG RDE system.

Section 18.1, title of form revised as follows:
Neurocognitive Evaluation Booklet Submission Fax Form

Page 35: Section 18.1, the contact information in Footnote #1 and 1g have been updated as follows:
For patients who receive partial or complete radiation therapy, submit the following materials ≤14 days after the last day of radiation to the NCCTG Operations Office, Radiation Coordinator, Cancer Center Statistics RO_FF_03_24-CC/NW Clinic, 200 First Street SW, Rochester, MN  55905.

g. Copies of pre-registration and planning contrasted MRI brain scans
Note: When films are submitted on CD(s), they must include a viewing tool.

Section 18.1, the second sentence in Footnote #3 has been revised for clarification as follows:
Images on CDs are preferred to film but must be DICOM compatible with a viewing tool.

Appendix I Consent Form
Page 2: Under the “Radiosurgery (SRS)” section, the protocol has been revised to allow for use of either a pinless system or one using a head frame:

- The first sentence of the first paragraph now reads “Radiosurgery utilizes immobilization (a head frame or a soft plastic mask that forms to the shape of your face that helps hold the head in place during treatment) to allow very precise targeting of tumors.”
- The first sentence of the second paragraph now reads “If a head frame is used you will be given a local anesthesia to numb your skin and make it easier to position the special head frame.”
- The fifth sentence of the second paragraph now reads “You will be given a steroid medicine through a needle into a vein in your arm before the radiosurgery to prevent swelling.”
- A new third paragraph has been added and reads “If a facemask is used, this will be placed over your face to keep your head from moving during the procedure. During the procedure, they will also confirm the exact location that needs to be treated using x-rays. For most patients, the actual time on the radiosurgery treatment machine is in the range of 30 to 90 minutes. The facemask will be removed after the treatment.”
Under the “Whole Brain Radiation Therapy” section, the following revision has been made to the first paragraph, last sentence as requested by the Adult CIRB:

The treatment is painless and bloodless, and there is no danger of infection. No head frame is used for whole brain radiotherapy although a soft plastic mask that helps hold the head in place during treatment may be utilized.

Page 3: Under the section “What are the risks of the study”, the following paragraph was moved from below the risks and side effect table to above the tables and revised as requested by the Adult CIRB:

The above following listed of long-term side effects can occur with either treatment (SRS or WBRT) and the risks may be increased if the patient receives both SRS and WBRT (i.e. patients on Arm B).

Under the “Very Likely” column in the table for “Risks and Side Effects of Radiosurgery,” the following has been added as this risk was inadvertently omitted:

**Localized hair loss**

Under the “Less Likely” column in the table for “Risks and Side Effects of Radiosurgery” the last bullet has been updated as follows since all patients will not use a head frame:

- Bleeding and/or infection around the head frame *(if a head frame is used)*

Page 4: Under the “Less Likely” column in the table for “Risks and Side Effects of Whole Brain Radiation,” the risks have been updated to include the following:

- **Dry mouth**
- **Taste changes**
- **Temporary ear and ear canal redness**

Page 4 Under the “Reproductive risks” section, revised as follows for clarification:

Therefore, pregnant women may not participate in the study. If you are a woman who can become pregnant, a urine or blood pregnancy test will be done within 7 days prior to radiosurgery. *(Using if the pregnancy test is done using blood, approximately 1 teaspoon of blood will be drawn from a vein by needle-stick).*

*If you are a man,* the treatment used in this study could affect your sperm and could potentially harm a child that you may father while on this study.

Page 5: The first sentence of the last paragraph under the “WHAT OTHER OPTIONS ARE THERE” section has been revised for better readability as follows:

In addition, if after treatment, brain metastases recur come back or new brain metastases develop, all of the above treatment options may be available for you.

The second sentence of the second paragraph under the “WHAT ABOUT CONFIDENTIALITY” section has been clarified as follows:

This is to ensure that no one will be able to tell that you took part in this study.
The bullet items under the “WHAT ABOUT CONFIDENTIALITY” section have been revised for better readability as follows:

- North Central Cancer Treatment Group (NCCTG);
- the Radiological Physics Center (RPC);
- the Local Institutional Review Board (IRB), a group of people who review the research study to protect your rights; and
- government agencies including the Office for Human Research Protections (OHRP) and the National Cancer Institute (NCI).
- the Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials.

The second sentence in the first paragraph of the “WHAT ARE THE COSTS” section has been expanded for clarification as follows:

Some health plans will not pay these costs for people taking part in research studies.

Under the section “WHAT ARE MY RIGHTS AS A PARTICIPANT”, the following revision was made as requested by the Adult CIRB:

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.
Appendix II  CANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES

Page 2: Information on purchasing the grooved peg board is no longer valid. Appendix II has been revised to remove out of date information and add a reference to the main protocol for the correct information as follows:

A grooved peg board must be available for neurocognitive testing. Please refer to Section 6.29 of the protocol for more information.

These peg boards can be purchased for approximately $105.00 at the following web address:

http://www.ausmed.com/medecat/rs/ecatalog/details.asp?productid=10225A

The following additional notes were added directly below the peg board note as requested by CTSU.

An individual certification does not certify an entire institution. If more than one individual wants to administer the Neurocognitive test, each individual must be certified.

The individual registering the patient does not have to complete the neurocognitive credentialing component unless they intend to be an examiner HOWEVER patients cannot be registered to the study until at minimum one person from the institution is approved for credentialing.

Page 3: Under CTSU Procedures for Patient Pre-Registration (Step 1), the following changes were made as requested by CTSU:

IMPORTANT: In order to allow ample processing time at the NCCTG Randomization Office, the CTSU patient registrars can only perform N0574 pre-registrations and randomizations during the hours of 9:00 a.m. to 4:00 p.m. Eastern Time.

Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 7:00 p.m., Mon-Fri, Eastern Time (excluding holidays).
Under **CTSU Procedures for Patient Randomization (Step 2)**, the following note was revised as requested by CTSU

**IMPORTANT:** Note that the CTSU Patient Registrar can only randomize patients during NCCTG’s Randomization Office hours (8:00 a.m. to 4:30 p.m. Central Time). In order to allow ample processing time at the NCCTG Randomization Office, the CTSU patient registrars can only perform N0574 pre-registrations and randomizations during the hours of 9:00 a.m. to 4:00 p.m. Eastern Time.

**Appendix V Administration of Neurocognitive Evaluations Instructions**

Page 1: The opening note statement has been revised for clarification as follows:

Note: The following material is the script taken directly from the online training needed for this protocol. This is to be used as a guidance tool for sites to use during the evaluations.

Page 2: The first and second paragraphs under “Test forms” have been revised to reference the appendix for the Neurocognitive Patient Completed Booklet as follows:

For the neurocognitive testing, the examiner should use the Neurocognitive Examiners Booklet (sample copy in Appendix IX), the Neurocognitive Patient Completed Booklet (Appendix VIII), as well as, the Administration of Neurocognitive Evaluations Instructions (Appendix V).

It is very important that the person administering the neurocognitive tests fax in a completed Neurocognitive checklist Booklet Submission Fax Form (Appendix VI) indicating who administered the tests with the appropriate contact information.
Appendix VI  Neurocognitive Booklet Submission Form
Page 1: Title revised and moved to top of page as follows:

Neurocognitive Booklet Evaluation Submission Form

Additional editorial/administrative changes:
- Added: Fax completed form to:
- Changed: To—Elana Farace, Ph.D.
- Changed: (Fax) # 717-531-0748
- Changed: Re: Neurocognitive Booklet Submission Form
- Changed: Attention: The 2 Neurocognitive booklets (Examiners and Patient completed) have been sent to you via surface mail, as of _________________(date).
- Added: Patient’s study ID #:

Appendix VII  Neurocognitive Booklet Order Form

The Booklet order form is contained in the forms packet and therefore has been removed from the appendices.
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:

<table>
<thead>
<tr>
<th>Neurocognitive Testing</th>
<th>Elana Farace, Ph.D.</th>
<th>Phone: 717-531-4152</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Associate Professor of Neurosurgery and Public Health Evaluation Sciences</td>
<td>Fax: 717-531-0748</td>
</tr>
<tr>
<td></td>
<td>Email: <a href="mailto:farace@psu.edu">farace@psu.edu</a></td>
<td>Email: <a href="mailto:efarace@hmc.psu.edu">efarace@hmc.psu.edu</a></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Cancer Trials Support Unit (CTSU) Address and Contact Information

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

<table>
<thead>
<tr>
<th>To Mail Forms or Data</th>
<th>Westat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CTSU Data Operations Center</td>
</tr>
<tr>
<td></td>
<td>1441 W. Montgomery Avenue</td>
</tr>
<tr>
<td></td>
<td>Rockville, MD 20850-2062</td>
</tr>
<tr>
<td></td>
<td>NCCTG Operations Office</td>
</tr>
<tr>
<td></td>
<td>Northwest Clinic, 3rd Floor</td>
</tr>
<tr>
<td></td>
<td>Mayo Clinic</td>
</tr>
<tr>
<td></td>
<td>200 First St SW</td>
</tr>
<tr>
<td></td>
<td>Rochester MN 55905</td>
</tr>
<tr>
<td></td>
<td>Please do not submit study data or forms to</td>
</tr>
<tr>
<td></td>
<td>CTSU Data Operations. Do not copy the CTSU</td>
</tr>
<tr>
<td></td>
<td>on data submissions</td>
</tr>
</tbody>
</table>

| All Other Questions For questions unrelated to patient     | CTSU General Information Line – 1-888-823- |
| eligibility, treatment, or data submission:                | 5923                                         |
|                                                            | or ctsucontact@westat.com. All calls and    |
|                                                            | correspondence will be triaged to the       |
|                                                            | appropriate CTSU representative.           |
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.ctsu.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 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.

<table>
<thead>
<tr>
<th>Time (proportion of expected events)</th>
<th>Stopping boundaries</th>
<th>Nominal boundary probabilities</th>
<th>Cumulative type I/II error</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>-3.5</td>
<td>0.000231/0.94</td>
<td>0.0002309/0</td>
</tr>
<tr>
<td></td>
<td>3.75/1.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.50</td>
<td>-</td>
<td>0.0055/0.46</td>
<td>0.0056/0.02</td>
</tr>
<tr>
<td></td>
<td>2.54/0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.75</td>
<td>2.02/1.02</td>
<td>0.022/0.15</td>
<td>0.024/0.057</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.00</td>
<td>1.72/1.72</td>
<td>0.043/0.43</td>
<td>0.050/0.10</td>
</tr>
</tbody>
</table>

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 DMSB 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 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: Submit 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.
Addendum 3 – October 24, 2008

Summary

- The goals for the study have been revised to have a neurocognitive endpoint.

- Evidence of systemic progression has been removed as a contraindication for patient eligibility.

- Protocol and forms have been revised to capture disease progression and to more clearly indicate these forms need to continue to be completed after progression.

- The Statistical section (Section 16) has been revised to correlate with changes to the goals of the study and changes in the total number of participants.

- Administrative/editorial changes

A replacement protocol is provided. Please replace the current copy with the one attached. Please keep this update with your protocol. Note: for sites participating through NCCTG, replacement pages are provided. Please incorporate into the protocol and keep this update with your protocol.

Title page Updated to reflect the addition of Addendum 3 and a revised NCI version date.

NCCTG Contact Information
Page 3: The following personnel has been added as a contact for questions regarding protocol document or regulatory issues:

Patricia A. Aggen
NCCTG Research Base Protocol Coordinator
Phone: 507/538-6232
Fax: 507/284-5280
E-mail: aggen.patricia@mayo.edu
Page 3  Wanda DeKrey has replaced Beverly Kowbel as the NCCTG Member Nurse:

Beverly L. Kowbel  Wanda DeKrey, R.N., OCN
NCCTG Member Nurse
Phone:  306-766-2681/780-6520
Email:  bev.kowbel@skef.sk.ca  wdekrey@altru.org

Schema
Page 7  Footnote at bottom of paged revised as follows:

*In the event of progressive brain metastases or systemic progression the patient remains in observation (see Section 13.31).

Section 2.0  Goals
Page 12  In section 2.1, the primary goal of the study has been revised. Before reviewing these changes it is important to recognize the “history” of this trial. N0574 is a continuation of the ACOSOG trial Z0300, which was closed by ACOSOG leadership in 2004. The trial as originally designed for ACOSOG had a primary neurocognitive endpoint. However at that time there was not comfort with a neurocognitive endpoint and the CTEP reviewers rightfully insisted on a survival endpoint. However since that time with publication of other trials it is now recognized that a survival question is not clinically relevant with the high death rate due to systemic disease and new level I evidence that suggests even a significant improvement in brain control has little impact on survival [Aoyama 2006]. In addition there is now greater appreciation of neurocognitive progression as a valid endpoint and the Food and Drug Administration now considers improvement in neurocognitive function or delay in expected decline approved endpoints in registration trials, since these endpoints directly relate to clinical benefit. Therefore with this information at hand and after extensive discussions with NCI leadership (Drs. Jeff Abrams and Larry Rubinstein) the primary study objective will be modified to a neurocognitive endpoint to assess whether patients randomized to receive SRS (Arm A) will experience less neurocognitive progression than patients randomized to receive SRS + WBRT (Arm B). The changes to the protocol are as follows

2.11  To ascertain in patients with one to three brain metastases whether there is equal (or better) overall survival neurocognitive progression at 3 months post-radiosurgery in patients who receive SRS alone (Arm A) compared to patients who receive SRS combined with WBRT (Arm B).

Page 13  In section 2.2, the following secondary goal has been added:

2.26  To compare in patients with one to three brain metastases the overall survival in patients who receive SRS alone (Arm A) compared to patients who receive SRS combined with WBRT (Arm B).
Section 3.0 Patient Eligibility
Page 13
Section 3.111 has been revised for clarification:

3.111 One to three presumed brain metastases from a **pathologically histologically** confirmed extra-cerebral tumor site (e.g. lung, breast, prostate, etc.). The **pathologic histologic** confirmation may have been from the primary tumor site, from another metastatic site (e.g. an osseous metastasis, adrenal metastasis, etc.), or from the metastatic brain lesion(s).

**NOTE:** Each lesion …….. ≤28 days prior to randomization (see *Magnetic Resonance Imaging (MRI) Guidelines* section 11.2).

Page 14
Section 3.129c has been removed as a pre-registration contraindication, as it has been a major point of confusion and is significantly hindering accrual of patients who would otherwise be potential candidates for the study. In addition this eligibility criteria was not part of the original protocol with ACOSOG and was only added later when NCCTG became lead for this protocol.

3.129c — Clinical or radiographical evidence of systemic progression (other than the study lesion(s), i.e. other than the brain metastases) within one month prior to randomization

The following note has been added to Section 3.131 for clarification.

**NOTE:** The pre-registration MRI scan may be used for the planning scan if obtained ≤14 days prior to randomization.

Section 4.0 Test Schedule
Page 15
Located under the Test Schedule, Footnotes 2, 4 and 5 have been revised for clarification as follows:

2 Pre-registration contrasted MRI brain scans must be obtained ≤28 days prior to randomization.

4 Randomization is ≤14 days after pre-registration (with planning MRI scan obtained the same day as randomization). For the vast majority of patients treatment will be delivered the same day as the planning scan and randomization. Follow-up will be based on the date the SRS treatment is completed. The **pre-registration MRI scan may be used for the planning scan if obtained ≤14 days prior to of randomization.**

5 Patients will continue to be followed per test schedule [even in the event of progressive disease (PD PROG)] until withdrawal, refusal, death or 5
years from randomization. In the event of PD in the brain or progression of systemic disease, an Event Monitoring Form should be completed but patient continues to be followed per the test schedule.

Section 6.0  Registration/Randomization Procedures (NCCTG members)
Page 16  The following informational note has been added to section 6.1:

Note: Individuals previously certified for the two phase III randomized motexafin gadolinium studies (e.g., the SMART trial for lung cancer brain metastases) do not need to be re-certified for this study but the certification worksheet from the original protocol for that individual must be faxed to Dr. Farace [(717) 531-0748] for documentation purposes (although reviewing the training video is highly recommended).

Pages 17, 18  In Sections 6.21 and 6.31, the name of the NCCTG Randomization Center has been updated to the NCCTG Registration Office.

Section 11.0  Treatment Evaluation/Imaging Guidelines
Page 27  In Section 11.2, the following note has been added at the end of this section for clarification purposes:

**NOTE:** The pre-registration MRI scan may be used for the planning scan if the minimum parameters for the planning MRI brain scan are met as outlined above.

Page 28  Section 11.4 has been revised as follows to correspond with primary endpoints of study:

11.4  Patients will be monitored for local recurrence, distant brain recurrence and progression until death or 5 years from study entry. **Patients will continue to be monitored after progression and should continue to complete study evaluations and should continue to be followed using the test schedule for observation (Section 4.0)**. Patients also will be monitored, whenever possible, for additional primaries and regional recurrence, with pathologic histological confirmation.

Section 13.0  Treatment in the Event of Recurrent Cerebral Metastases
Page 30  In Section 13.31, text has been added for clarification as follows:

13.31  Patients who have progressed will continue with evaluation as outlined under observation in Section 4.0. **An Event Monitoring Form must be completed to report progression in the brain or progression of systemic disease (see Section 18.0)**. However it is recommended to treat patients per Section 13.2.
Section 16.0 Statistical Considerations

The following statistical sections (Sections 16.1, 16.2, 16.3, 16.5 & 16.8) have been revised to correlate with the changes made to the goals of the study and number of participants.

Page 31

16.1 Introduction

This protocol is meant to be a continuation of the ACOSOG trial Z0300, which was closed by ACOSOG leadership as a result of the ACOSOG leadership restructuring following their Type 2 review in 2004. Since this is a continuation of the previous study, we have tried to make very few changes to the original protocol with regards to eligibility and treatment protocol so that we can include the 70 patients who have already been accrued by Z0300. Most of the changes are the result of switching from ACOSOG forms and formats to NCCTG forms and formats—no substantial changes have been made to the original study design and analysis plans. However it is recognized that a survival question is not clinically relevant with the high death rate due to systemic disease and new level I evidence that suggests even a significant improvement in brain control has little impact on survival [Aoyama, 2006]. In addition there is now greater appreciation of neurocognitive progression as a valid endpoint and the Food and Drug Administration now considers improvement in neurocognitive function or delay in expected decline approved endpoints in registration trials, since these endpoints directly relate to clinical benefit.

Therefore the primary study objective is to assess whether patients randomized to receive SRS (Arm A) will experience equal (or less better) neurocognitive progression survival than patients randomized to receive SRS + WBRT (Arm B).

16.2 Primary Endpoint

The putative six-month survival for patients receiving SRS + WBRT is approximately 60%. The annual hazard rate associated with this outcome is 1.022 (based on exponential distribution assumptions). If it is demonstrated that patients receiving SRS alone experience six-month survival lower than that of patients receiving SRS + WBRT by 10 points or more on the percent scale (that is, six-month survival of 50% or less), then the modalities will not be considered equivalent with respect to survival. This lower bound for six-month survival among patients
receiving SRS alone implies a test criterion hazard ratio (SRS divided by SRS + WBRT) of 1.33. Specifically, the study hypotheses are as follows: Let \( \lambda_1 \) designate the hazard rate for patients receiving SRS + WBRT, and let \( \lambda_2 \) designate the hazard rate for patients receiving SRS. We will test 

\[
H_0: \frac{\lambda_2}{\lambda_1} \geq 1.33 \text{ versus the alternative hypothesis } H_a: \frac{\lambda_2}{\lambda_1} < 1.33
\]

The neurocognitive primary endpoint is neurocognitive progression. Neurocognitive progression would be defined as a drop of at least one standard deviation from baseline in one of the five neurocognitive tests (all tests are standardized based on published norms) at the 3 month post-radiosurgery evaluation. In our primary analysis, we will only use evaluable patients, those who have survived for at least 3 months and undergone neurocognitive testing. Our power analyses reveal that the total accrual necessary for this neurocognitive endpoint would be 162 patients to have 120 evaluable (alive and able to do the neuropsychological assessments) patients would be needed for evaluation at the 3-month follow-up. Therefore by utilizing a neurocognitive endpoint as the primary endpoint, the required accrual to answer this important question would be 162 patients as compared to 458 to answer a survival primary endpoint.

Based on the literature, we assume that the proportion of patients with neurocognitive progression at the 3 month post-radiosurgery evaluation is 0.65 for patients undergoing SRS + WBRT (Arm B) [Li, 2007]. Our study is designed to ascertain if this proportion decreases for patients undergoing SRS alone (Arm A).

The primary analysis for neurocognitive progression survival (the primary outcome) will be a test of differences in the (binomial) proportion of patients who experienced neurocognitive progression within 3 months post-radiosurgery.

by randomized arm using the stratified logrank test. The stratification factors to be used will be those used in implementing the randomization scheme.

Page 31

16.21 Power
A type I error probability of 0.10 (two-sided) and desired power \( \geq 90\% \) is specified. Study size computations are based on the randomization to the arms with equal probability, the assumed baseline (SRS + WBRT) proportion of neurocognitive progression is 0.65 and the clinically consequential difference is an absolute decrease in that proportion of 0.25 (i.e. the proportion for the SRS arm will be 0.40 or less).

hazard rate given, the clinically consequential difference specified, and an assumed accrual rate of approximately 96 eligible patients
per year. A waiting period of 0.5 years following the completion of accrual and the final analysis is specified.

Using these assumptions, it is computed that an accrual period of five years is necessary [Rubinstein 1981]. The number of eligible patients required is 480.

It is our intent to include the 70 patients that have been accrued by Z0300 in our analysis. Based on the given parameters for the power calculation, this protocol requires a total of 112480 eligible evaluable patients (i.e. 56 patients in each arm) randomized equally between the two study arms (SRS versus SRS + WBRT). We plan on an over accrual of 35%, i.e. 4048 patients, to account for those patients that are not evaluable due to their not completing a neurocognitive evaluation at 3 months (due to death, patient refusal, etc.), ineligible patients found on eligibility review, patient cancellations (patients who are registered but then withdraw prior to initiation of assigned treatment), and major protocol violations (violations that result in a drastically different treatment regimen than that prescribed by the protocol). This results in a total target enrollment sample size of 480 + 4048 = 152528 patients. This is expected to yield the necessary 480 eligible patients. Since 70 patients have already been accrued through Z0300, this protocol anticipates enrolling a total of 528 – 70 = 458 patients. Assuming 96 accrual per year, it is anticipated that the accrual period will be completed in under 5 years and final analysis will begin 5.5 years after this protocol is first opened for accrual.

Three One formal interim analyses will be performed at the time at which 25%, 50%, and 75% of the projected total number of events have occurred. Patients have been evaluated for neurocognitive function at three months post-radiosurgery using two-sided O'Brien-Fleming type stopping boundary (O'Brien, 1979). 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.
### 16.3 Secondary Endpoints and Analysis

Secondary endpoints to be examined include **overall survival**, time to CNS failure and various QOL and related endpoints described in this protocol. If **non-inferiority** the **superiority** of SRS (compared to SRS + WBRT) with respect to **neurocognitive progression** survival is **has not been** established, then treatment preference may be determined by these other factors.

A low incidence of local failure has been achieved with the use of SRS + WBRT relative to WBRT alone or WBRT alone relative to surgery only [Kondziolka 1999]. Analyses will be performed to determine if CNS failure is unacceptably high for patients receiving SRS alone.

Finally, we will also conduct an analysis of the **primary overall survival** endpoint using a **stratified log-rank test as well as** Cox proportional hazards models that incorporate the stratification factors and adjust for other important prognostic factors such as location of primary tumor (e.g. lung, breast, etc.).

