N107C Title Page

Alliance for Clinical Trials in Oncology

N107C: Phase III Trial of Post-Surgical Stereotactic Radiosurgery (SRS) Compared with Whole Brain Radiotherapy (WBRT) for Resected Metastatic Brain Disease

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

Study Chairs: Paul D. Brown, M.D (NCCTG)*
M.D. Anderson Cancer Center
1515 Holcombe Boulevard. Unit 97
Houston, Texas 77030
Telephone (713) 563-2415
Telefax (713) 563-2302
Email: pdbrown@mdanderson.org

David Roberge, M.D. (NCIC)
CHUM – Notre Dame
Lachapelle, TS-3366
1560, rue Sherbrooke Est.
Montreal, Quebec H2L 4M1
Telephone (514) 890-8254
Telefax (514) 412-7537
Email: david.roberge.chum@ssss.gouv.qc.ca

***Investigator having NCI responsibility for this protocol**

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Study Staff

Statistician

Karla Ballman, Ph.D. √
Mayo Clinic
200 First Street Southwest
Rochester, Minnesota 55905
Telephone (507) 284-8803
Email: ballman.karla@mayo.edu

Study Co-Chairs

Radiation Oncology

Nadia Laack, M.D. (NCCTG)
Mayo Clinic
200 First Street Southwest
Rochester, Minnesota 55905
Telephone (507) 284-4561
Telefax (507) 284-0079
Email: laack.nadia@mayo.edu

Radiation Oncology

Jonathan Ashman, M.D. (NCCTG)
Mayo Clinic
13400 East Shea Boulevard
Scottsdale, Arizona 85259
Telephone (480) 301-8000
Telefax (480) 301-7687
Email: ashman.jonathan@mayo.edu

Pathology

Caterina Giannini, M.D. (NCCTG)
Mayo Clinic
200 First Street Southwest
Rochester, Minnesota 55905
Telephone (507) 284-1473
Email: giannini.caterina@mayo.edu

Correlative Research

Deepak Khuntia, M.D. √
Western Radiation Oncology
125 South Drive
Mountain View, California 94040
Telephone: (650) 940-7280
Email: khuntia@humonc.wisc.edu

Neuropsychology

Elena Farace, Ph.D. √
Penn State Hershey Medical Center
500 University Drive, CH 69
Hershey, Pennsylvania 17033
Telephone: (717) 531-7390
Email: efarace@hmc.psu.edu

Neuropsychology

Jane Cerhan, Ph.D. (NCCTG) √
Mayo Clinic
200 First Street Southwest
Rochester, Minnesota 55905
Telephone (507) 284-2933
Email: cerhan.jane@mayo.edu

√Study contributor(s) not responsible for patient care

Cooperative Groups Study Co-Chairs

NCCTG
Ian Parney, MD
Mayo Clinic
200 First Street Southwest
Rochester, Minnesota 55905
Telephone: (507) 284-8167
Email: parney.ian@mayo.edu

ACOSOG
Fred Barker, MD
Massachusetts General Hospital
55 Fruit Street Mail Stop Yawkey 9E
Boston, Massachusettes 02114
Telephone: (617) 724-8772
Email: barker@helix.mgh.harvard.edu

CALGB
James Urbanic, MD
Wake Forest University School of Medicine
Medical Center Boulevard
Winston-Salem, North Carolina 27157
Telephone: (336) 713-5642
Telefax: (336) 713-6565
Email: jurbanic@wakehealth.edu

RTOG
Costas G. Hadjipanayis, M.D., Ph.D.
Emory University School of Medicine
1365B Clifton Road, Suite 6200
Atlanta, Georgia 30322
Telephone: (404) 778-4472
Telefax: (404) 778-4472
Email: chadjip@emory.edu

SWOG
Laurie E. Gaspar, M.D.
University of Colorado HSC
Anschutz Cancer Pavilion
Post Office Box 6510, MS F706
Aurora, Colorado 80045
Telephone: (720) 848-0154
Telefax: (720) 848-0222
Email: laurie.gaspar@ucdenver.edu

Cancer Trials Support Unit (CTSU) Address and Contact Information

To submit site registration documents:	**For patient enrollments:**	**Submit study data**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only)	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	NCCTG Operations Office Attn: QAS for Study N107C NW Clinic, 3-24 CC 200 First Street Southwest Rochester Minnesota 55905 Tel: (507) 284-1370 Telefax: (507) 266-7240 Sites should submit forms via Fax or Mail. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (i.e. patient eligibility or treatment-related) Contact the Alliance Research Base Quality Assurance Specialist (listed in Protocol Resources table on next page).		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
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The CTSU Website is located at https://www.ctsu.org.		

Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays, interruptions or adjustments, dose modifications, adverse events, forms completion and submission	Carla Hilton Alliance Research Base Quality Assurance Specialist Telephone: (507) 284-1370 Telefax: (507) 266-7240 Email: hilton.carla@mayo.edu
Protocol document and consent form	Tamara Robles, MBA Alliance Protocol Coordinator Telephone: (773) 702-9902 Telefax: (312) 345-0117 email: roblest@uchicago.edu
Forms completion and submission	Carlene Dillavou Alliance Member Clinical Research Associate Telephone: (515) 244-7586 Telefax : (515) 244-3037 Email: cdillavou@iora.org
Drug administration, infusion pumps, nursing guidelines	T.J. Scheffler Hanson, R.N. Alliance Research Base Nurse Telephone: (507)284-2459 Email: scheffler.tempurance@mayo.edu Wanda DeKrey, R.N., OCN Alliance Member Nurse Telephone: (701) 780-6741 Email: wdekrey@altru.org
Radiation quality control	Kathryn Scherger Alliance Research Base Radiation Quality Control Coordinator Telephone: (507) 266-0006 Telefax : (507) 266-7240 Email : scherger.kathryn@mayo.edu
Non-paraffin Biospecimens	Roxann M. Neumann, RN, BSN, CCRP Alliance Research Base Biospecimen Resource Manager Telephone: (507) 538-0602 Telefax: (507) 266-0824 Email: neumann.roxann@mayo.edu Ann M. Thorson Alliance Research Base Biospecimen Resource Manager Telephone: (507) 284-0163 Telefax: (507) 266-0824 Email: thorson.ann@mayo.edu
Paraffin-embedded Tissue Pathology	Helen Tollefson Alliance Research Base Pathology Coordinator Telephone: (507) 266-0724 Telefax: (507) 284-9628 Email: tollefson.helen@mayo.edu
Adverse Events (CTEP-AERS, MedWatch, Non-AER)	Patricia G. McNamara Alliance Research Base SAE Coordinator Telephone : (507) 266-3028 Telefax : (507) 284-9628 Email : mcnamara.patricia@mayo.edu

*No waivers of eligibility per NCI

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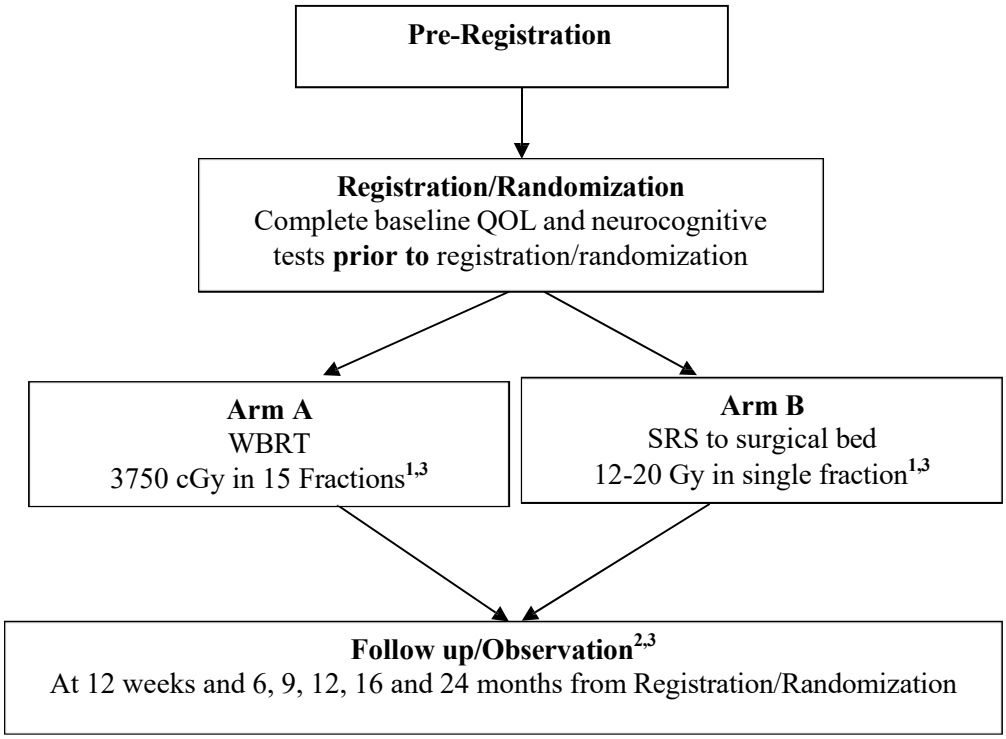
Schema



1. The unresected metastases will be treated with SRS (18-24 Gy depending on treatment arm) as outlined in the treatment section (see Section 