### 16.5 Neurocognitive Status

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 Data Monitoring Committee (DMC) will determine appropriate actions. The study team will request of the DMC that the results of this interim analysis be released.

Page 34

16.8 Inclusion of Women and Minorities

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Females</th>
<th>Males</th>
<th>Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic or Latino</td>
<td>02</td>
<td>24</td>
<td></td>
<td>22</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>15646</td>
<td>366104</td>
<td></td>
<td>52150</td>
</tr>
<tr>
<td>Ethnic Category: Total of all subjects*</td>
<td>15846</td>
<td>370106</td>
<td></td>
<td>528152</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Racial Category</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian or Alaskan Native</td>
<td>04</td>
<td>32</td>
<td></td>
<td>42</td>
</tr>
<tr>
<td>Asian</td>
<td>20</td>
<td>42</td>
<td></td>
<td>62</td>
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<td>Black or African American</td>
<td>474</td>
<td>3410</td>
<td></td>
<td>5114</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>40</td>
<td>1</td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>White</td>
<td>13839</td>
<td>32794</td>
<td></td>
<td>465133</td>
</tr>
<tr>
<td>Racial Category: Total of all subjects</td>
<td>15943</td>
<td>369109</td>
<td></td>
<td>152528</td>
</tr>
</tbody>
</table>

Section 18.0 Records and Data Collection Procedures

Page 35

A column was added in the Submission Timetable, under “Event Monitoring² (Completion of Active Monitoring Phase)” entitled “At PD only” with a corresponding X in the “Event Monitoring Form” row for clarification as follows:

<table>
<thead>
<tr>
<th>Forms</th>
<th>Active-Monitoring Phase (Compliance with Test Schedule)</th>
<th>Event-Monitoring ² (Completion of Active-Monitoring Phase)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial Material</td>
<td>Follow-up material</td>
</tr>
<tr>
<td>Pre-reg ≤2 weeks after reg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At end of treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At each evaluation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On-Study Form</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Screening Failure Form’</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Baseline Adverse Events/Symptoms</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>OP and Path Reports</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Measurement Form</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>RT material’</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response review material’</td>
<td>X’</td>
<td></td>
</tr>
<tr>
<td>Event-Monitoring Form</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[^{11}X\text{'}\]
Footnote 1c has been revised for clarification as follows:

c. Daily treatment records (Arm B only).

Footnote 1g and “note” at end of footnote 1 have been revised for clarification as follows:

g. Copies of pre-registration and planning contrasted MRI brain scans. Separate copies of the CD must be sent to the Radiation Coordinator and the Neuro Quality Control Specialist. Note: When films images are submitted on CD(s), they must include a viewing tool.

Footnote 3 has been revised for clarification as follows:

3. Both NCCTG and CTSU Sites submit the following to NCCTG Operations Office, Neuro Quality Control Specialist, RO_FF_03_24-CC/NW Clinic, 200 First Street SW, Rochester, MN 55905:

Submit the reports AND the following radiographic images free of marks that may obscure the lesions or bias the evaluation of the independent reviewer(s). Images on CDs are preferred to film but must be DICOM compatible with a viewing tool. The radiographic images must be identified with the NCCTG study number of N0574 and the assigned patient identification number. The radiographic images must be identified with the date the image was performed and the corresponding time point in the study (i.e. W-6, W-12, M-9 or M-24). See Section 11.9 for additional details.

a. Pre-registration and planning MRIs and reports (reports may not be available with planning scans but if available should be submitted). Separate copies of the CD must be sent to the Radiation Coordinator and the Neuro Quality Control Specialist.

Footnote 11 has been added for clarification as follows:

11. The Event Monitoring Form is required during the observation phase to report PD only. After reporting disease progression, patient should continue to be followed using the test schedule for observation (Section 4.0) and continue completing routine cycle forms.
Section 20.0 References

Page 37

The following references have been added:

<table>
<thead>
<tr>
<th>Author</th>
<th>Title</th>
<th>Source Details</th>
</tr>
</thead>
</table>

The following references have been removed:

<table>
<thead>
<tr>
<th>Author</th>
<th>Title</th>
<th>Source Details</th>
</tr>
</thead>
</table>

Appendix I Consent Form

Pages 1-4 of 8

Throughout the Consent Form references to “arm” have been changed to group to avoid confusion for the patient.

Page 1 of 8

Under “Why is this study being done?”, the following revisions have been made as recommended by the CIRB Continuing Review Committee:

- The purpose of this research study is to compare overall survival and to compare the effects (good and bad) of stereotactic radiosurgery (SRS) to stereotactic radiosurgery plus whole brain radiation therapy (WBRT) on you and your brain metastases.
- There may be microscopic tumor deposits that are not yet visible on imaging (the MRI scan) that may appear at some point in the future. This research study is being done to find out if adding WBRT to stereotactic radiosurgery (SRS) will offer any additional benefit to receiving stereotactic radiosurgery SRS alone in treating these possible microscopic tumor deposits in the brain since it is not known whether more treatment will be better or worse.

Page 1 of 8

Under “How many people will take part in this study?” the following revision has been made:

About 152,528 people will take part in this study.
Page 4 of 8

In the paragraph below, radiosurgery has been replaced with randomization to be consistent with Section 4 of the protocol and references to “arm” have been changed to “group”.

Reproductive risks: Being a part of this study while pregnant may expose the unborn child to significant risks. Therefore, pregnant women may not participate in the study. If you are a woman who can become pregnant, a urine or blood pregnancy test will be done within 7 days prior to radiosurgery randomization.

Appendix II

**Cancer Trials Support Unit (CTSU) Participation Procedures**

Under “CTSU Procedures for Patient Pre-Registration (Step 1)” and “CTSU Procedures for Patient Randomization (Step 2)” the NCCTG Randomization Center has been updated to NCCTG Registration Office.
North Central Cancer Treatment Group

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

Addendum 4 – March 25, 2011

Summary

- Contact Information for the Study Chair has been revised and placed below Dr. Brown’s name at the top of the page
- Contact information for Research Base Data Management Specialist has been removed
- Per NCI, the Secondary AML/MDS Report Form will no longer be used. Therefore, Sections 10.0 and 18.0 have been revised accordingly.
- Section 16.22 target accrual has been changed to reflect the observed rate of evaluable patients.
- Section 16.8 table has been adjusted due to changes in target accrual

Administrative/editorial changes

A replacement protocol is provided. Please replace the current copy with the one attached. Please keep this update with your protocol. Note: for sites participating through NCCTG, replacement pages are provided. Please incorporate into the protocol and keep this update with your protocol.

Title page

Dr. Paul Brown’s contact information has been revised with current contact information, as follows:

- Mayo Clinic
  - 200 First Street, SW
  - Rochester, MN 55905
  - 507/284-3559 brown.paul@mayo.edu
  - 507/284-5280 (FAX)

- The University of Texas MD Anderson Cancer Center
  - 1515 Holcombe Blvd, Unit 97
  - Houston, TX 77030
  - 713/563-2415 PDBrown@mdanderson.org

- Updated to reflect the addition of Addendum 4 and a revised NCI version date.
NCCTG Contact Information
Page 3: Due to the changes with titles of the NCCTG contacts the following information has been modified:

Butch Kvittem
NCCTG Research Base Quality Control Assurance Specialist

Sara M. Braun
NCCTG Research Base Research Protocol Specialist Development Coordinator

Patricia A. Aggen
NCCTG Research Base Research Protocol Specialist Coordinator

The Research Base Data Management Specialist contact has been removed (Vicki Bryhn). Please contact the NCCTG Research Base Quality Assurance Specialist (QAS) for technical questions regarding electronic form entry.

Section 6.0 Registration/Randomization Procedures (NCCTG members)
Page 17: In Section 6.29 the first web link has been removed, as this link is no longer active. The following text has been removed:

Section 10.0 Adverse Event (AE) Reporting and Monitoring
Page 25: Bullet point 2 in Section 10.21 has been revised with current information regarding the AdEERS forms and contact information. Changes are as follows:

In the rare event when Internet connectivity is disrupted, a 24-hour notification is to be made to NCI by telephone at: 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper AdEERS forms have been removed from the CTEP website and will NO LONGER be accepted. A report may be prepared using the Adverse Event Expedited Report—Single Agent or Multiple Agents paper template (accessible from the CTEP Home Page at http://ctep.cancer.gov). Contact the NCCTG SAE Coordinator (as identified on the NCCTG Protocol Resources page) for back-up submission instructions.

With the removal of the Secondary AML/MDS Report Form, new Section 10.22 has been added for clarification and the remaining section (now 10.23) has been revised in the second column, as follows:
10.22 Additional Instructions or Exceptions

- SECONDARY MALIGNANCIES (defined as “cancer caused by treatment for a previous malignancy”, e.g., treatment with radiation or chemotherapy) are to be reported through AdEERS.
- Secondary malignancies are not considered metastasis of the initial neoplasm. Secondary malignancy is unrelated to the first cancer that was treated, and may occur months or even years after initial treatment.
- Second Primary malignancy (malignancy not due to prior treatment) should not be reported through AdEERS.

10.23 Other Required Expedited Reporting

<table>
<thead>
<tr>
<th>EVENT TYPE</th>
<th>REPORTING PROCEDURE</th>
</tr>
</thead>
</table>
| Secondary AML/MDS | Reporting for this event required during and after completion of study treatment, via AdEERS using CTCAE v3.0: Report Myelodysplasia as “Blood/Bone Marrow - Myelodysplasia” and Leukemias as “Blood/Bone Marrow - Other (Specify, __)”.
| Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report | NCCTG Institutions Only: Complete a Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form within 5 working days.
If an AdEERS report has been submitted, this form does not need to be submitted.
Fax or mail to the NCCTG SAE Coordinator, NCCTG Operations Office, 200 First Street SW, Rochester, MN 55905, Fax (507)284-9628.
You must use CTCAE v3.0 for data submission with this form. The events reported on this form must also appear on the Case Report Forms (i.e., routine data) for this study. |
Section 16.0  Statistical Considerations

Pages 31/32: Text has been revised in Section 16.22 due to a revision in target accrual. Changes are as follows:

It is our intent to include the 70 patients that have been accrued by Z0300 in our analysis. Based on the given parameters for the power calculation, this protocol requires a total of 112 evaluable patients (i.e. 56 patients in each arm). We had originally planned on an over accrual of 35%, i.e. 40 patients, to account for those patients that are not evaluable due to their not completing a neurocognitive evaluation at 3 months (due to death, patient refusal, etc.). However, the observed rate of patients, after accruing the 152 patients, was 47%, hence, the amount of over accrual has been increased to 112%, i.e. 126 patients. This results in a total target enrollment sample size of 112 + 40 = 152 patients. We anticipate pre-registering 310 patients to register a total of 238 patients necessary for the study design and allotted over accrual. In summary, for this protocol, we will accrue an additional 238 – 70 (those accrued from ACOSOG Z0300) = 168 patients.

Page 34: In Section 16.8 text has been revised due to a revision in target accrual, as follows:

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Sex/Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>0</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>72</td>
</tr>
<tr>
<td>Ethnic Category: Total of all subjects*</td>
<td>72</td>
</tr>
<tr>
<td>Racial Category</td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
</tr>
<tr>
<td>Black or African American</td>
<td>64</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>66</td>
</tr>
<tr>
<td>Racial Category: Total of all subjects</td>
<td>72</td>
</tr>
</tbody>
</table>

Section 18.0  Records and Data Collection Procedures

Page 35: With the removal of the Secondary AML/MDS Report form, the row “Secondary AML/MDS Report Form” has been removed.
Summary

- Contact information has been updated to the current contacts for “NCCTG Research Protocol Specialist” and the NCCTG Research Base Nurse”.
- Consent form has been adjusted due to changes in target accrual noted in Addendum 4
- Administrative/editorial changes

A replacement protocol is provided. Please replace the current copy with the one attached. Please keep this update with your protocol. Note: for sites participating through NCCTG, replacement pages are provided. Please incorporate into the protocol and keep this update with your protocol.

Title page
Updated to reflect Update 1 and revised NCI version date.

NCCTG Contact Information
Page 3 Sara Braun has been replaced by Sanna McKinzie as the contact for “NCCTG Research Protocol Specialist”. E-mail and phone contact have been updated accordingly.

Marcia Salayi has been replaced by TJ Scheffler Hanson as the contact for “NCCTG Research Base Nurse”. E-mail has been updated accordingly.

Appendix I Consent Form
Page 1 of 8 Due to the revised target accrual for Addendum 4 the question “How many people will take part in the study?” has been updated to the current number, as follows:

About 452 238 people will take part in this study.
North Central Cancer Treatment Group

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

Addendum 5 – October 21, 2011

Summary

- In compliance with the NCI/CTEP mandate (dated May 28, 2010), expedited adverse event reporting requirements were converted from CTCAE v3.0 to CTCAE v4.0 (affected sections 10.1 and 10.11) while routine data collection via Case Report Forms (which includes the Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form) will remain using CTCAE v3.0 (clarifications added to sections 10.23, 10.3, and 10.31). Effective October 1, 2011, expedited reporting via AdEERS must use CTCAE v4.0 while the remainder of the data collection for legacy trials will continue to use CTCAE v3.0.
- Administrative update.

A replacement protocol is provided. Please replace the current copy with the one attached. Please keep this addendum with your protocol. Note: for sites participating through NCCTG, replacement pages are provided. Please incorporate into the protocol and keep this addendum with your protocol.

Title page
Updated to reflect the addition of Addendum 5 and a revised NCI version date.

NCCTG Address and Contact Information
Page 3: Patricia A. Aggen has been removed as the NCCTG Research Base Protocol Specialist.

Section 10.0 Adverse Event (AE) Reporting and Monitoring
Page 24: Section 10.1 and Section 10.11 have been revised as follows to update the required AE reporting from CTCAE v3.0 to CTCAE v4.0:

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 for adverse event monitoring and reporting. The CTCAE v3.0 can be accessed from the CTEP home page http://ctep.cancer.gov. CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized until September 30, 2011. CTCAE version 4.0 will be utilized for expedited adverse event reporting only, beginning October 1, 2011. (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE v3.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).
10.11 Adverse event monitoring and reporting is a routine part of every clinical trial…

Expedited adverse event reporting requires submission of an Adverse Event Expedited Reporting System (AdEERS)…

Effective with Addendum 8, and beginning July 1, 2011, expedited AdEERS reporting for this protocol has been updated by the NCI/CTEP to use CTCAE v4.0. Therefore:

1) Events reporting expedited reporting through AdEERS must be reported through the AdEERS system in CTCAE v4.0.

2) The events reported via AdEERS must ALSO be reported through routine reporting (i.e., Case Report Forms) using CTCAE v3.0.

3) Routine data collection via Case Report Forms, including the “Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form,” will remain using CTCAE v3.0 for this study.

Page 24: The second column for Secondary AML/MDS in Section 10.23 has been revised for clarification as follows:

Reporting for this event required during and after completion of study treatment, via AdEERS using CTCAE v3.0: Report Myelodysplasia as “Blood/Bone Marrow – Myelodysplasia” and Leukemias as “Blood/Bone Marrow – Other (Specify, ___)”.

Beginning October 1, 2011, AdEERS will only accept CTCAE v4.0 for this study. Report these events using “Neoplasms benign, malignant and unspecified (incl. cysts and polyps)” and including the appropriate adverse event:
- Leukemia secondary to oncology chemotherapy OR
- Myelodysplastic syndrome OR
- Treatment related secondary malignancy

The second column for “Other Grade 4 or 5 Events…” section in Section 10.23 has been revised for clarification as follows:

Complete a Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form within 5 working days, using CTCAE v3.0, of the date the clinical research associate (CRA) is aware of the event(s) necessitating the form.

Page 25: Section 10.3 and Section 10.31 have been revised for clarification. In Section 10.3, the first column header in the table has added CTCAE v3.0 and Section 10.31 has been revised as follows:

Submit to the NCCTG Research Base via the Nadir/AE Log the following Aes using CTCAE v3.0 experienced by a patient and not specified in Section 10.3:
North Central Cancer Treatment Group

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

Update 2 – October 21, 2011

**Summary**

Administrative/editorial changes.

A replacement protocol is provided. Please replace the current copy with the one attached. Please keep this update with your protocol. Note: for sites participating through NCCTG, replacement pages are provided. Please incorporate into the protocol and keep this update with your protocol.

**Title page**

Updated to reflect Update 2 and revised NCI version date.

**Appendix II  Adverse Event (AE) Reporting**

Page 6: With Addendum 5, the CTCAE was converted from v3.0 to v4.0. All appropriate protocol sections were updated accordingly with the exception of Appendix II. Therefore, the first sentence on page 6 has now been updated as follows:

This study will utilize the CTCAE version 3.0 4.0 for toxicity and Adverse Event (AE) reporting.
NORTH CENTRAL CANCER TREATMENT GROUP

PROTOCOL UPDATE TO NCCTG N0574

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

Status Change:

X Eligibility changes

□ Therapy / Dose Modifications / Study Calendar changes

X Informed Consent changes

□ Scientific / Statistical Considerations changes

□ Data Submission / Forms changes

X Editorial / Administrative changes

□ Other :

UPDATES:

Title page (page 1):
- The sponsor’s name has been updated to reflect the newly formed Alliance.
- Instructions to contact study personnel listed on the Protocol Resources page have been added
- Contact information for study chairs Dr. Jaeckle, Dr Pollock and Dr Deming have been added.
- The document history has been updated to add Update 3.

Study Staff (page 2):
- Contact information for the study statistician, neuropsychology co-chair and cooperative group co-chairs has been added.

CTSU Address and Contact Information (page 3):
- The CTSU contact information template has been updated with the current version.

Protocol Resources (page 4):
- Carla Hilton has replaced Butch Kvitttem as Quality Assurance Specialist (QAS)
- Contact information for Dr. Farace has been removed as redundant to Study Staff on page 2
- The email address for T.J. Temperance Scheffler has been corrected to remove a spelling error.

Table of Contents (pages 5-8):
- A new Word generated Table of Contents has replaced the Index page.
• Former Appendix I the patient informed consent form has been permanently removed from the protocol and is now a separate stand-alone document as per FDA mandate. The appendices have been renumbered accordingly.
• Appendix I ECOG Performance Status has been newly added.
• Former Appendix II CTSU Logistics has been removed as the CTSU pre-registration and registration information has been moved to Section 6.0 Registration/Randomization Procedures.

Schema (page 9):
• Footnote 2 has been added to clarify Event Monitoring.

Section 3.0 Patient Eligibility (pages 15-17):
• Section 3.0 Eligibility Criteria has been renumbered for brevity and clarity.
• Section 3.17 Neurocognitive Testing Credentialing is newly added.
• Section 3.18 Written Informed Consent is newly added.
• Section 3.21 Pregnancy, Nursing and Contraception has been updated as per the NCCTG template and to be consistent with Section 15.0 to include nursing women and specifying contraception is to be used throughout the study and for men, three months after.
• Section 3.22 MRI Scans has been revised to clarify that patients must have the ability to have an MRI scan to be eligible for the study.
• Section 3.5 Inclusion of Women and Minorities is newly added.

Section 4.0 Test Schedule (pages 18-24):
• Section 4.0 table has been revised as follows:
  • Column 1 Row 2 has been revised to add the words ‘physical’, ‘including’ and ‘recording of medications’.
  • Column 1 row 5 has been revised to add ‘urine or serum’ to pregnancy test.
  • Column 1 rows 8-10 have been revised to add ‘Mandatory’.
• Section 4.1 Patient Quality of Life (QOL) Questionnaire Booklets has been moved from the prior Section 8.1 as Section 8 is Dosage Modification due to Adverse Events in the current NCCTG protocol template.
• Section 4.2 Functional Independence Form has been moved from the prior Section 8.2 as Section 8 is Dosage Modification due to Adverse Events in the current NCCTG protocol template.
• Section 4.3 Neurocognitive Status Tests has been moved from the prior Section 8.3 as Section 8 is Dosage Modification due to Adverse Events in the current NCCTG protocol template and from Section 6.1 as this requirement was at times unnoticed until the site was attempting to register a patient to the study.
• Section 4.4 SRS Credentialing, Section 4.41 SRS Questionnaire and Section 4.42 SRS Phantom Study have been moved from former Section 6 Registration/Randomization in the prior protocol version as this requirement was often unnoticed until the site was attempting to register a patient to the study.

Section 6.0 Registration/Randomization Procedures (pages 25-29):
• Sections 6.11 Investigator Registration, 6.12 Site Registration Requirements – IRB Approval, 6.13 Site Registration Requirements-RTFI Form Submission to CTSU, Section 6.213, Section 6.214, and Section 6.312 have been moved to Section 6 from the former Appendix II CTSU Logistics to consolidate registration information.

Section 10.0 Adverse Event (AE) Reporting and Monitoring (pages 34-41):
- Section 10.1 Adverse Event Descriptions and Grading Scales has been revised to update the CTEP website address for the CTCAE version 4.0
- Section 10.11 Adverse Event Monitoring has been updated to the current NCI and NCCTG templates
- Section 10.12 CTCAE and Grading is newly added as per the current NCI and NCCTG templates
- Section 10.2 Expected vs. Unexpected has been revised to redefine expected adverse events as those listed in Section 15.0
- Section 10.3 Assessment of Attribution has been revised to clarify a causal relation is suspected for attributions of ‘definite’, ‘probable’ and ‘possible’.
- Section 10.31 Special Situations for Expedited Reporting is newly added as per the current NCI and NCCTG templates
- Section 10.4 Expedited Reporting Requirements: Studies Using Commercial Agents ONLY is newly added as per the current NCI and NCCTG templates
- Section 10.5 Other Required Expedited Reporting has been revised to remove the Secondary AML/MDS Reporting as per the current NCI and NCCTG templates

**Section 13.0 Treatment/Follow-up Decision at Evaluation of Patient (pages 43-44):**
- Section 13.0 title has been revised from the former title ‘Treatment in the Event of Recurrent Cerebral Metastases’

**Section 14.0 Body Fluid Biospecimens (page 44):**
- Section 14.0 title has been revised from the former title ‘Translational/Pharmacological Studies’

**Section 15.0 Drug Information (pages 44-46):**
- Section 15.0 title has been revised from the former title ‘Nursing Guidelines’
- Section 15.11 Risks and Side Effects for SRS has been revised to update the risks for SRS to the current NCCTG Pharmacy template and NCCTG Nursing Guidelines template.
- Section 15.21 Risks and Side Effects for WBRT has been revised to update the risks for WBRT to the current NCCTG Pharmacy template and NCCTG Nursing Guidelines template.
- Section 15.227 is newly added as per the current NCCTG Nursing Guidelines template.

**Section 16.0 Statistical Considerations (pages 47-51):**
- Section 16.7 Data Safety Monitoring has been revised to change the responsible DSMB to the Alliance DSMB and CDUS language has been added.

**Section 18.0 Records and Data Collection Procedures (pages 52-56):**
Section 18.0 has been entirely reformatted; the intent of the original content remains unchanged.

**Section 19.0 Budget (page 56):**
Section 19.0 Budget has been revised to clarify that all tests, exams and procedures are charged to the patient and that there is no change for the questionnaire or neurocognitive testing materials.

**Section 20.0 References (pages 56-59):**
Section 20.0 References has been reformatted.

**Appendix I to Appendix VII (pages 60-74):**
- Former Appendix I the patient informed consent form has been permanently removed from the protocol and is now a separate stand-alone document as per FDA mandate. The appendices have been renumbered accordingly.
- Appendix I ECOG Performance Status has been newly added.
• Former Appendix II CTSU Logistics has been removed as the CTSU pre-registration and registration information has been moved to Section 6.0 Registration/Randomization Procedures.

Informed Patient Consent Form

• Template page (page 1):
  • The template page for the NCI model consent form has been added back to the consent form as it was previously removed in error.

• Title page (page 2):
  • The title page has been revised to add the first paragraph in bold italics, an introduction to the consent form.

• Section ‘Why have I been asked to take part in this research study?’ (page 2):
  • The header has been revised from the former header ‘Who is Conducting This Study?’
  • The last 4 paragraphs of the section have been added to clarify the purpose of the consent form and describe the eligibility tests.

• Section ‘Why is this research study being done?’ (page 2):
  • The purpose of the study has been clarified and the Alliance cooperative group has been defined.

• Section ‘What will happen if I take part in this research study?’ (pages 3-5):
  • The header has been revised from the former header ‘What is Involved in the Study?’
  • The required exams, tests and procedures have been described in greater detail.
  • The QOL questionnaires, Functional Independence Form and patient neurocognitive testing have all been specified as mandatory for this study.
  • Group 1 (Stereotactic Radiosurgery, SRS) has been revised to add information describing the possible use of a facemask.
  • The follow-up exams, tests and procedures required after treatment have been described in greater detail.

• Section ‘Can I Stop Being in the Research Study?’ (page 5):
  • The Section ‘Can I Stop Being in the Research Study?’ has been added.

• Section ‘What Side Effects or Risks Can I Expect From Being in the Research Study?’ (pages 5-7):
  • The header has been revised from the former header ‘What are the risks of the study?’
  • The risks for SRS ‘Headache’ and “Localized hair loss which may be permanent” has been moved from the Likely to the Less Likely category.
  • The Rare but Serious Risks for SRS have been revised as follows:
    • These risks have been removed: Vomiting; Seizures; Weakness, paralysis, loss of sensation; Loss of hearing; Difficulty with speech; Decreased mental abilities and Death.
    • These risks have been added: Decreased brain function such as motor function (coordination/movement); Swelling of the brain in the treated area which may require steroids; Severe local damage to or death of normal brain tissue, which may require surgery to remove; Hardening of the arteries in the brain which rarely may lead to strokes many years after Stereotactic Radiosurgery; A second
new cancer caused by radiation, in the brain or nearby organs which rarely may occur many years after Stereotactic Radiosurgery; Damage to vision tracts with the possibility of permanent blindness

- The risk for WBRT ‘Decreased brain function such as motor function (coordination/movement) has been moved from ‘Less Likely’ to ‘Rare but Serious’
- The Rare but Serious Risks for WBRT have been revised as follows:
  - These risks have been removed: Vomiting; Seizures; Weakness, paralysis, loss of sensation; Loss of hearing; Difficulty with speech; Decreased mental abilities and Death.
  - These risks have been added: Severe local damage to or death of normal brain tissue, which may require surgery to remove; Hardening of the arteries in the brain which rarely may lead to strokes many years after whole brain radiotherapy; A second new cancer caused by radiation, in the brain or nearby organs which rarely may occur many years after whole brain radiotherapy; Eye damage with the possibility of permanent blindness

**Section ‘What other choices do I have if I do not take part in the research study?’ (page 8):**
- The header has been revised from the former header ‘What Other Options Are There?’

**Section ‘Will my medical information be kept private?’ (page 8):**
- The header has been revised from the former header ‘What About Confidentiality?’
- The Alliance has been added to the list of organizations that may access medical records
- The Clinical Trials notification has been added per current FDA regulations
- A ‘Note to Informed Consent Authors’ has been added per current FDA regulations
- A ‘Note to Local Investigators’ has been added per current FDA regulations.

**Section ‘What are the costs of taking part in this research study?’ (page 9):**
- The header has been revised from the former header ‘What Are the Costs?’

**Section ‘What happens if I am injured because I took part in this research study?’ (page 9):**
- The Section ‘What happens if I am injured because I took part in this research study?’ is newly added

**Section ‘What are my rights if I take part in this research study?’ (page 9):**
- The header has been revised from the former header ‘What Are My Rights as a Participant?’

**Section ‘Who can answer my questions about the research study?’ (page 9):**
- The header has been revised from the former header ‘Whom Do I Call if I Have Questions or Problems?’

**Section ‘Where can I get more information?’ (page 10):**
- The TTY telephone number has been removed.
- The Spanish language NCI website address has been added.
A replacement protocol document has been issued.
Update 4
08/08/2013

NORTH CENTRAL CANCER TREATMENT GROUP

PROTOCOL UPDATE TO 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

Update: X

Eligibility changes
Therapy / Dose Modifications / Study Calendar changes
Informed Consent changes
Scientific / Statistical Considerations changes
Data Submission / Forms changes
Editorial / Administrative changes

Status Change:
Activation
Closure
Suspension / temporary closure
Reactivation

Other:

IRB review of this update is required within 90 days. Expedited review is allowed. Please follow your local IRB guidelines.

In keeping with the new CTEP PIO requirements for protocol submission, the model consent document has been separated out from the protocol document. The content on the protocol update cover page matches the content of the model consent cover page.

The entire protocol has been modified to fit newly implemented CTEP document submission policies.

CHANGES TO THE PROTOCOL:

Study Staff:
- Under Neuropsychology, Dr. Jane Cerhan, Ph.D. and her contact information has been added to serve as a backup for Dr. Farace.

Protocol Resources:
- The Protocol Coordinator has been changed to Tamara Robles and her contact information added.
- Under the questions column, next to Tamara Robles, “regulatory issues” has been deleted.

Section 3.19b (Neurocognitive Testing Grooved Peg Board)
- Cross-reference to “Section 6.36” has been changed to “Section 6.26.”
Section 4.311 (Previously Credentialed)

- The first paragraph has been revised to include the new procedures for previously certified personnel. “Send documentation of the prior certification to the Research Protocol Specialist by mail or email at the address listed on the Protocol Resource page” has been replaced with “email documentation of the prior certification to the Alliance Regulatory Affairs Manager at thaynes2@uchicago.edu.”
- “The Research Protocol Specialist will send notice of the certification to the CTSU Regulatory Office” has been replaced with “the Alliance Regulatory Manager will email notice of the certification to the CTSU Regulatory Office.”

Section 4.312 (Not Previously Credentialed)

- In the last sentence of the second paragraph, “the Research Protocol Specialist at the telephone number or email address listed on the Protocol Resource page of the protocol” has been deleted and replaced with “the CTSU Help Desk.”
- In the second sentence of the fourth paragraph, “Research Protocol Specialist” has been replaced with “Alliance Regulatory Manager at thaynes2@uchicago.edu who will email” In the fifth sentence, “the Protocol Specialist will send” has been deleted as a result.
- In the last sentence of the forth paragraph, “N107C” has been replaced with “N0574.”
- In the fifth paragraph, “Research Protocol Specialist” has been replaced with “Dr. Farace.”

Section 4.42 (SRS Phantom Study)

- In the first sentence “An SRS phantom study with RPC must be successfully completed” has been replaced with “Radiological Physics Center (RPC) Questionnaire for Stereotactic Radiosurgery (SRS) with Gamma Knife or with Linear Accelerator or successful irradiation of the RPC SRS phantom. The questionnaire or phantom information is available on the RPC web site, http://rpc.mdanderson.org, under “Credentialing.” Complete this form and submit electronically on the RPC website.”
- The paragraph has been revised to include the new procedures for notifying the Alliance Regulatory Affairs Manager of the site’s credentialing. Therefore, “the RPC will notify NCCTG of the site’s SRS credentialing. NCCTG will record and then forward this information to the CTSU Regulatory Office” has been changed to “the RPC will notify the Alliance Regulatory Affairs Manager at thaynes2@uchicago.edu of the site’s credentialing who will email notice to the CTSU Regulatory Office.
- In the last sentence, “N107C” has been replaced with “N0574.”

Section 6.11 (Investigator Registration)

- In the last sentence, the PMB telephone number “(301) 496-5725” has been changed to “(240) 276-6575.”

Section 6.121 (Site IRB Approval)

- In the last sentence, “N107C” has been replaced with “N0574.”

Section 7.12 (Performance of SRS at a Site Other than the Registered Site)

- In the first sentence, the word “be” has been added.

Section 10.4 ( Expedited Reporting Requirements)

- In the section title, “Studies using Commercial Agent(s) ONLY” has been deleted.
- Below the section title, “Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 days of the Last Administration of the Investigational Agent/Intervention 1, 2” has been changed to “Late Phase 2
and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies within 30 Days of the Last Treatment 1.

- Under the hospitalization chart, the Note “Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR” has been changed to “Additional Instructions or Exclusions to Expedited Reporting
  - These instructions supersede the table above
  - Grade 1-3 events listed in Section 15 of the protocol or hospitalization resulting from such do not require AdEERS reporting, but should be reported via routine AE reporting.

- The subscript 2 has been deleted.

Section 18.211
- “N107C” has been replaced with “N0574.”

Section 18.212
- “N107C” has been replaced with “N0574.”

Section 18.213
- “NCCTG Operations Office, Attn: RPS for N107C, Plummer 4 200 First Street SW, Rochester MN 55905” has been replaced with “Dr. Elena Farace at the address listed on the Study Staff page of the protocol.”

Changes to the Model Consent

IRB Instructions
- At the end of the model consent, the former local IRB Instructions have been deleted.

A replacement protocol document and model consent have been issued.

_____________________________________________________________

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL
Phase III Randomized Trial of the Role of Whole Brain Radiation Therapy in Addition to Radiosurgery in Patients with One to Three Cerebral Metastases

X Update:
- Eligibility changes
- Therapy / Dose Modifications / Study Calendar changes
- Informed Consent changes
- Scientific / Statistical Considerations changes
- Data Submission / Forms changes
- Editorial / Administrative changes
- Other : CTEP-AERS updates

☐ Status Change:
- Activation
- Closure
- Suspension / temporary closure
- Reactivation

IRB review of this update is required within 90 days. Expedited review is allowed. Please follow your local IRB guidelines.

References to the “Adverse Event Expedited Reporting System (AdEERS)” have been changed to “CTEP Adverse Event Reporting System (CTEP-AERS)” throughout the protocol.

CHANGES TO THE PROTOCOL:

Title Page:
- In keeping with new CTEP PIO requirements the following has been removed from the title page: “Alliance”, “North Central Cancer Treatment Group” Cancer and Leukemia Group B (CALGB), American College of Surgeons Oncology Group (ACOSOG).” As a result, the name of the lead group is the “Alliance for Clinical Trials in Oncology.”

Study Staff:
- Dr. Cerhan’s title has been modified from “Neuropsychology” to “Neuropsychology Study Co-Chair.”

Protocol Resources:
- Within the table, the reference to “AdEERS” has been changed to “CTEP-AERS” as this reporting system will be retired in May 2014. The CTEP Adverse Reporting System is live and open for use in place of AdEERS.
- Within the table, reference to “AML/MDS” has been removed.
Schema

- Footnote 3 has been added to the therapy regimen for Arm A, the therapy regimen for Arm B, and to Observation.
- The words “Follow up” have been added to the Observation phase for clarity.
- Footnote 3 has been added to distinguish treatment from follow up/observation, and to show each cycle’s duration.

Section 4.0 (Test Schedule)

- The words “Follow up” have been added to the “Observation” column.
- Footnote 9 has been added to “Follow up/Observation.”
- Footnote 9 has been for added to “Treatment.”
- Footnote 9 has been added for clarity.

Section 10.11 (Adverse Event Monitoring)

- In the first paragraph, “Expedited adverse event reporting requires submission of an Adverse Event Expedited Reporting System (AdEERS) report(s)” has been changed to “Expedited adverse event reporting requires a CTEP Adverse Event Reporting System (CTEP-AERS) report(s).”
- The following sentence has been added to the second paragraph: “In addition, effective with Update 5, the CTEP-AERS is live for use in place of AdEERS.”

Section 10.41 (Contact Information for NCI Safety Reporting)

- Within the table, the URL referenced for accessing the expedited reports has been changed.
- All references to “AdEERSMD” have been changed to “AEMD.” Within the table, the “AEMD Help Email” has been revised accordingly.
- The phone number “301-840-8202” for the “Technical (e.g., IT or computer issues ONLY) Help Phone*” has been deleted.
- Within the table, the FAQ link has been changed.
- Within the table, the URL referenced for accessing the “CTEP-AERS Computer Based Training” has been revised accordingly.

Section 13.35 (Definition of Cancel)

- The following sentence has been added: “The patient will go directly to the observation phase of the study.”

Section 18 (Records and Data Collection Procedures)

- Within the Initial Material(s) Table, the following three forms have been added:
  - “Patient (FACT-Br) Compliance Form”
  - Neurocognitive Testing Booklet Compliance Form”
  - End of Active Treatment/Cancel Notification Form”
- In addition, footnotes 5 and 6 have been added for clarity.
- Within the Test Schedule Material(s) table,
  - After “At end of treatment,” footnote 8 and the phrase, “(week 6 follow up)” have been added for clarity.
  - After “At each evaluation during observation” footnote 8 and the phrase, “(week 12 and 6, 9, 12, 24, 36, 48, 60 months follow up)” have been added for clarity.
  - Footnote 8 has been added for clarity.
  - Reference to the “Patient QOL (FACT-Br) Questionnaire Booklet Compliance Form” has been changed to “Patient (FACT-Br) Booklet Compliance Form.”
o Reference to the “Patient Neurocognitive Testing Booklet Compliance Form” has been changed to “Neurocognitive Testing Booklet Form.”

o Within the “At the end of treatment (weeks 6 follow up),” footnote 5 has been added to the Functional Independence form.

- Within the Follow-up Material(s) Table, “Every 3 months” has been changed to “See Section 4.0”

**CHANGES TO THE MODEL CONSENT**

No changes were made to the model consent.

A replacement protocol document and model consent have been issued.

**THIS STUDY REMAINS CLOSED TO NEW PATIENT ACCRUAL**

**ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL**
Phase III Randomized Trial of the Role of Whole Brain Radiation Therapy in Addition to Radiosurgery in Patients with One to Three Cerebral Metastases

**Update:**
- Eligibility changes
- Therapy / Dose Modifications / Study Calendar changes
- Informed Consent changes
- Scientific / Statistical Considerations changes
- Data Submission / Forms changes

**Editorial / Administrative changes:**
- This amendment consists of administrative changes only; therefore, the Alliance does not require IRB approval of this update. Please follow local IRB guidelines.

**Changes to the Protocol:**

**Title Page**
- At the top of the second page table, the title of “Study Participants” has been updated to “Participating Organizations.” In addition, the rows beneath the title table “NCCTG” has been updated to “ALLIANCE / Alliance for Clinical Trials in Oncology (Lead) and “All CTSU Sites” has been updated to “ECOG-ACRIN / ECOG-ACRIN Medical Research Foundation, Inc., NRG / NRG Oncology Foundation Inc. and SWOG / SWOG.”

**Changes to the Model Consent**

No changes were made to the model consent.

A replacement protocol document and model consent have been issued.

THIS STUDY REMAINS CLOSED TO NEW PATIENT ACCRUAL

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL
N0574 Title Page

Alliance for Clinical Trials in Oncology

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

For any communications regarding this protocol, please call the protocol resource person on the following page

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Email: rdeming@mercydesmoines.org

*Investigator having NCI responsibility for this protocol
Drug Availability:
Not Applicable

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Participating Organizations

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<tr>
<td>ECOG-ACRIN Medical Research Foundation, NRG/NRG Oncology Research Foundation Inc. and SWOG/SWOG</td>
<td>August 8, 2006</td>
</tr>
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</table>

Study Staff

Study Statistician:
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Telefax: (410) 502-1419
Email: kleinla@jhmi.edu

✓Study contributor(s) not responsible for patient care.
### Cancer Trials Support Unit (CTSU) Address and Contact Information

<table>
<thead>
<tr>
<th>The CTSU Public website is located at: <a href="http://www.ctsu.org">www.ctsu.org</a></th>
<th>The CTSU Registered Member website is located at <a href="http://members.ctsu.org">http://members.ctsu.org</a></th>
</tr>
</thead>
</table>
| To submit site registration documents:               | CTSU Regulatory Office  
1818 Market Street, Suite 1100  
Philadelphia, Pennsylvania 19103  
Telephone: (866) 651-CTSU  
Telefax: (215) 569-0206 |
| For patient enrollments:                             | Please refer to patient enrollment in Section 6.0 for instructions how to pre-register and register patients. |
| Submit study data directly to NCCTG unless otherwise specified in the protocol, Section 18: | NCCTG Operations Office  
Attn: QAS for Study N0574  
NW Clinic, 3-24 CC  
200 First Street Southwest  
Rochester Minnesota 55905 |

**NOTE:** Data management will be performed by NCCTG. NCCTG sites will submit all forms via NCCTG Remote Data Entry System. **Case report forms** (with the exception of eligibility checklists), **clinical reports, and transmittals** must be sent to NCCTG unless otherwise directed by the protocol. Do **not** send study data or case report forms to the CTSU Data Operations. Do not copy the CTSU on data submissions.

**Data query and delinquency reports** will be sent directly to the enrolling site by NCCTG Operations Office. Please send query responses and delinquent data to the NCCTG and do not copy the CTSU Data Operations.

The **study protocol and all related forms and documents** must be downloaded from the protocol-specific web page of the CTSU Member website located at https://www.ctsu.org. Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol.

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<th>Contact:</th>
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<td>For patient eligibility or treatment-related questions</td>
<td>Contact the NCCTG Research Base Quality Assurance Specialist listed in Protocol Resources table on next page.</td>
</tr>
</tbody>
</table>
| For questions unrelated to patient eligibility, treatment, or data submission | Contact the CTSU Help Desk by phone or e-mail:  
CTSU General Information Line – (888) 823-5923 or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative. |
<table>
<thead>
<tr>
<th>Questions:</th>
<th>Contact Name:</th>
</tr>
</thead>
</table>
| Patient eligibility*, test schedule, treatment delays, interruptions or adjustments, dose modifications, adverse events, forms completion and submission | Carla Hilton  
NCCTG Research Base Quality Assurance Specialist  
Telephone: (507) 284-1370  
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| Protocol document and consent form                                                                                                    | Tamara Robles, MBA  
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|                                                                                                                                      | Wanda DeKrey, R.N., OCN  
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| Radiation quality control                                                                                                            | Kathryn Scherger  
NCCTG Research Base Radiation Quality Control Coordinator  
Telephone: (507) 266-0006  
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| Adverse Events (CTEP-AERS, MedWatch, Non-AER, AML/MDS)                                                                                | Patricia G. McNamara  
NCCTG Research Base SAE Coordinator  
Telephone: (507) 266-3028  
Telefax: (507) 284-9628  
Email: mcnamara.patricia@mayo.edu                                                                                                         |
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Schema

1. In the event of progressive brain metastases or systemic progression, the patient remains in observation (see Section 13.31).

2. In the event of patient refusal/withdrawal or unacceptable adverse events, an Event Monitoring Form should be completed and patient continued to be followed per the test schedule.

3. **Treatment**
   Cycle 1 = starts day 1 of treatment and ends at week 6 follow up.
   **Follow up/Observation:**
   Cycle 2 = starts at 6 weeks and ends at week 12 follow up.
   Cycle 3 = starts at week 12 follow up and ends at 6 month follow up.
   Cycle 4 = starts at 6 month follow up and ends at 9 month follow up.
   Cycle 5 = starts at 9 month follow up and ends at 12 month follow up.
   Cycle 6 = starts at 12 month follow up and ends at 16 month follow up.
   Cycle 7 = starts at 16 month follow up and ends at 24 month follow up.
   Cycle 8 = starts at 24 month follow up and ends at 36 month follow up.
   Cycle 9 = starts at 36 month follow up and ends at 48 month follow up.
   Cycle 10 = starts at 48 months follow up and ends at 60 month follow up.
1.0 Background

1.1 Whole Brain Radiation Therapy

Extra-cerebral metastases are the most common malignancy affecting the brain. There are an estimated 100,000 to 170,000 new patients with brain metastases in the United States each year (Johnson and Young, 1996). As systemic therapy for malignancy improves, brain metastases will become an increasingly frequent management problem due to the impaired ability of chemotherapy to pass the blood-brain barrier. Survival for untreated patients with brain metastases is generally less than seven weeks. Standard palliative treatment, including glucocorticoids and whole brain radiation therapy (WBRT), extends median survival to three to six months by preventing or delaying neurologic progression (Posner, 1992). Radiation Therapy Oncology Group (RTOG) trials conducted during the 1970's demonstrated no difference in survival, or time to neurologic progression, among a wide range of WBRT regimens: 20 Gray (Gy) in 5 fractions, 30 Gy in 10 fractions, 30 Gy in 15 fractions, 40 Gy in 15 fractions, or 40 Gy in 20 fractions (Borgelt et al., 1980). About 40% of the patients in each treatment arm suffered neurologic progression. A follow-up RTOG trial found that favorable patients with controlled primary tumors fared no better with an escalated WBRT dose (50 Gy in 20 fractions) versus a dose of 30 Gy in 10 fractions. On that basis, 30 Gy in 10 fractions became the de facto regimen in the United States. Patients who received WBRT usually experienced mild acute toxicity, such as alopecia, skin reaction, and headache. More importantly, in long-term survivors, there are neurocognitive sequelae that may take months to years to manifest. A long-term study from the Memorial Sloan Kettering Cancer Center found an 11% risk of dementia in patients at one year following treatment with 3.0 Gy fraction sizes or greater (DeAngelis et al., 1989). Therefore, many institutions have adopted the 2.5 Gy fraction size as the standard protocol for patients with a good prognosis.

1.2 Resection of Brain Metastases Followed by Whole Brain Radiation Therapy

Although most patients with brain metastases succumb to systemic cancer progression, there is a select subgroup of patients with good performance status and limited systemic disease who are likely to die of neurological progression if treated by WBRT alone. Aggressive surgical resection provides better local control of brain metastases in these patients and can markedly prolong survival. Patchell et al. demonstrated, in a randomized trial of patients with a single brain metastasis, that surgery and WBRT resulted in survival of 40 weeks versus 15 weeks with WBRT alone (Patchell et al., 1990). Vecht et al. reported similar results (Vecht et al., 1993). The necessity of administering WBRT following surgical resection of metastases is controversial. After complete surgical resection of a single metastasis (confirmed by post-operative magnetic resonance imaging (MRI)), Patchell et al. demonstrated in a second prospective randomized trial that the addition of WBRT markedly decreased the incidence of local recurrence (46% versus 10%), distant brain recurrence (37% versus 14%), and death from a neurologic cause (44% versus 14%) (Patchell et al., 1998). Here was no effect on overall survival or duration of functional independence, presumably due to successful salvage measures in the surgery alone group (delayed WBRT), or detrimental neurocognitive effects from WBRT. Surgery cannot be offered to all patients because many are poor medical candidates or have lesions in locations not amenable to resection. In addition, patients with multiple lesions have rarely been offered surgery because the morbidity was felt to be excessive (Kondziolka et al., 1999).
1.3 Radiosurgery With or Without Whole Brain Radiation Therapy

Stereotactic radiosurgery (SRS) is less invasive than conventional surgery and has become an increasingly accepted method of treating brain metastases due to the high rate of local control. SRS delivers high-dose radiation in a single session, to a stereotactically defined target volume, and minimizes the dose to surrounding normal tissue. Brain metastases are ideal targets for SRS because most lesions are small, pseudo-spherical and well demarcated from the surrounding brain tissue. Rates of local control in large series have averaged 80% to 90% (Flickinger et al., 1994). Although there are no randomized trials directly comparing SRS to surgery, the preponderance of retrospective data supports the equivalence of the modalities for small, single lesions. For instance, a retrospective, matched comparison analysis of 108 patients concluded that survival for patients with a single metastasis was similar whether they received SRS alone or surgery and WBRT (Muacevic et al., 1999).

A subgroup of patients who have multiple metastases may benefit from the addition of SRS to WBRT. A randomized trial from the University of Pittsburgh, of patients with two to four metastases, found a non-significant survival advantage for patients who received SRS + WBRT (11 months) versus for patients who received WBRT alone (7.5 months). Local control at one year was 100% for patients who received SRS + WBRT versus 8% for those who received WBRT alone (Kondziolka et al., 1999). The results of the RTOG 9508 trial have been presented in abstract form. In the study, patients with one to three brain metastases were randomized to WBRT + SRS boost or to WBRT alone. A statistically significant survival advantage was demonstrated for the patients in the WBRT + SRS arm that had a solitary brain metastasis, RPA class I, age <50 years, or non-small cell lung cancer or any squamous cell cancer (Sperduto et al., 2002). At one year, local control was significantly better for the WBRT + SRS boost arm.

As with excisional surgery, SRS is a focused treatment that would not be expected to address the risk of distant brain progression. Based on Patchell's randomized data, WBRT would be expected to decrease the risk of distant brain progression Patchell et al., 1990. Nevertheless, the role of WBRT + SRS remains undefined. Retrospective data from the University of California at San Francisco and the Memorial Sloan Kettering Cancer Center have demonstrated that freedom from progression of brain metastases was significantly worse for patients who received SRS alone versus those who received SRS + WBRT, (28% vs. 69% at 1 year). However, overall survival was similar due to successful salvage measures (Sneed et al., 1999). Similar data have been reported from the University of Pittsburgh (Flickinger et al., 1994) and from the Karolinska Institute in Stockholm (Kihlstrom et al., 1991). These studies are subject to retrospective biases, such as differences in selection criteria for WBRT and type of salvage treatment given. At the current time, it is unclear whether the addition of conventional WBRT results in either survival advantage or decreased risk of neurological death. Even if there is no survival advantage, quality of life may be improved and treatment may be cost effective, due to avoiding the psychological distress of brain recurrence and the future need for subsequent salvage therapy. On the other hand, the potential side effects of WBRT, including fatigue, alopecia, cognitive decline, and diminished hearing, may result in a decreased quality of life for the patient.
1.4 Quality of Life

Given the poor survival prognosis of patients in this study, quality of life (QOL) will be an important secondary endpoint. The primary QOL objective is to ascertain whether patients in Arm 1 (SRS) have better QOL than patients in Arm 2 (SRS + WBRT). Kondziolka et al. reported no neurologic or systemic morbidity for patients who had two to four brain metastases treated with SRS. Similar patients treated with WBRT developed mild scalp erythema and hair loss (Kondziolka et al., 1999). If the addition of WBRT does not give significant survival gain, yet additional side effects, SRS alone might be preferred. Hence, one-sided null hypotheses for improvement on Arm 1 (SRS) will be used.

The focus of the QOL and neurocognitive assessments will be at three months post-treatment. The three month time point is proposed as being late enough to capture major treatment effects, but early enough to avoid a substantial difference between-arm morbidity and mortality. Patient self-reported QOL, using the FACT-BR questionnaire (Weitzner et al., 1995), objective assessments of changes in cognitive signs and symptoms (e.g., speech impairment), and physician-assessed toxicities (e.g., nausea) will be collected.

The FACT-BR is a validated QOL instrument, comprising a general component (FACT-G, with five subscales (number of questions in parentheses): physical (8), social (8), emotional (3), functional (6), and relationship with doctor (3) Cella et al., 1993), and a disease-specific subscale (BR) of 20 questions (Weitzner et al., 1995). In the Weitzner study, only 14% of the patients (17/118) were unable to complete the questionnaire themselves, but the remainder completed multiple forms over time (Weitzner et al., 1995). Meyers reported a similar finding: 12/80 patients (15%) were unable to complete a baseline form (Meyers, 2000a). What, if any, help that is necessary for patients to complete testing for this study will be included in the analyses.

The results will be combined with survival data in a ‘quality-adjusted survival analysis’ (QAS) (Murray et al., 1995).

1.5 Functional Independence

The assessment of ‘function’ typically refers to the assessment of disability, as measured by the ability of the patient to perform activities of daily living (ADLs). Given the changes in ADLs that occur in patients with malignant brain tumors (e.g., the inability to work and care for themselves), functional independence will be an important measure of outcome. Functional independence has previously been equated with QOL (Patchell et al., 1990), but recent studies suggest it is distinct from both QOL and cognitive function (Meyers and Weitzner, 1995; Meyers, 1997).

The Barthel ADL Index is a well-validated, reliable tool measuring patient ability to perform ADLs and is easily administered by a nurse or physician (Wade 1992; Meyers 2000a). No special training is necessary to complete the test and its utility is recognized in the medical outcomes literature [Sabers et al., 1999]. The Barthel ADL Index has been shown to be sensitive to change and reflective of the degree of functional impairment in a study of patients with high-grade glioma, where it correlated with the Karnofsky Performance Status (KPS), r = 0.872. It also was reliable when administered verbally, as in cases when patients were unable to complete it in writing (Brazil et al., 1997).

A Barthel score of 20 implies complete independence. Any lower score suggests that the
patient requires some supervision. The bowel, bladder, toileting, feeding, dressing, and stairs categories are scored 0-2; grooming and bathing 0-1; transfer and mobility 0-3. Decreases of greater than or equal to 4 points are considered meaningful (Wade 1992).

We propose to include the Eastern Cooperative Oncology Group (ECOG) 0-4 performance status scale in this study as a secondary measure of ADL that will allow for comparison to other cancer trials. The ECOG rating is a numeric representation of an individual’s ability to perform normal activity, to do active work, and of their need for assistance.

1.6 Neurocognitive Status

Neurocognitive evaluation of patients with malignant brain tumors has established that they can experience measurable cognitive deficits (Anderson et al., 1990; Milner, 1963). A wide range of mechanisms resulting in cognitive dysfunction have been identified, including destruction of brain tissue, displacement of surrounding brain structure, increasing intracranial pressure, seizures, edema of adjacent brain tissue, and alterations of endocrine pattern and/or brain biochemistry. Specific cognitive effects may occur due to anatomic location, tumor size, growth rate, and developmental age at the time of onset. Virtually all types and patterns of neurocognitive dysfunction have been demonstrated secondary to brain tumors, including deficits in attention, concentration, memory, pure language or visuospatial abilities, logical reasoning, motor or sensory impulse, coordination, balance or gait disturbance, and emotional/behavioral disorders such as depression, abulia, agitation, hallucinations, delusions, and paranoia (Lezak, 1995).

More recently, neuropsychological studies have examined the following effects: specific tumor histology (Kramer et al., 1997), patient response to treatment relative to the operative approach to the tumor (Hutter et al., 1997; Villani et al., 1997), cranial radiation therapy (Armstrong et al., 1995; Armstrong et al., 2000; Crossen et al., 1994), and chemotherapy (McAllister et al., 2000) on patient outcome. Some studies have examined the success of medical treatment (methylphenidate) for cognitive and mood dysfunction of patients with brain tumors (Meyers et al. 1998) and cognitive function in long-term survivors (Archibald et al. 1994; Giovagnoli and Boiardi, 1994). These studies have demonstrated that as the evaluation, treatment, and survival of patients with malignant brain tumors becomes increasingly more sophisticated and successful, neurocognitive status is helpful in documenting patient outcome and QOL.

The neurocognitive tests to be used in this study were chosen on the basis of accepted standardization and psychometric principles, published normative data relative to routine demographics, relevance to general neurocognitive status, and brevity of the overall battery. The tasks selected have either low associated practice effect or include multiple equivalent formats (e.g., memory test, fluency test). Lezak reports that patients with brain tumors can tolerate this degree of cognitive testing without difficulty (Lezak, 1995).

1.7 Summary

This study is designed to test the hypothesis that in patients with one to three brain metastases, WBRT adds no additional benefit to SRS. Patient entry will be stratified in order to achieve well-balanced groups with regard to the extent of systemic disease. As SRS will presumably control the detected metastatic lesions, the WBRT dose needs to be sufficient only to control metastatic aggregates below the detection threshold of contrasted MRI brain scans. A WBRT dose of 24 Gy in 8 fractions was studied in France,
in a randomized prophylactic cranial irradiation (PCI) trial for patients with small cell lung cancer, and in a recent German randomized PCI trial that used 25 Gy in 10 fractions for patients with non-small cell lung cancer (Stuschke et al., 1999). In both of these studies, the PCI dose controlled sub-clinical brain metastases. Arm 2 will therefore test a WBRT dose of 30 Gy in 12 fractions. Salvage treatment guidelines will be defined in order to assure uniformity of treatment between Arm 1 and Arm 2. If patients in Arm 1 suffer a limited local recurrence or a distant brain recurrence, they will be directed to undergo repeat SRS without WBRT. Common Toxicity Criteria (CTC) scoring, QOL questionnaires, functional independence measurements, neurocognitive testing, and post-treatment adverse events will be obtained at serial follow-up visits in order to ascertain any differences in long-term outcome.

2.0 Goals

2.1 Primary Objective

To ascertain in patients with one to three brain metastases whether there is less neurocognitive progression at 3 months post-radiosurgery in patients who receive SRS alone (Arm A) compared to patients who receive SRS combined with WBRT (Arm B).

2.2 Secondary Objectives

2.21 Time to CNS Failure
To ascertain in patients with one to three brain metastases whether there is equal (or greater) time to central nervous system (CNS) failure (brain) in patients who receive SRS alone (Arm A) compared to patients who receive SRS combined with WBRT (Arm B).

2.22 Quality of Life (QOL)
To ascertain in patients with one to three brain metastases whether there is improved QOL in patients who receive SRS alone (Arm A) compared to patients who receive SRS combined with WBRT (Arm B).

2.23 Functional Independence
To ascertain in patients with one to three brain metastases whether there is longer duration of functional independence in patients who receive SRS alone (Arm A) compared to patients who receive SRS combined with WBRT (Arm B).

2.24 Long-Term Neurocognitive Status
To ascertain in patients with one to three brain metastases whether there is better long-term neurocognitive status in patients who receive SRS alone (Arm A) compared to patients who receive SRS combined with WBRT (Arm B).

2.25 Post-Treatment Adverse Events
To tabulate and descriptively compare the post-treatment adverse events associated with the interventions.

2.26 Overall Survival
To compare in patients with one to three brain metastases the overall survival in patients who receive SRS alone (Arm A) compared to patients who receive SRS combined with WBRT (Arm B).
3.0 Patient Eligibility

3.1 Pre-Registration (Step 1) Inclusion Criteria

3.11 Number and Size of Brain Metastases
One to three presumed brain metastases from a pathologically confirmed extra-cerebral tumor site (e.g. lung, breast, prostate, etc.). The pathologic confirmation may have been from the primary tumor site, from another metastatic site (e.g. an osseous metastasis, adrenal metastasis, etc.), or from the metastatic brain lesion(s). Note: Each lesion must measure < 3.0 cm in maximal extent on the contrasted pre-treatment MRI brain scan obtained ≤ 28 days prior to randomization (see Magnetic Resonance Imaging (MRI) Guidelines Section 11.2).

3.12 Standard Tumor-Staging Procedures
All standard tumor-staging procedures necessary to define baseline extra-cranial disease status completed ≤ 42 days prior to pre-registration.

3.13 Treatment with a Gamma Knife or Radiosurgery
Ability to be treated with either a gamma knife or a linear accelerator-based radiosurgery system. Note: A treating center must have completed stereotactic radiosurgery credentialing (see Section 4.4).

3.14 Age
≥ 18 years of age.

3.15 Quality of Life (QOL) Questionnaires
Ability to complete questionnaire(s) by themselves or with assistance.

3.16 SRS Credentialed by RPC
The site’s SRS facility is Radiological Physics Center (RPC) approved. See Section 4.4 of the protocol for information how to obtain this credentialing.

3.17 Neurocognitive Testing Credentialing
The site study team member performing neurocognitive testing of patients must have credentialing confirming completion of the training for neurocognitive testing. See Section 4.3 for information how to obtain this credentialing.

3.18 Written Informed Consent
Provide written informed consent

3.19a ECOG Performance Status
ECOG performance status 0, 1, or 2. See Appendix I.

3.19b Neurocognitive Testing Grooved Peg Board
Grooved peg board available for Neurocognitive Testing. See Section 6.26 for further information.
3.2 Pre-Registration (Step 1) Exclusion Criteria

3.21 Pregnancy, Nursing and Contraception
Any of the following:
- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception throughout the study and for male patients for 3 months beyond study treatment.

3.22 MRI scans
Inability to complete an MRI scan with contrast of the head (i.e., such as the presence of a pacemaker or other MRI non-compatible metal in the body).

3.23 Allergy to Gadolinium
Known allergy to gadolinium.

3.24 Prior Resection of Metastases
Prior resection of cerebral metastasis.

3.25 Location of Brain Metastases
A lesion that is located ≤ 5 mm of the optic chiasm or within the brainstem.

3.26 Prior Chemotherapy
Prior chemotherapy ≤ 7 days prior to pre-registration.

3.27 Planned Chemotherapy
Planned chemotherapy during the SRS and WBRT.

3.28 Prior Cranial Radiation Therapy

3.29a Other Tumor Types
Primary germ cell tumor, small cell carcinoma, or lymphoma.

3.29b Leptomeningeal metastasis

3.3 Registration/Randomization (Step 2) Inclusion Criteria

3.31 Number of Unresected Lesions
Planning MRI confirmed one to three lesions. Each lesion must measure < 3.0 cm in maximal extent on the contrasted planning MRI brain scan. Note: The pre-registration MRI scan may be used for the planning scan if obtained ≤ 14 days prior to randomization.

3.32 Urine or Serum Pregnancy Test
Negative urine or serum pregnancy test done ≤ 7 days prior to randomization, for women of child bearing potential only.
3.4 Registration/Randomization (Step 2) Exclusion Criteria
None.

3.5 Inclusion of Women and Minorities
Both men and women of all races and ethnic groups are eligible for this study.
## 4.0 Test Schedule

<table>
<thead>
<tr>
<th>Tests and procedures</th>
<th>≤ 21 days prior to pre-reg</th>
<th>≤ 14 days prior to randomization</th>
<th>Follow up/Observation&lt;sup&gt;5, 9&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weeks</td>
</tr>
<tr>
<td>History and Physical Exam, including Weight, Recording of Medications and ECOG Performance Status</td>
<td>X&lt;sup&gt;7&lt;/sup&gt;</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Radiation Oncology Consultation</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Neuro History and Exam</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Urine or Serum Pregnancy Test</td>
<td>X&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>MRI Scan</td>
<td>X&lt;sup&gt;2&lt;/sup&gt; X&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Adverse events Assessment</td>
<td>X&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>Mandatory</strong> Quality of Life (QOL) questionnaire: FACT-BR (See Section 4.1)</td>
<td>X&lt;sup&gt;6&lt;/sup&gt;</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>Mandatory</strong> Functional Independence: Barthel ADL Index (See Section 4.2)</td>
<td>X&lt;sup&gt;6&lt;/sup&gt;</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>Mandatory</strong> Patient Neurocognitive Tests Questionnaire (see Section 4.3)&lt;sup&gt;8&lt;/sup&gt;</td>
<td>X&lt;sup&gt;6&lt;/sup&gt;</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Footnotes for Table 4.0 appear on the following page
Footnotes for Table 4.0
1. Patient, if female of childbearing potential, must have a negative urine or serum pregnancy test result ≤ 7 days prior to randomization.

2. Pre-registration contrasted MRI brain scans must be obtained ≤ 28 days prior to randomization.

3. Report all adverse events that have occurred since the previous visit including late effects of radiation.

4. Randomization is ≤ 14 days after pre-registration (with planning MRI scan obtained the same day as randomization). For the vast majority of patients, treatment will be delivered the same day as the planning scan and randomization. Follow-up will be based on the date the SRS treatment is completed. The pre-registration MRI scan may be used for the planning scan if obtained ≤ 14 days prior to of randomization.

5. Patients will continue to be followed per test schedule (even in the event of progressive disease (PD)) until withdrawal, refusal, death or 5 years from randomization. In the event of PD in the brain or progression of systemic disease, an Event Monitoring Form should be completed and patient continued to be followed per the test schedule.

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 forwarded) and do not need to be repeated immediately after randomization.

7. All standard tumor-staging procedures necessary to define baseline extra-cranial disease status (as deemed appropriate by the treating oncology physician) completed ≤ 42 days prior to pre-registration.

8. There are two questionnaire booklets utilized for patient neurocognitive testing; the Neurocognitive Examiner’s Booklet and the Neurocognitive Patient Completed Booklet. The Examiner’s Booklet is completed by the study staff administering the neurocognitive tests to the patient and includes the HVLT, Grooved Peg Board and COWAT A and B tests and also the scoring for Trail Making A and B tests. The Neurocognitive Patient Completed Booklet is completed by the patient and includes the Trail Making A and B tests.

9. **Treatment**
   Cycle 1 = starts day 1 of treatment and ends at week 6 follow up.
   **Follow up/Observation:**
   Cycle 2 = starts at 6 weeks and ends at week 12 follow up.
   Cycle 3 = starts at week 12 follow up and ends at 6 month follow up.
   Cycle 4 = starts at 6 month follow up and ends at 9 month follow up.
   Cycle 5 = starts at 9 month follow up and ends at 12 month follow up.
   Cycle 6 = starts at 12 month follow up and ends at 16 month follow up.
   Cycle 7 = starts at 16 month follow up and ends at 24 month follow up.
   Cycle 8 = starts at 24 month follow up and ends at 36 month follow up.
   Cycle 9 = starts at 36 month follow up and ends at 48 month follow up.
   Cycle 10 = starts at 48 months follow up and ends at 60 month follow up.
4.1 Patient Quality of Life (QOL) Questionnaire Booklets
The Patient Quality of Life (QOL) Questionnaire booklet contains the FACT-BR questionnaire (See Appendix III).

Please obtain a supply of all necessary booklets before registering patients. Booklets should be ordered using the Booklet Order Form included in the Forms Packet.

Questionnaire booklets are to be completed prior to randomization and at the beginning of the scheduled study visits as per Section 4.0 and returned to study staff. Patient and Examiner Questionnaire Booklets must be used; copies are not acceptable for submission. The patient’s self-reported QOL questionnaire booklet may require 10 to 15 minutes to complete. Since the patient may experience cognitive deterioration during treatment, a ‘significant other’ (e.g., a spouse) may help the patient complete the questionnaire, if necessary. The responder, identified in consultation with the patient and his/her physician, will be recorded on the forms. As further measures of possible cognitive decline during treatment, physician-assessed ratings will be made of neurological signs and symptoms and treatment adverse events (See Appendix III).

Be sure to include the patient’s initials and study ID number on the booklet. Retain a copy of the completed booklet at the treating institution and mail the original completed booklet to NCCTG Operations Office, Att’n: QAS for N0574, NW Clinic, 3-24 CC, 200 First Street SW, Rochester, MN 55905.

4.2 Functional Independence Form
The Functional Independence form contains the Barthel ADL Index and is located in the Forms Packet. 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, this will require approximately five minutes.

Be sure to include the patient’s initials and study ID number on the form. Retain a copy of the completed form at the treating institution and mail the original completed form to NCCTG Operations Office, Att’n: QAS for N0574, NW Clinic, 3-24 CC, 200 First Street SW, Rochester, MN 55905.

4.3 Neurocognitive Status Tests

4.31 Neurocognitive Testing Certification
Note: Patients may not be pre-registered to this study until at least one member from the site study team has received certification to perform neurocognitive testing.

This study requires that the member of the study staff (i.e., physician, nurse, CRA, etc.) who will administer the neurocognitive testing to patients be credentialed by Dr. Elena Farace, Penn State Hershey Medical Center. Each individual member of the study staff who will be administering the neurocognitive testing must be credentialed.
4.311 Previously Credentialed:
Members of site study teams previously credentialed to perform neurocognitive testing for any one of the following studies:

ACOSOG Z0300;
ECOG E3F05;
or the two phase III randomized motexafin gadolinium studies (i.e., the SMART trial for lung cancer)

do not need to be re-certified for this study but are required to email documentation of the prior certification to the Alliance Regulatory Affairs Manager at thaynes2@uchicago.edu. In this email, be sure to include the name and number of the prior study, the approximate date of the certification and the CTEP site codes of all the institutions the credentialing should be registered at. The CTEP site code will consist of 5 characters; the first two are the state where the institution is located and the last three are digits (i.e., Mayo Clinic in Rochester, Minnesota is MN026). The Alliance Regulatory Manager will email notice of the certification to the CTSU Regulatory Office. The CTSU will list the certification on the CTSU Regulatory Support System (RSS). Study teams may check the status of their certification by logging into the CTSU website, clicking the blue ‘Regulatory’ tab then clicking the beige ‘Site Registration’ tab then entering the CTEP site code and protocol number N0574 in the search boxes and clicking ‘Go’.

Even for previously certified individuals, reviewing Appendix IV Administration Procedures for Neurocognitive Testing in the protocol and reviewing the N0574 neurocognitive testing training video posted on the CTSU website is highly recommended. If several months pass between neuropsychological administrations, additional practice with volunteers is recommended.

4.312 Not Previously Credentialed:
Any individual member of a site study team who wishes to perform neurocognitive testing is required to be credentialed. Credentialing is specific to one individual person; it does not certify an entire study site or study team. If not previously credentialed, the study team member must follow this process:

Review Appendix IV Administration Procedures for Neurocognitive Testing in the protocol. Please have access to this document while you view the N0574 neurocognitive testing training video posted on the CTSU website. Please allow enough time for the video to download. If you have difficulties downloading the video, please check with your institution’s computer support/help desk first before contacting the CTSU Help Desk

Print and complete the neurocognitive practice test located in Appendices VI and VII with a colleague (not a patient). Fax the entire original completed practice tests to Dr. Farace at the telefax number listed on the Study Staff page of the protocol and retain a copy at the site.
Dr. Farace will review the practice tests. If there are concerns, she will email or call the member of the site study team to review. If there are no concerns, she will confirm the site study team member’s certification by email and copy the Alliance Regulatory Affairs Manager at thaynes2@uchicago.edu who will email notice of the certification to the CTSU Regulatory Office. The CTSU will list the certification on the CTSU Regulatory Support System (RSS). Study teams may check the status of their certification by logging into the CTSU website, clicking the blue ‘Regulatory’ tab then clicking the beige ‘Site Registration’ tab then entering the CTEP site code and protocol number N0574 in the search boxes and clicking ‘Go’.

If there are questions about testing procedures, please contact Dr. Farace at the telephone number or email address listed on the Protocol Resource page.

Credentialing does not expire. However, if a number of months go by between testing patients, please ensure readiness to test by reviewing Appendix IV Administration Procedures for Neurocognitive Testing in the protocol and/or viewing the training video posted on the CTSU website and/or performing practice testing with a colleague.

4.32 Ordering of Patient Neurocognitive Testing Booklets
The study site should obtain all necessary neurocognitive patient testing questionnaire booklets before pre-registering patients. Booklets should be ordered using the Booklet Order Form included in the Forms Packet. Neurocognitive patient testing questionnaire booklets must be used; copies are not acceptable for submission.

4.33 Timing of Neurocognitive Testing
Patient neurocognitive testing booklets are to be completed prior to randomization and at the beginning of the scheduled study visits as per Section 4.0 and returned to study staff.

4.34 Neurocognitive Tests Format
There are two questionnaire booklets utilized for patient neurocognitive testing: the Neurocognitive Examiner’s Booklet and the Neurocognitive Patient Completed Booklet. The Examiner’s Booklet is completed by the study staff administering the neurocognitive tests to the patient and includes the HVLT, Grooved Peg Board and COWAT A and B tests and also the scoring for Trail Making A and B tests. The Neurocognitive Patient Completed Booklet is completed by the patient and includes the Trail Making A and B tests.

Note that the Neurocognitive Examiner’s Booklet contains six different versions of the Hopkins Verbal Learning Test (HVLT) questionnaires labeled form 1, form 2, form 3, form 4, form 5 and form 6 to prevent patient recall from a prior test. Only one HVLT form is to be used at each visit. Although selection of the form is at the discretion of the treating physician, it is recommended for
convenience and consistency that Form 1 is used at baseline, Form 2 at second assessment (i.e. 6 weeks), Form 3 at third assessment (i.e. 3 months), etc. Most importantly, the patient should get all 6 forms once before getting a form for the second time (i.e. repeating the cycle). The questionnaire booklet requires approximately 20 to 30 minutes to complete and includes the following tests:

- **Memory**: Hopkins Verbal Learning Test (HVLT) (Brandt, 1991).
- **Fine Motor Control** (5 minutes): Grooved Pegboard Test (Matthews, 1964)
- **Fluency**: Controlled Oral Word Association Test from the Multilingual Aphasia Examination (COWAT) (Benton and Hamsher, 1978).
- **General Mental Ability**: Trail Making Test A and B (Reitan, 1958).
- **Delayed Memory**: Recall and Recognition of Word List encoded from the HVLT (Brandt, 1991).

If the credentialed site study team member administering the neurocognitive tests has questions or is unsure about a patient's ability to complete the tests, please contact Dr. Farace as adjustments may be made depending on the patient's situation.

4.35 Submission of Completed Neurocognitive Test Questionnaire Booklets
Completed test forms must be signed by the credentialed site study team member administering the neurocognitive tests. Be sure to include the patient’s initials and study ID number on both the Neurocognitive Examiner’s Booklet and the Neurocognitive Patient Completed Booklet. Retain copies of the completed neurocognitive booklets at the treating institution and mail the original of the completed booklet to Dr. Elena Farace at the address listed on the Study Staff page of the protocol.

Please be sure to fax the Neurocognitive Tests Submission Fax Form (Appendix V) to Dr. Elena Farace at the telefax number listed on the Study Staff page of the protocol.

4.36 Quality Control for Patient Neurocognitive Testing Booklets
Throughout the study, Dr. Farace will review all patient questionnaire booklets for quality control purposes and to reduce inter-rater subjectivity in scoring. Procedural deviations will be identified and the site study team member performing the neurocognitive testing will be notified of the results of the review as needed. If significant procedural variations are noted, re-training of the test administrator will be required. Completed patient questionnaire booklets should be mailed to Dr. Farace as soon as possible to ensure that the quality control review can be done in a timely manner.
4.4 SRS Credentialing
In order to utilize Stereotactic Radiosurgery (SRS) with a Gamma Knife or Linear Accelerator on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements are available on the Radiological Physics Center (RPC) website at http://rpc.mdanderson.org/rpc/; click ‘Credentialing’ then ‘NCCTG.’ To determine if these requirements have already been met by your institution, select “Credentialing Status Inquiry.”

4.41 SRS Questionnaire
An SRS questionnaire must be completed and submitted, or if the questionnaire has been previously submitted, must be updated by the institution and submitted to the RPC electronically from the RPC website for review. The questionnaire is available on the RPC web site, http://rpc.mdanderson.org, under ‘Credentialing.’

4.42 SRS Phantom Study
Radiological Physics Center (RPC) Questionnaire for Stereotactic Radiosurgery (SRS) with Gamma Knife or with Linear Accelerator or successful irradiation of the RPC SRS phantom. The questionnaire or phantom information is available on the RPC web site, http://rpc.mdanderson.org, under “Credentialing.” Complete this form and submit electronically on the RPC website. If an institution has previously been credentialed to enter patients onto earlier NCCTG SRS protocols and their treatment equipment has not changed since the initial credentialing, the institution is not required to perform the phantom irradiation study. However, if the institution’s treatment equipment has changed, then they will be required to re-credential by performing the phantom irradiation study. Institutions that previously had only completed the SRS questionnaire to be credentialed for NCCTG SRS protocols are strongly encouraged to perform a phantom irradiation study during their participation in this protocol. Instructions for requesting and irradiating the phantom are available on the RPC website at http://rpc.mdanderson.org/rpc/; select ‘Credentialing’ then ‘NCCTG’. Upon review and successful completion of the phantom irradiation, the RPC will notify the Alliance Regulatory Affairs Manager at thaynes2@uchicago.edu of the site’s SRS credentialing who will email notice to the CTSU Regulatory Office. Study teams may check the status of their certification by logging into the CTSU website, clicking the blue ‘Regulatory’ tab then clicking the beige ‘Site Registration’ tab then entering the CTEP site code and protocol number N0574 in the search boxes and clicking ‘Go’.

Note: The above credentialing requirements are a change in the “Site Registration Requirements” as compared to previous NCCTG requirements. If a center’s radiosurgery unit was credentialed for N107C or an RTOG brain SRS protocol by successfully irradiating and passing the SRS phantom study and their treatment equipment has not changed, the site does not need to be re-credentialed for this study. If you are unsure of your status go to the RPC web site at http://rpc.mdanderson.org/rpc/; select
“Credentialing” and then “NCCTG.” To determine if these requirements have already been met by your institution, select “Credentialing Status Inquiry.”

5.0 Stratification Factors

5.1 Age
Years: 18 to 59 vs. ≥ 60.

5.2 Extra-Cranial Disease Controlled
Months: ≤ 3 vs. > 3.

5.3 Number of Brain Metastases
1 vs. 2 vs. 3.

6.0 Registration/Randomization Procedures

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

6.1 Pre-Registration Requirements

For CTSU Sites only:

6.11 Investigator Registration
Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch (PMB), CTEP, DCTD, NCI. These forms are available on the members section of the CTSU website or by calling the PMB at (240) 276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

6.12 Site Registration Requirements – IRB Approval

6.121 Site IRB Approval
Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study teams may check the status of their site by logging into the CTSU website, clicking the blue ‘Regulatory’ tab then clicking the beige ‘Site Registration’ tab then entering the CTEP site code and protocol number N0574 in the search boxes and clicking ‘Go’.

6.122 Continuing IRB Review
In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less
than annually). If the necessary documentation is not submitted in advance of attempting patient pre-registration, the pre-registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

6.123 End of Continuing IRB Review
When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the CTSU is no longer necessary.

6.13 Site Registration Requirements – RTFI Form Submission to CTSU
As per NCI policy, all radiation therapy facilities participating in NCI sponsored protocols must be active in the Radiological Physics Center (RPC) Quality Assurance monitoring program. For institutions enrolling through the CTSU, a Radiation Therapy Facilities Inventory (RTFI) form must be on file with the CTSU. CTSU requires a one-time submission of the RTFI form for each study for each facility used by a site. If the RTFI has been previously submitted to the CTSU, it does not need to be resubmitted unless updated have occurred at the facility. A copy of the RTFI may be downloaded from the CTSU website and submitted to the CTSU Regulatory Office.

6.2 Pre-Registration (Step 1)

6.21 Pre-Registration Procedures

For NCCTG sites only:
6.211 Prior to performing the planning MRI, fax to (507) 284-0885 a completed NCI Cooperative Group Pre-registration Eligibility Checklist to the NCCTG Registration Office between 8 a.m. and 4:30 p.m. Central Time Monday through Friday. At the time of pre-registration, the patient will receive an NCCTG patient identification number.

6.212 Prior to accepting the pre-registration, the Random Center personnel will verify the following:
- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information (*U.S.A. institutions only*)

For CTSU Sites only:
6.213 Contact the CTSU Patient Registration Office by calling (888) 462-3009 between 9:00 a.m. and 5:30 p.m. Eastern Time, Monday to Friday. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs (i.e., within one hour), call the registrar cell phone at (301) 704-2376. Complete the following forms:
- CTSU Patient Enrollment Transmittal Form
- NCI Cooperative Group Pre-registration Eligibility Checklist
Fax these forms to the CTSU Patient Registrar at (888) 691-8039 between the hours of 9:00 a.m. and 5:30 p.m., Mon-Fri, Eastern Time (excluding holidays); however, please be aware that registrations received after 5:00 p.m. will be processed the next day. The CTSU registrar will check the investigator and site information provided to ensure that all regulatory and special credentialing requirements have been met. The registrar will also check the forms for completeness and will follow-up with the site to resolve any discrepancies. Once investigator eligibility is confirmed and enrollment documents deemed complete, the CTSU registrar will contact the NCCTG Registration Office within the confines of their office hours to obtain assignment of a unique NCCTG patient identification number. This number is to be used on all future forms and correspondence. The CTSU registrar will relay the patient identification number to the enrolling site and follow up with a pre-registration confirmation via e-mail or fax.

Randomization must take place within 14 days of patient pre-registration.

6.214 CTSU Prestudy Requirements for Patient Pre-Registration
- Patient must meet all pre-registration inclusion criteria, and no exclusion criteria should apply.
- Patient has signed and dated all applicable consents and authorization forms.
- All applicable baseline laboratory tests and pre-study evaluations performed.
- Baseline Quality of Life questionnaire (FACT-Br questionnaire) and the Functional Independence Form (Barthel ADL Index) must be completed after informed consent and prior to randomization.
- Baseline neurocognitive testing must be completed after informed consent and prior to randomization.

For all sites (NCCTG and CTSU Sites):
6.22 Pre-Registration Tests/Procedures
Pre-registration tests/procedures must be completed within the guidelines specified on the test schedule (see Section 4.0).

6.23 Required Grading of Baseline Symptoms
All required baseline symptoms (see Section 10.5) must be documented and graded.

6.24 Confirmation of Eligibility
A radiation oncologist has seen the patient and confirms the patient is a suitable candidate for this study.

6.25 Patient Questionnaire Booklets
Patient questionnaire booklets (The Quality of Life (FACT-Br) questionnaire, the Neurocognitive Examiners Booklet and the Neurocognitive Patient Completed Booklet) are available at site.

6.26 Grooved Peg Board
Grooved peg board available for Neurocognitive testing.
(These peg boards can be purchased at the following web addresses:

Version Date 10/31/14
Update #06
Note: If site already has a Grooved Pegboard from Lafayette Instruments, this may be used and will not have to be purchased.

6.3 Randomization (Step 2)

6.31 Randomization Procedures

For NCCTG sites only:
6.311 After performing the planning MRI, fax to (507) 284-0885 a completed NCI Cooperative Group Randomization Eligibility Checklist to the NCCTG Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

For CTSU Sites only:
6.312 After performing the planning MRI, call the CTSU Patient Registrar cell phone at (301) 704-2376 to randomize the patient. Be prepared to give your contact information and the patient’s identification number assigned at pre-registration.

IMPORTANT: Note that the CTSU Patient Registrar can only randomize patients during CTSU Office hours (9:00 a.m. to 5:30 p.m. Central Time).

Complete the following forms:
- CTSU Patient Enrollment Transmittal Form (include patient identification number assigned at pre-registration)
- NCI Cooperative Group Randomization Eligibility Checklist

Fax these forms to the CTSU Patient Registrar at (888) 691-8039. The CTSU registrar will check these forms for completeness and follow-up with the site to resolve any discrepancies. Once randomization forms are deemed complete, the CTSU registrar will contact the NCCTG Registration Office within the confines of their office hours to obtain a randomization assignment. The CTSU registrar will then relay the treatment assignment to the randomizing site and follow up with a randomization confirmation via e-mail or fax.

Treatment must begin within < 7 days of patient randomization, but may begin on the same day a patient randomization. (For the vast majority of patients, treatment will be delivered the same day as the planning MRI and randomization.)

For all sites (NCCTG and CTSU Sites):
6.32 Treating Physician and Site
Treatment on this protocol must commence at the accruing membership under the supervision of a CTSU or an NCCTG member physician.

6.33 Start of Treatment
Treatment cannot begin prior to randomization and must begin ≤ 7 days after randomization.
6.34 Completion of Tests/Procedures
Tests/procedures must be completed prior to randomization within the guidelines specified on the test schedule (see Section 4.0 for further details).

6.35 Randomization Groups
After the patient has been randomized into the study, the values of the stratification factors (Section 5.0) will be recorded, and the patient will be randomly assigned to one of the following treatment groups:

- SRS
- SRS + WBRT

7.0 Protocol Treatment

7.1 Prior to Treatment

7.11 Baseline QOL, Functional Independence and Neurocognitive Tests
After informed consent is obtained from the patient and prior to randomization, baseline QOL, functional independence, and neurocognitive tests must be completed. Patients must undergo radiosurgery treatment \( \leq \) 7 days after randomization.

7.12 Performance of SRS at a Site Other than the Registering Site
The radiosurgery can be delivered at a different site than the site pre-registering the patient as long as treatment guidelines are followed and the site delivering the SRS has been credentialed for SRS by the Radiological Physics Center (RPC). Note: Please inform RPC, NCCTG Registration and CTSU that your site will register the patient and perform SRS at a different site; please include the sites’ names and CTEP site codes. Without this information, the registration of the patient may be refused or delayed.

7.13 SRS Dose
The SRS dose has been selected in order to provide a high rate of local control with minimum risk of radionecrosis. Due to the additive biological effect of WBRT to the target lesion and surrounding normal tissue, the SRS dose has been decreased slightly when WBRT is given. The SRS dose is decreased modestly for larger lesions in order to account for the volume effect on complication rates.

7.14 Chemotherapy Prohibited During SRS and WBRT
Chemotherapy is not allowed during the SRS and WBRT.

7.2 Radiosurgery (SRS) Guidelines

Radiosurgery for patients on this protocol can only be performed at RPC approved facilities. See protocol Section 6.1 for details.

If all lesions cannot be treated on the same day, all lesions MUST be treated \( \leq \) 7 days of treatment of the first lesion. The radiosurgery can be delivered at a different site than the site pre-registering the patient (see Section 7.12).
7.21 Medications
Patients may be given an intravenous bolus dose of 8 to 16 mg of dexamethasone or 40 to 80 mg of SoluMedrol at the time of SRS, at the discretion of the treating physician.

7.22 Equipment

7.221 Modality
Gamma knife or X-rays with nominal energy of 4 megavoltage (MV) or greater for accelerator-based treatments, including mini-multi-leaf technology or linear accelerators mounted on robotic arms utilizing skull tracking software.

7.222 Calibration
The calibration of linear accelerators used in this study shall be verified by the Radiological Physics Center (RPC).

7.23 Target Volume Definitions
The volumes shall be defined by a planning MRI brain scan, with the patient in the treatment position. ICRU-50 nomenclature target volumes are defined as follows:

7.231 Gross Tumor Volume (GTV)
This is defined as the contrast enhanced tumor seen on planning MRI. The maximal cross-sectional diameter must be < 3.0 cm.

7.233 Clinical Target Volume (CTV)
This is defined as the GTV for this study.

7.24 Target Dose

7.241 Prescription Specification
The dose should be prescribed to the highest isodose line encompassing the CTV, which can range from 50% to 80% of the maximum dose.

7.242 Dose Definition
Dose is specified in Gray (Gy) to muscle.
7.243 Prescription Dose
The total prescribed dose is determined by treatment arm and tumor size.

<table>
<thead>
<tr>
<th>Arm A (SRS only):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesions &lt; 2.0 cm receive 24 Gy</td>
</tr>
<tr>
<td>Lesions 2 – 2.9 cm receive 20 Gy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm B (SRS and WBRT):</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRS:</td>
</tr>
<tr>
<td>Lesions &lt; 2.0 cm receive 22 Gy</td>
</tr>
<tr>
<td>Lesions 2 – 2.9 cm receive 18 Gy</td>
</tr>
<tr>
<td>WBRT:</td>
</tr>
<tr>
<td>Refer to prescribed dose and fractionation in Whole Brain Radiation Therapy (WBRT) Guidelines section.</td>
</tr>
</tbody>
</table>

7.244 Dose Uniformity
It is acknowledged that isodose coverage varies with the equipment used. Efforts should be made to cover the GTV with as uniform a dose as possible.

7.245 Dose Conformity
The ratio of the prescription isodose volume to the target volume (GTV) should be between 1.0 and 2.0. It is understood that this ratio may be difficult to achieve with some very small lesions. For lesions less than 5 mm in size, a ratio up to 3.0 is acceptable.

7.25 Treatment Technique
An immobilization/patient localization system is mandatory for this study. Multiple isocenter techniques are permitted.

7.26 Normal Tissue/Critical Structures
The treatment parameters should be modified to optimize the fit of the prescription volume to the target volume while minimizing dose to critical structures. The dose to the optic chiasm should be less than 8 Gy.

7.27 Dose Calculation and Reporting

7.271 Treatment Time
The monitor units or time required to deliver the prescribed dose shall be calculated and submitted.

7.272 Dose Uniformity
The maximum and minimum doses in the CTV shall be calculated and reported. These may be extracted from isodose distributions, calculated separately or derived from Dose Volume Histograms (DVHs).

7.273 Conformity Index
The PITV, defined as the ratio of the prescription isodose volume to the target volume, shall be calculated and reported. If the prescription
isodose volume is calculated from a DVH, that DVH shall be submitted (see QA Documentation).

7.274 Prescription Isodose Line
The total dose delivered to the prescription isodose line shall be calculated and reported.

7.275 Normal Tissue and Critical Organ Dose Points
Documentation of the highest point dose to the optic chiasm or a DVH of the optic chiasm shall be submitted (see QA Documentation).

7.276 Isodose Distribution
A hard copy of the isodose distribution for each target must be submitted. Isodose distributions should be displayed on three orthogonal planes or, if not possible, on multiple transverse slices through each target.

7.3 Whole Brain Radiation Therapy (WBRT) Guidelines

For ARM B Only

Radiation therapy for patients on this protocol can only be delivered at facilities which are approved by your cooperative group.

Note: For patients randomized to Arm B: SRS and WBRT, initiation of WBRT is ≤ 14 days following SRS.

7.31 Equipment

7.311 Modality
X-ray beams with a nominal energy between 4 and 6 MV.

7.312 Calibration
The calibration of therapy machines to deliver WBRT used in this study shall be verified by the RPC.

7.32 Target Volume

7.321 Definition
The Target Volume consists of the entire brain and meninges, including the frontal lobe as well as the posterior halves of the globes of the eyes, with the optic disk and nerve, superior to the vertex, and posterior to the occiput. The caudal border shall be below the skull base at the top of the C2 vertebral level.

7.322 Localization
The planning target volume shall be defined by means of a simulator.
7.33 Target Dose

7.331 Prescription Point
The prescription point in the cranial volume is at or near the center. For multi-convergent beams, the prescription point is usually at the intersection of the beam axes. Note: Regardless of the location of the central axis, the dose should be prescribed at the center on the cranial volume (midway between the maximum separation).

7.332 Dose Definition
The absorbed dose is specified below in Gy to muscle.

7.333 Tissue heterogeneity
No corrections for bone attenuation shall be made.

7.334 Prescribed dose and fractionation
The total dose to the prescription point is 30 Gy. This dose is delivered in 12 fractions of 2.5 Gy. All radiation fields shall be treated once each day. The treatment shall be given 5 days a week.

7.335 Dose Uniformity
The dose variations in the target volume shall be within +7% (-5% of the prescription-point dose).

7.336 Treatment Interruptions
No corrections shall be made for treatment interruptions less than seven days. For interruptions greater than seven days, please contact Dr. Paul Brown using the contact information listed on the protocol’s title page.

7.34 Treatment Technique

7.341 Patient Position
It is recommended that the patient be treated supine.

7.342 Beam Configuration
The cranial volume is treated with two lateral, equally weighted photon beams. The fields shall extend at least 1 cm beyond the periphery of the scalp. “Compensating beams” that block hot spots (these hot spots are typically present along the midline due to less tissue present in these regions compared to mid-brain) are allowed to achieve better dose homogeneity.

7.343 Field Shaping
Filed Shaping shall be done with blocks that are at least 5 half-value layers (HVL) thick. Multi-leaf collimation is allowed.

8.0 Dosage Modifications Based on Adverse Events
None.
9.0 Ancillary Treatment

9.1 Concomitant Medications
Patients may be currently receiving hormonal agents, steroids, and/or anticonvulsants.

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Adverse Events Descriptions and Grading Scales
CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized until September 30, 2011. CTCAE version 4.0 will be utilized for expedited adverse event reporting only, beginning October 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE v3.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

10.11 Adverse Event Monitoring
Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE. Next, determine whether the event is expected or unexpected (see Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.3). With this information, determine whether an adverse event should be reported as an expedited report (see Section 10.4). Important: Expedited adverse event reporting requires a CTEP Adverse Event Reporting System (CTEP-AERS) report(s). Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.4 and 10.5. All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.4 and 18.0).

Effective with Addendum 5 and beginning October 1, 2011, expedited AdEERS reporting for this protocol has been updated by the NCI/CTEP to use CTCAE v4.0. In addition, effective with Update 5, the CTEP-AERS is live for use in place of AdEERS. Therefore:

1) Events reporting expedited reporting through CTEP-AERS must be reported through the CTEP-AERS system in CTCAE v4.0.

2) The events reported via CTEP-AERS must ALSO be reported through routine reporting (i.e., Case Report Forms) using CTCAE v3.0.

3) Routine data collection via Case Report Forms, including the “Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form,” will remain using CTCAE v3.0 for this study.

10.12 CTCAE and Grade
Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT). Grade is an essential element of the Guidelines and, in general, relates to severity for the purposes of regulatory reporting to NCI.
Note: A severe AE, as defined by the above grading scale, is NOT the same as...
10.2 Expected vs. Unexpected

- The determination of whether an AE is expected is based on information provided in Section 15.0 of this protocol.

- Unexpected AEs are those not listed in the information provided in Section 15.0 of this protocol.

**Note**: “Unexpected adverse experiences” means any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

- **Definite** - The adverse event is clearly related to the agent(s).
- **Probable** - The adverse event is likely related to the agent(s).
- **Possible** - The adverse event may be related to the agent(s).
- **Unlikely** - The adverse event is doubtfully related to the agent(s).
- **Unrelated** - The adverse event is clearly NOT related to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.31 Special Situations for Expedited Reporting

10.311 An expedited report is not required for a specific protocol where an AE is listed as expected. These events must still be reported via routine reporting as specified in Section 10.5. The protocol-specific guidelines supersede the NCI Adverse Event Reporting Guidelines (See Section 10.4) for AE reporting.

10.312 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies or birth defects, must be reported immediately if they occur at any time following treatment with an agent under an IND/IDE since they are considered to be a serious AE and must be reported to the sponsor as specified in 21 CFR 312.64(b).
10.313 Death
Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24 hours.
Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Reportable Categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: An unexpected cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as Grade 5 “Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)” under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (i.e., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.314 Secondary Malignancy

- A secondary malignancy is a cancer caused by treatment for a previous malignancy (i.e., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- CTEP requires all secondary malignancies that occur following treatment with an agent under an IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:
  - Leukemia secondary to oncology chemotherapy (i.e., Acute Myelocytic Leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy
• Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.315 Second Malignancy
A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS.
10.4 Expedited Reporting Requirements:

**Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies within 30 Days of the Last Treatment**

**FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)**

*Note:* Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64). An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

**ALL SERIOUS** adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<thead>
<tr>
<th>Hospitalization</th>
<th>Grade 1 Timeframes</th>
<th>Grade 2 Timeframes</th>
<th>Grade 3 Timeframes</th>
<th>Grade 4 &amp; 5 Timeframes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resulting in Hospitalization ≥ 24 hrs</td>
<td>10 Calendar Days</td>
<td>24-Hour 5 Calendar Days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not resulting in Hospitalization ≥ 24 hrs</td>
<td>Not required</td>
<td>10 Calendar Days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Additional Instructions or Exclusions to Expedited Reporting

- These instructions supersede the table above
- Grade 1-3 events listed in **Section 15** of the protocol or hospitalization resulting from such do not require CTEP-AERS reporting, but should be reported via routine AE reporting.

**Expedited AE reporting timelines are defined as:**

- “24-Hour; 5 Calendar Days” - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- “10 Calendar Days” - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

1Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

**Expedited 24-hour notification followed by complete report within 5 calendar days for** All Grade 4, and Grade 5 AEs

**Expedited 10 calendar day reports for** Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization, Grade 3 adverse events

**Effective Date:** May 5, 2011

Version Date 10/31/14

Update #06
Refer to 10.41 for NCI Contact Information or Technical Help regarding CTEP-AERS reporting.

In the rare event when internet connectivity is disrupted, a 24 hour notification must be made to NCI by telephone. An electronic report must be submitted immediately upon establishment of internet reconnection.

10.41  Contact Information for NCI Safety Reporting

<table>
<thead>
<tr>
<th>Website for submitting expedited reports</th>
<th><a href="https://eapps-ctep.nci.nih.gov/ctepaers/">https://eapps-ctep.nci.nih.gov/ctepaers/</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>AEMD Help Phone (for CTEP)*</td>
<td>301-897-7497 Monday through Friday, 7:00 AM to 7:00 PM (US Eastern Time)</td>
</tr>
<tr>
<td>CIP Help Phone for SAE reporting*</td>
<td>301-897-1704 Monday through Friday, 7:00 AM to 7:00 PM (US Eastern Time)</td>
</tr>
<tr>
<td>Fax for expedited report supporting Medical Documentation for CTEP trials</td>
<td>301-230-0159 (back-up FAX: 301-897-7404)</td>
</tr>
<tr>
<td>Fax for expedited report supporting Medical Documentation for CIP trials</td>
<td>301-897-7402</td>
</tr>
<tr>
<td>AEMD Help Email:</td>
<td><a href="mailto:aemdl@tech-res.com">aemdl@tech-res.com</a></td>
</tr>
<tr>
<td>CIP SAE Reporting Email</td>
<td><a href="mailto:CIPSAEReporting@tech-res.com">CIPSAEReporting@tech-res.com</a></td>
</tr>
<tr>
<td>Technical (e.g., IT or computer issues ONLY) Help Phone*</td>
<td>1-888-283-7457</td>
</tr>
<tr>
<td>CTEP-AERS Technical Help Email</td>
<td><a href="mailto:nctictephelp@ctep.nci.nih.gov">nctictephelp@ctep.nci.nih.gov</a>.</td>
</tr>
<tr>
<td>CTCAE v4 Help/Questions Email</td>
<td><a href="mailto:ncticcaehelp@mail.nih.gov">ncticcaehelp@mail.nih.gov</a></td>
</tr>
</tbody>
</table>

*Office phone and fax are accessible 24 hrs per day 7 days a week (The CTEP-AERS MD phone line is staffed from Monday through Friday, 7:00 AM to 7:00 PM ET. Any phone call after these hours will go to voicemail. Please leave contact information and the phone call will be returned the following business day.
10.5 Other Required Expedited Reporting

<table>
<thead>
<tr>
<th>EVENT TYPE</th>
<th>REPORTING PROCEDURE</th>
</tr>
</thead>
</table>
| Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report | **NCCTG Institutions Only**: Complete a Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form within 5 working days, using CTCAE v3.0, of the date the clinical research associate (CRA) is aware of the event(s) necessitating the form. If a CTEP-AERS report has been submitted, this form does not need to be submitted.

10.51 Adverse Events and Symptoms/Conditions to be Graded at Baseline
Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per Common Terminology Criteria for Adverse Events (CTCAE) v3.0 grading unless otherwise stated in the table below:

<table>
<thead>
<tr>
<th>CTCAE v3.0 Category</th>
<th>Adverse Events/Symptoms</th>
<th>Baseline</th>
<th>Each Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatology/Skin</td>
<td>Hair loss/Alopecia (scalp or body)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Rash: dermatitis associated with radiation - radiation</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Neurology</td>
<td>Cognitive disturbance</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Neuropathy – motor</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>CNS necrosis</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Ocular/Visual</td>
<td>Retinopathy</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Auditory/Ear</td>
<td>Hearing, patients without baseline audiogram and not enrolled in a monitoring program</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Otitis, external ear</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

10.52 Adverse Event Submission Using Case Report Forms (CRFs)
Submit via appropriate NCCTG Case Report Forms (i.e., paper or electronic, as applicable) the following AEs using CTCAE v3.0 experienced by a patient and not specified in Section 10.4:

10.521 Grade 2 AEs deemed possibly, probably, or definitely related to the study treatment or procedure.

10.522 Grade 3 and 4 AEs regardless of attribution to the study treatment
10.523 Grade 5 AEs (Deaths)

10.5231 Any death within 30 days of the patient’s last study treatment or procedure.

10.5232 Any death more than 30 days from the patient’s last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.53 Submission of Late Occurring Adverse Events
Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Treatment Evaluation/Imaging Guidelines

11.1 Response criteria
The response score will be rated as one of the following (follow-up MRI brain scans will be compared to the planning MRI brain scan):

**Complete response:** Radiographic disappearance of brain metastasis (es)

**Partial response:** Greater than 50% reduction in the size of each lesion radiographically, using perpendicular diameters

**Stable disease:** 0 to 50% reduction in the size of each lesion radiographically, using perpendicular diameters

**Disease progression:** Increase of > 25% in the size of any lesion or a new, non-contiguous lesion (in the brain)

**Note:** Tumor progression of the treated SRS lesions will be evaluated independently of the development of new lesions. Radionecrosis will not be considered tumor progression.

11.2 Magnetic Resonance Imaging (MRI) Guidelines
The diagnostic MRI brain scan will fall into one of three categories: pre-registration, planning and follow-up. The planning MRI brain scan will be used to determine final eligibility and used for planning of the SRS treatment. The pre-registration MRI brain scan will be used to determine preliminary patient eligibility. The pre-registration MRI brain scan is without parameters since it is performed prior to study entry.

The minimum parameters for the planning MRI brain scan and the follow-up MRI brain scans are:

- Sagittal T1 pre-contrast images
- Coronal and axial post-contrast images
- 5mm or less slice thickness
- Scanner should be at least a 1.5 Tesla magnet
Note: The same technique must be used for each of the diagnostic MRI brain scans at follow-up.

Note: The pre-registration MRI scan may be used for the planning scan if the minimum parameters for the planning MRI brain scan are met as outlined above.

11.3 Monitoring of Symptoms and for Treatment Failure
Patients will be monitored for clinical evidence of progression of neurological symptoms and treatment failure. Patients will be assessed with a physical and neurological examination and contrasted MRI brain scan at baseline (prior to randomization) and post-treatment at weeks 6 and 12, months 6, 9, 12, 16, 24, 36, 48, and 60. Follow-up visits are required +/- 14 days for weeks 6 and 12, +/- 1 month for months 6, 9, 12, and 16, and +/- 4 month for months 24, 36, 48, and 60. At each scheduled study visit, a QOL (FACT-Br) questionnaire, Functional Independence form (Barthel ADL Index) and neurocognitive status tests will be completed.

11.4 Monitoring for Recurrence and Progression
Patients will be monitored for local recurrence, distant brain recurrence and progression until death or 5 years from study entry. Patients will continue to be monitored after progression and should continue to complete study evaluations and should continue to be followed using the test schedule for observation (Section 4.0). Patients also will be monitored, whenever possible, for additional primaries and regional recurrence, with pathologic confirmation.

11.5 Response Rate
The follow-up MRI brain scans will be compared to the planning MRI brain scan and will be used to score a response rate for each lesion and to detect distant brain recurrence. Every effort will be made to distinguish between disease progression and radionecrosis including, as indicated, MRI, SPECT (single photon emission computed tomography), PET (positron emission tomography), or surgical resection.

11.6 Time to CNS Failure
Time to CNS failure will be measured from the date the patient is randomized on this study to the date of diagnosis of disease progression.

11.7 Survival
Survival time will be measured from the date the patient is randomized on this study to death, due to any cause. Death will be scored either as due to neurological cause (any CNS event such as an intracranial mass, hemorrhage, or hydrocephalus) or non-neurological cause. A copy of the death certificate should be submitted. Autopsy reports should be obtained, whenever possible, and sent by fax NCCTG Operations Office at (507) 266-7240.

11.8 Response Review
Radiologic Images: All radiologic images must be free of marks that might obscure the lesions or bias the evaluation of the reviewer(s). The following MRI brain scans are to be submitted ≤1 week of completion (Note: this applies to ALL NCCTG and CTSU sites):

- Pre-registration and planning
- Completion of therapy (six weeks after SRS)
• Best response (These images may be submitted once best response has been radiographically established.)
• Disease progression
• The MRI brain scans performed at Month 12 should be submitted, in the absence of any change post-completion of therapy. These studies will be reviewed by the NCCTG PIs for final classification of disease progression versus radionecrosis.

Submit all materials (images on CDs are preferred to film but must be DICOM compatible) to NCCTG Operations Office, Att’n: RT Coordinator, NW Clinic 3-24-CC, 200 First Street SW, Rochester, MN 55905

In the absence of any change post-completion of therapy, the MRI brain scans performed at Month 12 should be submitted. These studies will be reviewed by the NCCTG study chairs for final classification of disease progression versus radionecrosis.

Note: Reimbursement will not be given for any cost incurred for submitting these materials.

12.0 Descriptive Factors
None.

13.0 Treatment/Follow-Up Decision at Evaluation of Patient

13.1 Treatment of Recurrence
Directions for the treatment of recurrence are important in order to assure the comparability of patient outcomes between treatment arms. Clinical judgment in the management of palliative patients is paramount. At the discretion of the treating physician, the study chair should be contacted for guidance.

13.2 Retreatment Guidelines

13.21 One to Three New Lesions
Patients who develop recurrence to the brain following study treatment should be retreated with SRS alone if one to three NEW lesions are present in the absence of rapidly progressive systemic disease (please note it is NOT recommended that a brain metastases previously treated with SRS be retreated with SRS). WBRT should be withheld unless more than three lesions recur in a rapid fashion or the patient refuses SRS.

13.22 More than Three Metastases
For more than three metastases, WBRT alone should be given, reserving SRS for salvage. WBRT should be considered (especially in those patients not previously treated with WBRT) in patients with progressive metastases that have received SRS to these (specific) lesions.

13.221 The salvage WBRT dose guidelines are as follows:

Arm A: Initial WBRT of 30 Gy in 10 fractions.
If needed repeat WBRT of 25 Gy in 10 fractions.

Arm B: Repeat WBRT 25 Gy in 10 fractions.
13.23 Treatment other than SRS and WBRT
An abbreviated course of treatment for the patient may be more appropriate, depending on systemic disease progression. Palliative surgery is recommended for patients with a symptomatic lesion not responsive to high-dose steroids when there is no evidence of rapidly progressive systemic disease. Chemotherapy is administered at the discretion of the treating physician.

13.24 Patient and Physician Discussion of Additional Treatment
All patients should be instructed to communicate with their study doctor (i.e. treating physician) prior to accepting any additional therapy.

13.3 Treatment / Follow up Decision

13.31 Treatment After Progression
Patients who have progressed will continue with evaluation as outlined under observation in Section 4.0. An Event Monitoring Form must be completed to report progression in the brain or progression of systemic disease (see Section 18.0). However, it is recommended to treat patients per Section 13.2.

13.32 Treatment Not Completed
If a patient does not complete treatment, they will go to observation.

13.33 Patient Withdrawal
Patients who refuse continued observation (i.e., withdraw from the study) will go to event-monitoring.

13.34 Patient Refusal of Treatment
If a patient refuses a treatment assignment (and is classified as a cancel), it is necessary to provide follow-up information. The patient will go directly to the observation phase of the study. On-study material and the End of Active Treatment/Cancel Notification Form, including the Radiation Therapy Reporting Form (site must write the reason the radiation was not given on the blank space of the form prior to submitting) must be submitted.

13.35 Definition of Cancel
A patient is deemed a cancel if he/she is removed from the study for any reason before any study treatment is given. The patient will go directly to the observation phase of the study. On-study material and the End of Active Treatment/Cancel Notification Form, including the Radiation Therapy Reporting Form (site must write the reason the radiation was not given on the blank space of the form prior to submitting) must be submitted.

14.0 Body Fluid Biospecimens
None.

15.0 Radiation Therapy Risks and Nursing Guidelines

15.1 Stereotactic Radiosurgery (SRS)

15.11 Risks and Side Effects
Risks and side effects related to the Stereotactic Radiosurgery (SRS) include the
following:

**Likely**
- Temporary pain associated with the head frame placement (if a head frame is used)

**Less Likely**
- Headache
- Localized alopecia which may be permanent
- Nausea
- Vomiting
- Allergic reaction to the local anesthesia (rash, itching, nausea, or difficulty breathing)
- Bleeding and/or infection around the head frame (if a head frame is used)

**Rare but serious**
- Decreased brain function such as motor function (coordination/movement)
- Swelling of the brain in the treated area which may require steroids
- Brain necrosis, which may require surgery to remove
- Stroke
- A secondary malignancy in the brain or nearby organs
- Damage to vision tracts with the possibility of permanent blindness

15.12 Nursing Guidelines

15.221 Instruct patient regarding possible localized hair loss.

15.222 Corticosteroid use not required per protocol.

15.223 Report any neurologic changes to physician.

15.224 Remind all patients of the need to use adequate contraception throughout the study and for male patients for 3 months beyond study treatment.

15.2 Whole Brain Radiotherapy (WBRT)

15.21 Risks and Side Effects
Risks and side effects related to the Whole Brain Radiation Therapy (WBRT) include the following:

**Likely**
- Alopecia, which may be permanent
- Temporary scalp erythema and drying
- Fatigue
Less Likely
- Nausea
- Memory loss, which can occur in the first few months after whole brain radiotherapy and may be permanent
- Cataract formation
- Xerostomia
- Taste changes
- Temporary ear and ear canal redness, plugging or drainage
- Headaches
- Increased sleepiness (occurring four to ten weeks after radiation therapy is complete and lasting for several days up to two weeks)

Rare but serious
- Decreased brain function such as motor function (coordination/movement)
- Brain necrosis, which may require surgery to remove
- Stroke
- Secondary malignancy, in the brain or nearby organs
- Eye damage with the possibility of permanent blindness

15.22 Nursing Guidelines
15.221 Advise patient of probable hair loss, redness and dryness of the scalp.
15.222 Instruct patient in corticosteroid use per MD order. 
   Note: corticosteroid use not required per protocol.
15.223 Observe for signs and symptoms of neurology changes. Report any changes to physician immediately.
15.224 Advise patient of probable taste changes. Suggest hard candy to minimize dry mouth and taste changes.
15.225 Observe patient for possible skin reaction to external ear, inner canal inflammation. Report changes to the physician.
15.226 Assess for increased fatigue; instruct patient in energy–saving life–style.
15.227 Remind all patients of the need to use adequate contraception throughout the study and for male patients for 3 months beyond study treatment.
16.0 Statistical Considerations

16.1 Introduction
This protocol is meant to be a continuation of the ACOSOG trial Z0300, which was closed by ACOSOG leadership in 2004. Since this is a continuation of the previous study, we have tried to make very few changes to the original protocol with regards to eligibility and treatment protocol so that we can include the 70 patients who have already been accrued by Z0300. However it is recognized that a survival question is not clinically relevant with the high death rate due to systemic disease and new level I evidence that suggests even a significant improvement in brain control has little impact on survival (Aoyama et al., 2006). In addition there is now greater appreciation of neurocognitive progression as a valid endpoint and the Food and Drug Administration now considers improvement in neurocognitive function or delay in expected decline approved endpoints in registration trials, since these endpoints directly relate to clinical benefit.

Therefore the primary study objective is to assess whether patients randomized to receive SRS (Arm A) will experience less neurocognitive progression than patients randomized to receive SRS + WBRT (Arm B).

16.2 Primary Endpoint
The primary endpoint is neurocognitive progression. Neurocognitive progression is defined as a drop of at least one standard deviation from baseline in one of the five neurocognitive tests (all tests are standardized based on published norms) at the 3 month post-radiosurgery evaluation. In our primary analysis, we will only use evaluable patients, those who have survived for at least 3 months and undergone neurocognitive testing. Based on the literature, we assume that the proportion of patients with neurocognitive progression at the 3 month post-radiosurgery evaluation is 0.65 for patients undergoing SRS + WBRT (Arm B) (Li et al., 2007). Our study is designed to ascertain if this proportion decreases for patients undergoing SRS alone (Arm A).

The primary analysis for neurocognitive progression (the primary outcome) will be a test of differences in the (binomial) proportion of patients who experienced neurocognitive progression within 3 months post-radiosurgery.

16.2.1 Power
A type I error probability of 0.10 (two-sided) and desired power of 85% is specified. Study size computations are based on the randomization to the arms with equal probability, the assumed baseline (SRS + WBRT) proportion of neurocognitive progression is 0.65 and the clinically consequential difference is an absolute decrease in that proportion of 0.25 (i.e. the proportion for the SRS arm will be 0.40 or less).

16.2.2 Accrual and Sample Size
It is our intent to include the 70 patients that have been accrued by Z0300 in our analysis. Based on the given parameters for the power calculation, this protocol requires a total of 112 evaluable patients (i.e. 56 patients in each arm). We had originally planned on an over accrual of 35%, i.e. 40 patients, to account for those patients that are not evaluable due to their not completing a neurocognitive evaluation at 3 months (due to death, patient refusal, etc.). However, the observed rate of patients, after accruing the 152 patients, was 47%, hence, the amount of over accrual has been increased to 112%, i.e. 126 patients. This results
in a total target enrollment sample size of 112 + 126 = 238 patients. We anticipate pre-registering 310 patients to register a total of 238 patients necessary for the study design and allotted over accrual. In summary, for this protocol, we will accrue an additional 238 – 70 (those accrued from ACOSOG Z0300) = 168 patients.

16.23 Interim Analyses
One formal interim analysis will be performed at the time at which 50% of the patients have been evaluated for neurocognitive function at three months post-radiosurgery using two-sided O-Brien-Fleming type stopping boundary (O’Brien and Fleming, 1979). 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 analyses cutoff values (z-scale), boundary probabilities and cumulative Type I error for the log-rank statistics at the two analyses times (interim and final) are in the table below.

<table>
<thead>
<tr>
<th>Time (proportion of evaluable pts)</th>
<th>stopping boundaries (H0/H1)</th>
<th>nominal boundary probabilities (H0/H1)</th>
<th>cumulative type I/II error</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.50</td>
<td>±2.54 / ±0.19</td>
<td>0.011 / 0.85</td>
<td>0.011 / 0.024</td>
</tr>
<tr>
<td>1.00</td>
<td>±1.66 / ±1.66</td>
<td>0.097 / 0.097</td>
<td>0.10/ 0.85</td>
</tr>
</tbody>
</table>

16.3 Secondary Endpoints and Analysis
Secondary endpoints to be examined include overall survival, time to CNS failure and various QOL and related endpoints described in this protocol. If the superiority of SRS (compared to SRS + WBRT) with respect to neurocognitive progression has not been established, then treatment preference may be determined by these other factors.

A low incidence of local failure has been achieved with the use of SRS + WBRT relative to WBRT alone or WBRT alone relative to surgery only (Kondziolka et al., 1999). Analyses will be performed to determine if CNS failure is unacceptably high for patients receiving SRS alone.

Finally, we will also conduct an analysis of the overall survival endpoint using a stratified log-rank test as well as Cox proportional hazards models that incorporate the stratification factors and adjust for other important prognostic factors such as location of primary tumor (e.g. lung, breast, etc.).

16.4 Quality of Life
The primary QOL objective is to ascertain at 3 months (12 weeks) post-treatment whether patients assigned to Arm 1 (SRS) have better QOL than patients on Arm 2 (SRS + WBRT). The potential side effects of the additional WBRT treatment (e.g., fatigue, alopecia, cognitive decline, and diminished hearing) suggest the combination Arm 2 will have reduced QOL. Furthermore, a recent study (Kondziolka et al., 1999) found there was no neurologic or systemic morbidity related to SRS. Hence, one-sided null hypotheses for improvement on Arm 1 (SRS) will be used. The 3 month time point is proposed as being late enough to capture major treatment effects, but early enough to avoid a substantial difference between-arm morbidity and mortality.

The QOL will be assessed at baseline (prior to randomization), at weeks 6 and 12, and at
months 6, 9, 12, 16, 24, 36, 48 and 60 (essentially QOL will be obtained out to 5 years after the completion of the SRS treatment). The three specific QOL endpoints of primary interest proposed are: brain subscale (using the Br subscale total score) and physical and emotional functioning (using the respective subscale totals of the FACT-Br). The primary analysis will be based on the corresponding change scores from baseline to month 3, using two-sample t-tests and associated confidence intervals. The Bonferroni adjustment will be used to adjust the $\alpha$ level (Type I error) for the 3 endpoints to 0.05/3, and hence 0.016 will be the 1-sided significance level for each of the 3 treatment comparisons.

The relationship of the existence of missing data at specific time points to both baseline assessment data and data from the immediate prior assessment, both using disease status and scores, will provide a basis of assessing the degree to which missing data may be informative (non-random). The existence of a significant amount of non-random missing data will trigger attempts to impute missing data. In addition, the instances of surrogate responders will be treated as both missing and non-missing data in order to assess the degree to which the analyses are robust to assumptions about the nature of missing or surrogate responder data.

Exploratory Generalized Estimating Equations (GEE) analysis (Horton and Lipsitz, 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. Various methods of handling missing data will be used, and the robustness of the analyses to various assumptions about missing data will be investigated. Also, the data will be analyzed according to whether the patient completed the instruments, both with respect to assessing the consistency of scoring and detecting differences between arms.

The Quality-Adjusted Survival (QAS) analysis will adjust each patient’s time on study, by weighting neurological signs and symptoms (a variety of weighting schemes will be explored); the resultant weighted sum is defined as the patient’s QTIME. Subtracting the impact of AEs and re-treatment gives the QAS for each patient (Murray et al., 1995). The QAS values will be compared between treatment arms by the two-sample t-test.

Functional Independence: The duration of functional independence, where Barthel ADL Index score is maintained at or above baseline level, will be compared between treatment arms by the logrank test. A patient whose Barthel ADL Index score has not decreased from baseline will be censored at the last valid Barthel ADL Index assessment time. Kaplan-Meier plots of functional independence will be presented, by treatment and estimates of the corresponding median durations will be obtained. Similar, exploratory analyses will be performed based on a decrease of $\geq 4$ Barthel points, and for decrease to 3 or 4 in ECOG scores.

16.5 Neurocognitive Status
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 and Lipsitz, 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.

16.6 Other Analyses
Additional supporting and exploratory statistical analyses will be conducted using proportional hazard regression and logistic regression. These additional analyses will
focus on host and tumor features that might provide prognostic information for patients with multiple brain metastases, though statistical power will be limited.

16.7  Data Safety Monitoring
In accordance with NCI’s current DMC policy, the Alliance Data Safety Monitoring Board (DSMB) is responsible for reviewing safety data for this trial at least twice a year. Both reviews will be based on reports provided by the Mayo Clinic Cancer Center Statistical Office.

This study will also be monitored by the Clinical Data Updated System (CDUS). Cumulative complete CDUS data will be electronically submitted quarterly to the Cancer Therapy Evaluation Program (CTEP) until all patients are off-study at which time a final report is submitted. Quarterly reports are due January 31, April 30, July 31 and October 31.

16.8  Inclusion of Women and Minorities

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Sex/Gender</th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
<td>Males</td>
<td>Unknown</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>72</td>
<td>162</td>
<td>234</td>
</tr>
<tr>
<td><strong>Ethnic Category: Total of all subjects</strong>*</td>
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<td>166</td>
<td>238</td>
</tr>
<tr>
<td>Racial Category</td>
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<td></td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Black or African American</td>
<td>6</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>White</td>
<td>66</td>
<td>142</td>
<td>208</td>
</tr>
<tr>
<td><strong>Racial Category: Total of all subjects</strong></td>
<td>72</td>
<td>166</td>
<td>238</td>
</tr>
</tbody>
</table>

**Ethnic Categories:**
- **Hispanic or Latino** – a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term “Spanish origin” can also be used in addition to “Hispanic or Latino.”
- **Not Hispanic or Latino**

**Racial Categories:**
- **American Indian or Alaskan Native** – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
- **Asian** – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)
- **Black or African American** – a person having origins in any of the black racial groups of Africa. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American.”
- **Native Hawaiian or other Pacific Islander** – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
- **White** – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.
17.0 Pathology Considerations/Tissue Biospecimens
None.

18.0 Records and Data Collection Procedures
18.1 Submission Timetable

Pre-Registration Material(s)

<table>
<thead>
<tr>
<th>Case Report Form (CRF)</th>
<th>Active-Monitoring Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Registration Screening Failure Form</td>
<td>Complete only if patient is NOT randomized after he/she is pre-registered</td>
</tr>
</tbody>
</table>

Active-Monitoring Phase
(Compliance with Test Schedule Section 4.0)

Initial Material(s)

<table>
<thead>
<tr>
<th>CRF</th>
<th>Active-Monitoring Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>On-Study Form</td>
<td>≤ 14 days after randomization</td>
</tr>
<tr>
<td>Response Review Material</td>
<td></td>
</tr>
<tr>
<td>Baseline Adverse Event Form</td>
<td></td>
</tr>
<tr>
<td>Pretreatment Measurement Form</td>
<td></td>
</tr>
<tr>
<td>Operative and Pathology Reports</td>
<td></td>
</tr>
<tr>
<td>Patient Quality of Life (FACT-Br) Questionnaire Booklet</td>
<td></td>
</tr>
<tr>
<td>Functional Independence</td>
<td></td>
</tr>
<tr>
<td>Patient Neurocognitive Testing Booklet</td>
<td></td>
</tr>
<tr>
<td>Patient Neurocognitive Testing Booklet Submission Fax Form</td>
<td></td>
</tr>
<tr>
<td>Patient (FACT-Br) Compliance Form</td>
<td></td>
</tr>
<tr>
<td>Neurocognitive Testing Booklet Compliance Form</td>
<td></td>
</tr>
<tr>
<td>End of Active Treatment/Cancel Notification Form</td>
<td></td>
</tr>
</tbody>
</table>

1. Both NCCTG and CTSU Sites submit the following to NCCTG Operations Office, QAS for N0574, NW Clinic 3-24 CC, 200 First Street SW, Rochester, MN 55905. Submit the reports AND the radiographic images free of marks that may obscure the lesions or bias the evaluation of the independent reviewer(s). Images on CDs are preferred to film but must be DICOM compatible with a viewing tool. The radiographic images must be identified with the NCCTG study number of N0574 and the assigned patient identification number. The radiographic images must be identified with the date the image was performed and the corresponding time point in the study (e.g., week 6, week 12, month 9 or month 24). As outlined below all pre-randomization and completion of therapy MRI should be submitted. See Section 11.8 for additional details. All paperwork and images should be de-identified, and labeled with study number, patient initials and study ID number.

   a. Pre-registration and planning MRI and reports (reports may not be available with planning scans but if available should be submitted). Separate copies of these CDs must be sent to the Radiation Coordinator and the QAS for N0574.
   b. Completion of therapy MRI (six weeks after SRS) and report
   c. Best response MRI and report
   d. Disease progression MRI and report
e. The MRI brain scans performed at Month 12 and the report should be submitted, in the absence of any change post-completion of therapy. These studies will be reviewed by the NCCTG PIs for final classification of disease progression versus radionecrosis.

2. Original questionnaire booklets must be used; copies are not acceptable for this submission.


4. Submit original Patient Neurocognitive Testing Questionnaire Booklets to Dr Elena Farace at the address listed on the Study Staff page of the protocol. Be certain to also fax the Neurocognitive Booklet Submission to Dr. Farace at the telefax number listed on the Study Staff page of the protocol.

5. This form must be completed only if the Patient QOL Questionnaire Booklet contains absolutely NO patient provided assessment information.

6. Submit <=2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy.

### Test Schedule Material(s)

<table>
<thead>
<tr>
<th>CRF</th>
<th>Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)</th>
<th>At each evaluation during observation(^8) (week 12 and 6,9,12,24,36,48,60 month follow up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation/Treatment Form</td>
<td>X(^1)</td>
<td></td>
</tr>
<tr>
<td>Evaluation/Observation Form</td>
<td></td>
<td>X(^2)</td>
</tr>
<tr>
<td>End of Active Treatment/Cancel Notification Form</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Adverse Event Form</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Active Monitoring Measurement Form</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Radiation Therapy Material</td>
<td>X(^3)</td>
<td></td>
</tr>
<tr>
<td>Response Review Material</td>
<td>X(^4)</td>
<td>X(^4)</td>
</tr>
<tr>
<td>Functional Independence</td>
<td>X(^5)</td>
<td>X(^5)</td>
</tr>
<tr>
<td>Patient Quality of Life (FACT-Br)</td>
<td>X(^5)</td>
<td>X(^5)</td>
</tr>
<tr>
<td>Questionnaire Booklet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient (FACT-Br) Booklet Compliance Form</td>
<td>X(^6)</td>
<td>X(^6)</td>
</tr>
<tr>
<td>Patient Neurocognitive Testing Booklets</td>
<td>X(^7)</td>
<td>X(^7)</td>
</tr>
<tr>
<td>Neurocognitive Testing Booklet Compliance Form</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Patient Neurocognitive Testing Booklet Submission Fax Form</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Notification Form – Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADR/AER</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late Adverse Event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Primary</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Cycle 1 only.
2. Complete at each evaluation during Observation (see Section 4.0)

3. **Both NCCTG and CTSU Sites submit the following to NCCTG Operations Office**
   For patients who do not receive any scheduled radiation therapy, submit the Radiation Therapy Reporting Form with the reason radiation was not given to the address given at the end of this paragraph. For patients who receive partial or complete radiation therapy, submit the following materials ≤ 14 days after the last day of radiation to the NCCTG Operations Office, RT Coordinator, NW Clinic 3-24 CC, 200 First Street SW, Rochester, MN 55905. **All paperwork and images should be de-identified, and labeled with study number, patient initials and study ID number.**

   a. RT reporting form. (Arm B only).
   b. SRS reporting form.
   d. Dosimetry calculations (Arm B only), monitor unit calculations (Arm B only), color copies of required DVHs (as applicable and including CTV) and color copies of the required isodose curves.
   e. Copies of representative simulation films (and/or Beams Eye View, BEV) of all treated fields (Arm B only).
   f. Copies of representative port films (and/or Digitally Reconstructed Radiographs, DRR) of all treated fields (Arm B only).
   g. Copies of pre-registration and planning contrasted MRI brain scans. **Separate copies of the CD must be sent to the Radiation Coordinator and the QAS for N0574.**

   Note: When images are submitted on CD(s), they must include a viewing tool.

4. **Both NCCTG and CTSU Sites submit the following** to NCCTG Operations Office, QAS for N0574, NW Clinic 3-24 CC, 200 First Street SW, Rochester, MN 55905. Submit the reports AND the radiographic images free of marks that may obscure the lesions or bias the evaluation of the independent reviewer(s). Images on CDs are preferred to film but must be DICOM compatible with a viewing tool. The radiographic images must be identified with the NCCTG study number of N0574 and the assigned patient identification number. The radiographic images must be identified with the date the image was performed and the corresponding time point in the study (e.g., week 6, week 12, month 9 or month 24). As outlined below all pre-randomization and completion of therapy MRI should be submitted. See Section 11.8 for additional details. **All paperwork and images should be de-identified, and labeled with study number, patient initials and study ID number.**

   a. Pre-registration and planning MRI and reports (reports may not be available with planning scans but if available should be submitted). **Separate copies of these CDs must be sent to the Radiation Coordinator and the QAS for N0574.**
   b. Completion of therapy MRI (six weeks after SRS) and report
   c. Best response MRI and report
   d. Disease progression MRI and report
   e. The MRI brain scans performed at Month 12 and the report should be submitted, in the absence of any change post-completion of therapy. These studies will be reviewed by the NCCTG PIs for final classification of disease progression versus radionecrosis.


6. This form must be completed **only** if the Patient QOL Questionnaire Booklet contains absolutely **NO** patient provided assessment information.
7. Submit original Patient Neurocognitive Testing Questionnaire Booklets to Dr. Elena Farace at the address listed on the Study Staff page of the protocol. Be certain to also fax the Neurocognitive Booklet Submission to Dr. Farace at the telefax number listed on the Study Staff page of the protocol.

8. **Treatment**
   Cycle 1 = starts day 1 of treatment and ends at week 6 follow up.

**Follow up/Observation:**
- Cycle 2 = starts at 6 weeks and ends at week 12 follow up.
- Cycle 3 = starts at week 12 follow up and ends at 6 month follow up.
- Cycle 4 = starts at 6 month follow up and ends at 9 month follow up.
- Cycle 5 = starts at 9 month follow up and ends at 12 month follow up.
- Cycle 6 = starts at 12 month follow up and ends at 16 month follow up.
- Cycle 7 = starts at 16 month follow up and ends at 24 month follow up.
- Cycle 8 = starts at 24 month follow up and ends at 36 month follow up.
- Cycle 9 = starts at 36 month follow up and ends at 48 month follow up.
- Cycle 10 = starts at 48 months follow up and ends at 60 month follow up.

**Follow-up Material(s)**

<table>
<thead>
<tr>
<th>CRF</th>
<th>Event Monitoring Phase¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>See Section 4.0</td>
</tr>
<tr>
<td>Event Monitoring Form</td>
<td>X¹</td>
</tr>
<tr>
<td>Autopsy Reports</td>
<td></td>
</tr>
<tr>
<td>Death Certificate</td>
<td></td>
</tr>
</tbody>
</table>

1. If a patient is still alive 5 years after randomization, no further follow-up is required.

2. The Event Monitoring Form is required during the observation phase to report PD only. After reporting disease progression, patient should continue to be followed using the test schedule for observation (See Section 4.0) and continue completing routine cycle forms.

3. Submit if available.

18.2 Additional Submission Instructions

18.21 CTSU Sites

18.211 CTSU sites will fax forms (except Patient and Examiner Questionnaire Booklets, see Section 18.0) to NCCTG Operations Office, Attn: N0574 QAS at (507) 266-7240.

18.212 CTSU sites will submit original Patient QOL Questionnaire Booklet and Functional Independence form to the NCCTG Operations Office, Attn: QAS for N0574, NW Clinic 3-24, 200 First Street SW, Rochester MN

18.213 CTSU sites will submit original Patient Neurocognitive Testing Questionnaire Booklets to Dr Elena Farace at the address listed on the Study Staff page of the protocol.
18.22 Labeling of Submitted Materials
Each site will be responsible for insuring that all materials contain the patient’s initials, study ID number, and NCCTG protocol number. Patient’s name must be removed.

18.23 Incomplete or Missing Materials
Any materials deemed incomplete by the NCCTG Operations Office will be considered “not received” and will not be edited or otherwise processed until the missing information is received. A list of the missing documents will be made available to the institution responsible for the patient.

18.24 Overdue Lists
A list of overdue materials and forms for study patients will be generated monthly. The listings will be sorted by location and will include the patient study registration number. NCCTG will contact the patients’ institutions in order to obtain the overdue material.

18.25 Correction Forms
If a correction is made by NCCTG, a correction form will be sent to the institution to make the correction on the institution’s form. In cases of disagreement with a given correction, a query letter may be written.

19.0 Budget

19.1 Costs Charged to Patient
Routine clinical care

19.2 Tests to be Research Funded
None.

19.3 Other Budget Concerns
There will be no charges associated with QOL or neurocognitive assessments.
20. References


Matthews, C.G. and H. Klove. Instruction manual for the Adult Neuropsychology Test Battery, Madison WI, University of Wisconsin Medical School, 1964.


## ECOG Performance Status Criteria

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>Normal activity. Fully active, able to carry on all pre-disease performance without restriction.</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).</td>
</tr>
<tr>
<td>Grade 2</td>
<td>In bed &lt;50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>In bed &gt;50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Dead.</td>
</tr>
</tbody>
</table>
Appendix II: Administration of FACT-Br Questionnaire

Instructions for Study Staff

The instructions given below are intended to serve as a guide for the administration of the Quality of Life (QOL) FACT-Br questionnaire. The FACT-Br should be self-administered by the patient.

1. Following patient’s check-in at clinic, the patient should be taken to a quiet area where he/she may complete the questionnaire without interruption. Adequate time should be provided to the patient so that the questionnaire can be completed at the beginning of the clinic visit.

2. The patient will be given the questionnaire PRIOR to being seen by the physician or nursing staff or having any tests/procedures done at the clinic visit, as indicated in the protocol.

3. The patient should be instructed to read the brief directions at the top of the page. After the patient's correct understanding has been confirmed, he/she should be encouraged to complete every item in order. Some patients may feel that a given question is not applicable to them and will therefore skip the item altogether. Patients should be encouraged to check the response that is most applicable. If, for example, a patient is not currently receiving any treatment, the patient should check "not at all" to the question "I am bothered by side effects of treatment."

4. The FACT-Br must be completed by the patient alone, without coaching or suggestions as to the “correct” answer by health care personnel, relatives, or anyone else

   OR

   If the patient has experienced cognitive deterioration during treatment, a ‘significant other’ (e.g., a spouse) should complete the FACT-Br on behalf of the patient, without coaching or suggestions as to the “correct” answer by health care personnel, other relatives, or anyone else. The respondent must sign the back of the questionnaire.

5. The study staff may provide clarification but should not rephrase questions, suggest answers, or discuss answers.

6. The study staff will collect the questionnaire as soon as it has been completed, check to see that each question has been answered, and remind the patient/respondent to answer any questions that may have been missed. If the patient/responder declines to answer some or any of the questions, the study staff should enter an explanatory comment on the questionnaire.

7. The questionnaire must be completed in the clinic, at the beginning of the visit. The questionnaire may not be taken home nor may it be completed at a later time.

   NOTE: Varying the environment in which the questionnaire is completed by allowing completion at other times than the time of the clinic visit introduces unnecessary variables into the study.

8. The information provided by the patient in the completed questionnaire is confidential and should not be discussed with, or shown to, anyone who is not a member of the study team.
Below is a list of statements that other people with your illness have said are important. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

### PHYSICAL WELL-BEING

<table>
<thead>
<tr>
<th>Statement</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I have a lack of energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. I have nausea</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Because of my physical condition, I have trouble meeting the needs of</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. I have pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. I am bothered by side effects of treatment</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. I feel ill</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. I am forced to spend time in bed</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### SOCIAL/FAMILY WELL-BEING

<table>
<thead>
<tr>
<th>Statement</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. I feel close to my friends</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9. I get emotional support from my family</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. I get support from my friends</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11. My family has accepted my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12. I am satisfied with family communication about my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13. I feel close to my partner (or the person who is my main support)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box □ with an ‘X’ and go to the next section.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>14. I am satisfied with my sex life</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
## EMOTIONAL WELL-BEING

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>15. I feel sad</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>16. I am satisfied with how I am coping with my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>17. I am losing hope in the fight against my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18. I feel nervous</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19. I worry about dying</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20. I worry that my condition will get worse</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

## FUNCTIONAL WELL-BEING

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>21. I am able to work (include work in the home)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>22. My work (include work in the home)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>23. I am able to enjoy life</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>24. I have accepted my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>25. I am sleeping well</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>26. I am enjoying the things I usually do for fun</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>27. I am content with the quality of my life right now</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

## ADDITIONAL CONCERNS

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>28. I am able to concentrate</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>29. I have had seizures (convulsions)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>30. I can remember new things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>31. I get frustrated that I cannot do things I used to</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>32. I am afraid of having a seizure (convulsion)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>33. I have trouble with my eyesight</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>ADDITIONAL CONCERNS</td>
<td>Not at all</td>
<td>A little bit</td>
<td>Somewhat</td>
<td>Quite a bit</td>
<td>Very much</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------------</td>
<td>------------</td>
<td>--------------</td>
<td>----------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>34. I feel independent.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>35. I have trouble hearing.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>36. I am able to find the right word(s) to say what I mean.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>37. I have difficulty expressing my thoughts.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>38. I am bothered by the change in my personality.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>39. I am able to make decisions and take responsibility</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>40. I am bothered by the drop in my contribution to the family.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>41. I am able to put my thoughts together.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>42. I need help caring for myself (bathing, dressing, eating, etc.).</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>43. I am able to put my thoughts into action.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>44. I am able to read like I used to.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>45. I am able to write like I used to.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>46. I am able to drive a vehicle (my car, truck, etc.).</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>47. I have trouble feeling sensations in arms, hands or legs.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>48. I have weakness in my arms or legs.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>49. I have trouble with coordination.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>50. I get headaches.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Welcome to the NCCTG trial on the effect of whole-brain radiation following radiosurgery in patients with one to three brain metastases. I am Dr. Elana Farace, neuropsychologist from the Department of Neurosurgery at the University of Virginia. I am here to teach you what you need to know about the neurocognitive measures in the N0574 protocol.

Rationale:
The primary outcome measure chosen for the study is survival, but we are particularly interested in neurocognition, functional status, and quality of life in these patients. These additional measures will allow us to better understand the impact of treatments on all aspects of a patient with brain metastases.

Neurocognitive testing battery selected for this study

The tests in this battery are:
- Brief
- Repeatable
- Inexpensive
- Sensitive to change in patient function
- Simple enough that most patients can complete them
- Able to be given across sites
- Published measures
- Standardized, with known reliability and validity

The tests to be given are the:
- Hopkins Verbal Learning Test (HVLT) a test of verbal memory
- Trail Making Tests A&B
  - Trails A is a test of visual scanning and visual perception
  - Trails B is a test of divided attention
- Controlled Oral Word Association Test (COWA) a test of verbal fluency
- Grooved Pegboard, a test of fine motor control

Timing of test battery:
No test takes more than five minutes to give. Each has a “discontinue rule” that if it is taking longer than five minutes to give that you can stop the test.
**Test Schedule:**

The neurocognitive and QOL tests in the protocol will be administered on this schedule. As you can see, we monitor patients more closely at the beginning of the study, but it is important to follow them over time to determine the longer-term effects of treatments.

<table>
<thead>
<tr>
<th>1. Pre-intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Week 6</td>
</tr>
<tr>
<td>3. Month 3</td>
</tr>
<tr>
<td>4. Month 6</td>
</tr>
<tr>
<td>5. Month 9</td>
</tr>
<tr>
<td>6. Month 12 (Year 1)</td>
</tr>
<tr>
<td>7. Month 16</td>
</tr>
<tr>
<td>8. Month 24 (Year 2)</td>
</tr>
<tr>
<td>9. Month 36 (Year 3)</td>
</tr>
<tr>
<td>10. Month 48 (Year 4)</td>
</tr>
<tr>
<td>11. Month 60 (Year 5)</td>
</tr>
</tbody>
</table>

**Test forms:**

For the neurocognitive testing, the examiner should use the Neurocognitive Examiners Booklet (sample copy in Appendix VII), the Neurocognitive Patient Completed Booklet (Appendix VI), as well as, the Administrative Procedures for Neurocognitive Testing (Appendix IV). The examiners complete the Neurocognitive Examiners Booklet (sample copy contained in Appendix VII). They also use the Administration of Neurocognitive Evaluations Instructions to conduct the tests. Patient responses are recorded directly onto the Neurocognitive Examiners Booklet.

It is very important that the person administering the neurocognitive tests fax a completed Neurocognitive Tests Submission Fax Form (Appendix V) indicating who administered the tests with the appropriate contact information.

**Setting up for Neuropsychological Testing**

**Set up of testing situation:**
- Private room
- Door that closes
- Quiet
- Alone with just the patient-- No family members
- May want to hang a sign that says “do not disturb”
- Some tests are timed – it is very important not to be interrupted during these
- Desk for you both to write on (clipboard works in a pinch)
- Stopwatch or other second timer
- Black ink pens (one for you and one for the patient)
Testing tips
- Do not indicate to the patient how well they are doing
- Hide your writing from the patient so they cannot get feedback on how they are performing
- However, it is OK to be generically encouraging (make sure you make the same response whether patient is performing well or not)
- Please do not assist them in any way if they struggle with a task; we need an accurate view of what they can do themselves.

Hopkins Verbal Learning Test

Purpose:
- The HVLT is a great memory test that gives a wealth of information about memory and takes less than 5 minutes to administer.
- The test consists of 12 nouns in 3 semantic categories that are read aloud (with a one-second interval between each word) for three consecutive trials, each trial followed by a free-recall test.
- Keep the order of the words the same across trials.
- Repeat instructions before each trial to minimize forgetting.
- After all 3 trials are given, there is a 20-30 minute delay during which other neurocognitive tests are administered.
- After the 20-30 minute delay, you will ask the patient to recall words from the list again to test delayed recall.
- Finally, you will test recognition memory for words in the list. A longer list of 24 items containing the 12 words on the list and other distracter words will be read aloud and the patient will respond “yes” if the word was on the original list, and “no” if not.

Alternate forms:
- You have six alternate forms of this test.
- You only complete ONE test at each visit in the study.
- This is important so that you are testing new memory, not old learning from a previous version of the test, or what we call a “practice effect.”
- Do not ever repeat the same form of a test on two successive visits.

Materials needed:
- HVLT Administration Sheet

Administration:
- For Trial 1, say this:
  “I am going to read a list of words. Listen carefully, for when I stop, you are to say back to me as many of the words as you can remember. It doesn’t matter in what order you repeat them. Just try to remember as many as you can.”

- Read the list of words, with a one-second interval between each of the 12 words.

“What words were on the list?”
- Mark an X in the YES box if the word the patient states was on the list
- Mark an X in the NO box if the patient does not say the word.
• If the patient repeats a word, you can ignore it
• If the patient gives you another word, you can ignore it
• To be correct, the word has to be the exact word
• Make sure to speak loudly and clearly
• When the subject indicates that he or she can recall no more words, the examiner rereads the list after giving a second set of instructions.

“Now I am going to read the same list of words again, and once again when I stop, I want you to tell me as many words as you can remember, including words you said the first time. It doesn’t matter in what order you say them. Try to remember and say as many as you can, whether or not you said them before.”

“What words were on the list?”

• Repeat same instructions for Trial 3
• Note: Use a post it to remind yourself to go back to this test so you can test delayed memory and recognition in 20-30 minutes.
• Proceed to the Trail Making Tests

HVLT Delay
• After a 20-30 minute delay, during which the subject would be engaged in the other neurocognitive tests required in Study N0574
• Ask the subject to recall the words for the list.

“Remember that list of words I had you repeat back to me earlier? I want you to say as many of those words as you can remember now.”
• Mark an X in the YES box if the word the patient states was on the list
• Mark an X in the NO box if the patient does not say the word
• Then test recognition. For the recognition trial say:

“Now I am going to read you a list of words. You tell me if the word I read was included in the list of words you were learning. Just say “yes” or “no”.”

• Mark an X in the correct box corresponding to whether the patient says Yes or NO to whether the word was in the original list.

• Sign and date the form and you are done!

Trail Making Tests A & B

Purpose:
• Trails A is a test of visual scanning and visual perception.
• Trails B is a test of divided attention
• Both tests take less than 5 minutes to administer
• The tests consist of numbers in Trails A, and numbers and letters in Trails B, arranged on a page.
• The patient is asked to draw a line in a “connect the dots” test so this is a test where the patient themselves draws on the form, which is found in the patient completed booklet.
Materials needed:
- Stopwatch
- A black pen for the patient to use
- Trails A and B sample (Patient completed booklet)

Administration:

Sample Test A:
Place the Sample Test A in front of the patient and say this and point to the numbers you are pointing out:

"On this page (point) are some numbers. Begin at number 1 (point to "1") and draw a line from one to two (point to "2"), two to three (point to "3"), three to four (point to "4"), and so on, in order until you reach the end (point to the circle marked "end"). Draw the lines as fast as you can. Do not lift your pencil from the paper and do not try to erase. Ready? Begin."

- Start timing with stopwatch
- If the subject makes a mistake on Sample A, point it out and explain it. The following explanations of mistakes are acceptable:

"You started with the wrong circle. This is where you start."

"You skipped this circle (point to the one omitted). You should go from number one (point) to two (point), two to three (point) and so on until you reach the circle marked "END".

“You need to cross into the circles as you draw like this.”

“Please don’t lift your pencil off the paper.”

- After the mistake has been explained, the examiner marks out the wrong part with a has line and says:

Restart by saying:
“Please keep the pencil on the paper and continue on to the next circle. Go on from here."

- Point to the last circle completed correctly in sequence

“Work as fast as you can. Ready? Begin.”

- If the subject succeeds this time, go on to PART A of the test. If not repeat the procedure until the subject does succeed or it becomes evident that he or she cannot do it.
- If the subject completes the sample item correctly, and in a manner that shows that he or she knows what to do, say:

"Good! Let’s try the next one."

Turn the page and give PART A of the test.
Trails A Test
"On this page are numbers from 1 to 25. Do this the same way. Begin at number one (point) and draw a line from number one to two (point), two to three (point), three to four (point), and so on, in order until you reach the "end" (point). Remember work as fast as you can. Ready? Begin."

- Start timing now
- If the subject makes an error immediately call it to his or her attention and have the subject proceed from the point where the mistake occurred. Do not stop timing.
- When the subject completes Trails A Test, stop timing and remove the test sheet.
- If the patient takes more than 5 minutes (300 seconds) to complete the test, discontinue the test and mark 300 seconds on the form.
- Record the time in seconds
- Record the number of errors, that is the number of times you had to correct the patient.
- Proceed immediately to Part B

Sample Test B
"On this page are some numbers and letters. Begin at number one (point) and draw a line from one to A (point to "A"), A to two (point to "2"), two to B (point to "B"), B to three, (point to "3"), three to C (point to "C"), and so on until you reach the end (point to the circle marked "END"). Remember, first you have a number (point to "1"), then a letter (point to "A"), then a number (point to "2"), then a letter (point to "B"), and so on. Draw the lines as fast as you can. Ready? Begin."

- Start timing with stopwatch
- If the subject makes a mistake proceed as on Sample Test A
- If the patient succeeds, go on to Trails B Test

Trails B Test
"On this page are both numbers and letters. Do this the same way. Begin at number one (point to '1') and draw a line from one to A (point to ‘A’), A to two (point to ‘2’), two to B (point to ‘B’), B to three (point to ‘3’), three to C, and so on, in order until you have reached the end (point to the circle marked "END"). Remember, first you have a number, then a letter and so on. Do not skip around, but go from one circle to the next in proper order. Draw the lines as fast as you can and don’t lift your pen off the paper. Ready? Begin."

- If the subject makes an error immediately call it to his or her attention and have the subject proceed from the point where the mistake occurred. Do not stop timing.
- When the subject completes the Trails B Test, stop timing and remove the test sheet.
- Record the time in seconds
- Record the number of errors, that is the number of times you had to correct the patient.
- Sign and date the form and proceed to the Controlled Oral Word Association Test

Benton Controlled Oral Word Association Test (COWAT)

Purpose:
- The Controlled Oral Word Association Test is a test of verbal fluency and is sensitive to patients’ changes in patients’ language skills.
- The test takes less than 5 minutes to administer.
The patient is given a letter and asked to name all the words they can think of that begin with that letter.

**Materials needed:**
- Stopwatch
- COWAT answer sheets

**Alternate forms:**
- You have two alternate forms of this test.
- You only complete ONE test at each visit in the study.
- Do not ever repeat the same form of a test from on two successive visits.

**Administration:**

"I am going to say a letter of the alphabet and I want you to say as quickly as you can, all the words that you can think of which begin with that letter.

You may say any words at all, except proper names, such as the names of people or places.

So if the letter is “r” you would not say "Rochester" or "Robert".

Also, do not use the same word again with a different ending, such as "eat" and "eating".

For example, if I say "s", you could say "son", "sit", "shoe" or "slow". Can you think of other words beginning with the letter "s"?

- Wait for the patient to give a word. If they succeed, indicate to them that they are performing correctly, and move on to the test.
- If the patient does not understand, repeat the directions.
- If the subject has succeeded in giving an appropriate word beginning with the demonstration letter, say:

"That is fine, now I am going to give you another letter and again you will say all the words beginning with that letter that you can think of. Remember, no names of people or places, just ordinary words. Also, if you should draw a blank, I want you to keep on trying until the time limit is up. You will have a minute for each one."

The first letter is **C**.” (or F).

- Start Timing **NOW**
- If the subject discontinues before the end of the time period, encourage them to find more words. If they are silent for 15 seconds, repeat the basic instructions and letter. No extension on the time limit is made in the event that the instruction is repeated in the course of the test.
- Make sure to continue through the full 60 seconds even if patient cannot name a word.
- Record every word the patient says. Write each word on a new line. If patient speaks quickly try to write at least first few letters. However, all incorrect responses should be recorded verbatim.
- If a word is wrong, draw a line through it as you go.
• Spelling does not count against the patient (or the tester)
• Keep writing even if patients list more than 20 words for which there are blanks. We need to know how many words the patient can name in 60 seconds.
  If the patient produces a word which may or may not be a proper noun (e.g. frank/Frank) or is a word with two or more meanings (e.g., can; catch) the tester should query the patient after the timing has stopped. However, during the testing, the words should simply be recorded and the patient should not be interrupted. At the end of each one-minute test of a letter, the patient should be asked what they meant by the responses to clarify, and the response should be marked out if in error. Repetition of the word is acceptable if the subject definitely indicates the alternative meaning. Proper nouns are not accepted.
• Continue the test with the letters "F" and "L" (or “A” and “S”) allowing one minute for each

**Grooved Pegboard**

**Purpose:**
- The Grooved Pegboard Test is a test of fine motor coordination.
- The test is sensitive to left versus right hand motor impairment and overall motor slowing
- The test takes less than 5 minutes to administer
- The patient is asked to place pegs into a pegboard with their left and right hands.

**Materials needed:**
- Stopwatch
- Grooved pegboard with pegs
- Scoring sheet

**Administration:**

**Handedness testing:**
- Ask the patient if they are right or left handed and mark the corresponding box
- Ask the patient if they have always been right or left handed, or if anyone ever made them change handedness as they used to do in school and mark the corresponding box
- Ask the patient which hand they use for wiring, drawing, or throwing a ball
- Based on the answers to these questions, the patient’s dominant hand is their RIGHT hand if they have always been right-handed AND no one has ever made them change handedness AND are always or usually right-handed when writing, drawing, or throwing a ball. Otherwise, the patient is LEFT hand dominant

**Pegboard Administration:**
- Place the pegboard centered in front of the subject with the tray at the top of the board.
- Empty the pegs from the compartment into the tray
- "This is a pegboard and these are the pegs."
  - Point out the board and the pegs. Pick up a peg. Show them the peg and say:
  - "All the pegs are the same. They have a groove, that is, a round side and a square side and so do the holes in the board. What you must do is match the groove of the peg with the groove of the board and put these pegs into the holes like this."
  - Demonstrate this by filling in the top row
  - Allow the patient to practice with 3-4 pegs if they wish
• Remove the pegs, putting them back in the tray

“When I say go, begin here and put the pegs into the board as fast as you can, ONLY using your (their dominant) hand. Fill the top row completely from this side to this side (starting at the opposite side of their dominant hand.) Do not skip any holes, fill each row the same way you filled the top row. Any questions? Ready, as fast as you can. Go.”

• Have the patient fill the board with their right hand from left to right as you would read a book. This keeps them from having already placed pegs get in their way and slow them down.
• With the left hand patients fill the board from right to left. Again this keeps them from having already placed pegs get in their way and slow them down.
• Begin timing when they start to place the pegs.
• Make sure to keep track of any pegs that are dropped inadvertently and tally them on the scoring sheet.
• Record, in seconds, the time it takes to finish putting all the pegs in.
• If a subject takes longer than five minutes the trial must be discontinued.
• Record the number of pegs placed at the end of the trial.
• Repeat this with the non-dominant hand starting from the opposite side of the board
• Sign and date the form and proceed to HVLT delayed memory testing.
Fax completed form to: **Elana Farace, Ph.D. at (717) 531-0480**

From: __________________________

Date: __________________________

Re: Neurocognitive Booklet Submission

Attention: **2 Neurocognitive booklets** (Examiners and Patient completed) have been sent to you via surface mail, as of ______________________________(date).

<table>
<thead>
<tr>
<th>Contact Information:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person administering test:</td>
</tr>
<tr>
<td>Name of site:</td>
</tr>
<tr>
<td>Phone:</td>
</tr>
<tr>
<td>Email:</td>
</tr>
<tr>
<td>Patient’s study ID #:</td>
</tr>
</tbody>
</table>

Page _____ of _____
Appendix VI: Neurocognitive Patient Completed Booklet

Page 1 of 5

Version Date 10/31/14
Update #06
TRAIL MAKING

Part A

SAMPLE
Trail Making A Sample (TMAS)

TRAIL MAKING
Part B
SAMPLE

End

D

Begin

1

A

B

2

3

C

4
FOR
PRACTICE
USE
ONLY

Neurocognitive Test Checklist (NTC)

page 1 of 15

Indicate all the neurocognitive tests that were conducted at this visit:

- [ ] Hopkins Verbal Learning Test
  (Mark only one HVLT)
  - [ ] Grooved Pegboard Test
  - [ ] Benton Controlled Oral Word Association (COWAT A)
  - [ ] Benton Controlled Oral Word Association (COWAT B)
  - [ ] Trail Making A Sample
  - [ ] Trail Making A
  - [ ] Trail Making B Sample
  - [ ] Trail Making B

Comments regarding the administration of the neurocognitive tests:

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

Completed by: __________________________ Date: ___/___/____

N0574
App. IX
3/15/2006
FOR PRACTICE USE ONLY
Hopkins Verbal Learning Test - Form 1 (HVT1)

FORM 1: four-legged animals, precious stones, human dwellings
(Mark an "X" in the appropriate box for each item that was said (Yes) or not said (No) by the patient.)

<table>
<thead>
<tr>
<th>FREE RECALL</th>
<th>Trial 1</th>
<th>Trial 2</th>
<th>Trial 3</th>
<th>30' RECALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>LION</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>EMERALD</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>HORSE</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>TENT</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>SAPPHIRE</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>HOTEL</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CAVE</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>OPAL</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>TIGER</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>PEARL</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>COW</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>HUT</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

For NCCGT Use Only

# Corrected
# Correct

RECOGNITION
(Mark an "X" in the appropriate box for each word that the patient heard (Yes) or did not hear (No) form the above list.)

<table>
<thead>
<tr>
<th>Yes No</th>
<th>Yes No</th>
<th>Yes No</th>
<th>Yes No</th>
<th>Yes No</th>
<th>Yes No</th>
<th>Yes No</th>
</tr>
</thead>
<tbody>
<tr>
<td>HORSE</td>
<td>No</td>
<td>bat</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>raby*</td>
<td>No</td>
<td>CAVE</td>
<td>No</td>
<td>balloon</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>house*</td>
<td>No</td>
<td>OPAL</td>
<td>No</td>
<td>TIGER</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>HUT</td>
<td>No</td>
<td>EMERALD</td>
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<td>SAPPHER</td>
<td>No</td>
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<td>dog*</td>
<td>No</td>
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<tr>
<td>TENT</td>
<td>No</td>
<td>mountain</td>
<td>No</td>
<td>cart*</td>
<td>No</td>
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</table>

For NCCGT Use Only:

# True-Positives: 5 of 12
# False-Positive Errors: 0
Discrimination Index:
(# True-Positives) - (#False-Positives) = 5

Completed by: ____________________________
Date: 3/15/2006

Version Date 10/31/14
Update #06
FOR PRACTICE USE ONLY

Hopkins Verbal Learning Test - Form 2 (HVLT2)

Page 3 of 15

FORM 2: kitchen utensils, alcoholic beverages, weapons
(Mark an "X" in the appropriate box for each item that was said (Yes) or not said (No) by the patient.)

<table>
<thead>
<tr>
<th>FREE RECALL</th>
<th>Trial 1</th>
<th>Trial 2</th>
<th>Trial 3</th>
<th>30' RECALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>FORK</td>
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<td>Yes</td>
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<tr>
<td>RUM</td>
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<td>PAN</td>
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</tr>
<tr>
<td>PISTOL</td>
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</tr>
<tr>
<td>SWORD</td>
<td></td>
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<tr>
<td>SPATULA</td>
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<tr>
<td>BOURBON</td>
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</tr>
<tr>
<td>VODKA</td>
<td></td>
<td></td>
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<tr>
<td>POT</td>
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<tr>
<td>BOMB</td>
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<tr>
<td>RIFLE</td>
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<tr>
<td>WINE</td>
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</tbody>
</table>

For NCCTG Use Only

# Corrected ______ ______ ______ ______ ______

# Correct ______ ______

RECOGNITION
(Mark an "X" in the appropriate box for each word that the patient heard (Yes) or did not hear (No) form the above list.)

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<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
</tr>
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<tbody>
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<td>spoon*</td>
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<td>doll</td>
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<td>whiskey*</td>
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<tr>
<td>harmonica</td>
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<td>can opener*</td>
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<td>SWORD</td>
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<td>pencil</td>
<td></td>
</tr>
<tr>
<td>knife*</td>
<td></td>
<td>RUM</td>
<td></td>
<td>twot</td>
<td></td>
<td>BOMB</td>
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<td>BOURBON</td>
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</table>

For NCCTG Use Only:

# True-Positives: ______ of 12

*Related: ______ of 6

(# True-Positives) - (#False-Positives) = ______

Unrelated: ______ of 6

Completed by: ____________________________

Date: ______/____/____ (mm/dd/yyyy)

N0574

App. IX

3/15/2006

Version Date 10/31/14

Update #06
FOR PRACTICE USE ONLY

Hopkins Verbal Learning Test - Form 3 (HVLT3)

**FORM 3:** musical instruments, fuels, food flavorings

(Mark an "X" in the appropriate box for each item that was said (Yes) or not said (No) by the patient.)

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<tr>
<th>FREE RECALL</th>
<th>Trial 1</th>
<th>Trial 2</th>
<th>Trial 3</th>
<th>30° RECALL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>SUGAR</td>
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<td>TRUMPET</td>
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<tr>
<td>VIOLIN</td>
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<tr>
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<tr>
<td>VANILLA</td>
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<td></td>
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</tr>
<tr>
<td>WOOD</td>
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</tr>
<tr>
<td>CLARINET</td>
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<tr>
<td>FLUTE</td>
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<td>CINNAMON</td>
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For NCTCG Use Only

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<th># Correct</th>
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</tbody>
</table>

RECOGNITION

(Mark an "X" in the appropriate box for each word that the patient heard (Yes) or did not hear (No) form the above list.)

<table>
<thead>
<tr>
<th>Yes No</th>
<th>Yes No</th>
<th>Yes No</th>
<th>Yes No</th>
<th>Yes No</th>
<th>Yes No</th>
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<td>WOOD</td>
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<td>salt*</td>
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<td>priest</td>
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For NCTCG Use Only:

<table>
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<tr>
<th># True-Positives:</th>
<th># False-Positive Errors:</th>
<th>Discrimination Index:</th>
</tr>
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<tbody>
<tr>
<td>of 12</td>
<td></td>
<td>(# True-Positives) - (#False-Positives) =</td>
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Completed by: ____________________________  Date: __/__/____
FOR PRACTICE USE ONLY

Hopkins Verbal Learning Test - Form 4 (HVLT4)

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</thead>
<tbody>
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<td>Yes</td>
<td>No</td>
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<td>CANARY</td>
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<tr>
<td>SHOES</td>
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<td>EAGLE</td>
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<tr>
<td>NAILS</td>
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</tbody>
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For NCCGT Use Only: #Corrected: ___ ___ ___ ___ ___ ___ ___ ___ ___ # Correct: ___ ___ ___ ___ ___ ___ ___ ___ ___

RECOGNITION
(Mark an "X" in the appropriate box for each word that the patient heard (Yes) or did not hear (No) form the above list.)

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<thead>
<tr>
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<tr>
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<tr>
<td>chapel</td>
<td>SCREWDRIVER</td>
</tr>
<tr>
<td>NAILS</td>
<td>sock*</td>
</tr>
<tr>
<td>CANARY</td>
<td>apple</td>
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</tbody>
</table>

For NCCGT Use Only: # True-Positives: ___ of 12 # False-Positive Errors: ___ Related: ___ of 6

Discrimination Index: (# True-Positives) - (#False-Positives) = ___

Unrelated: ___ of 6

Completed by: _____________________________ Date: / / 2006

Version Date 10/31/14 Update #06
FOR PRACTICE USE ONLY

Hopkins Verbal Learning Test - Form 5 (HVLT5)

**FORM 5:** occupations/professions, sports, vegetables

(Mark an "X" in the appropriate box for each item that was said (Yes) or not said (No) by the patient.)

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<th></th>
<th>Trial 1</th>
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<th>Trial 1</th>
<th>Trial 2</th>
<th>Trial 3</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
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<td>BEAN</td>
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<td>POTATO</td>
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</tr>
</tbody>
</table>

**RECOGNITION**

(Mark an "X" in the appropriate box for each word that the patient heard (Yes) or did not hear (No) form the above list.)

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
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</table>

**For NCTG Use Only**

<table>
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<tr>
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<th># False-Positive Errors:</th>
<th>Discrimination Index:</th>
</tr>
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<tbody>
<tr>
<td>of 12</td>
<td>of 6</td>
<td>(# True-Positives) - (#False-Positives) =</td>
</tr>
</tbody>
</table>

**For NCTG Use Only**

Completed by: ___________________________ Date: __________/________/______

N0574

Version Date 10/31/14 Update #06
**FREE RECALL**

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<td>No</td>
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</tr>
<tr>
<td>WALL</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>HERRING</td>
<td>Yes</td>
<td>No</td>
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</tr>
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<td>CEILING</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>SNOW</td>
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<td>No</td>
<td>Yes</td>
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**30' RECALL**

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<tr>
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<td>HERRING</td>
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**RECOGNITION**

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**For NCCTG Use Only**

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**For NCCTG Use Only:**

- **# True-Positives:** 9 of 12
- **# False-Positive Errors:**
- **Discrimination Index:**

**Completed by:** N0574
**Date:** 3/15/2006
FOR PRACTICE USE ONLY

Grooved Pegboard Scoring Sheet (GPS)

Date of Test: ______/_____/______

The patient is: □ Right-handed
□ Left-handed
□ Mixed-handed

Has the patient always been Right/Left/Mixed handed? □ Always the same
□ Handedness has changed

Which hand does the patient use for the following (mark only ONE box for each activity listed):

<table>
<thead>
<tr>
<th>Activity</th>
<th>Always Right</th>
<th>Usually Right</th>
<th>Either Hand</th>
<th>Usually Left</th>
<th>Always Left</th>
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<tbody>
<tr>
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<tr>
<td>Drawing</td>
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<tr>
<td>Throwing a ball</td>
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</tr>
</tbody>
</table>

Dominant Hand*: □ Right
□ Left

Seconds:  ______  Number in:  ______  Number Dropped:  ______

Non-Dominant Hand: □ Right
□ Left

For NCCTG Use Only: TOTALS:  ______  ______  ______

*Based on the answers to the questions above, patient is right-hand dominant if they are: right-handed AND have always been right-handed AND are always or usually right-handed when writing/drawing/throwing a ball. If otherwise, patient is left-hand dominant.

Completed by: ___________________________ Date: ______/_____/______

For NCCTG Use Only: TOTALS:  ______  ______  ______
### Benton Controlled Oral Word Association Test A (COWATA)

**Date of Test:**

<table>
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For NCCTG Use Only

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<tr>
<th>Sum C:</th>
<th>Sum F:</th>
<th>Sum L:</th>
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<tbody>
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<td><img src="image" alt="" /> + CORRECTION</td>
<td><img src="image" alt="" /> = <img src="image" alt="" /> (ADJUSTED SCORE)</td>
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</tr>
</tbody>
</table>

**PERCENTILE RANK =** \(\text{percentile}\)  
**INTERPRETATION:**

---

_Completed by: ___________________________  
Date: __/__/____/____/____/____  
_N0574  
_App. IX  
_3/15/2006_
**FOR PRACTICE USE ONLY**

Benton Controlled Oral Word Association Test B (COWATB)

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<table>
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</tr>
</tbody>
</table>

**For NCCTG Use Only**

Sum F: _________  Sum A: _________  Sum S: _________

TOTAL: _________ + CORRECTION _________ = _________ (ADJUSTED SCORE)

PERCENTILE RANK = _________ (percentile)  INTERPRETATION: _________

(Benton & Hamsher, 1996)

Completed by: ________________  Date: ____/__/____

Version Date 10/31/14  Update #06
Trail Making A and B Scoring (TMABS)

Trail Making Test Date: ___/___/___

Trail Making A Scoring
Time to complete: ______ seconds (discontinue after 5 minutes)
Number of errors: ______

Trail Making B Scoring
Time to complete: ______ seconds (discontinue after 5 minutes)
Number of errors: ______

Completed by: ________________________________ Date: ___/___/___

Version Date 10/31/14
Update #06
TRAIL MAKING

Part A

SAMPLE

7 8 2

1 4 3

6 5

End

Begin
TRAIL MAKING

Part B

SAMPLE

Begin

End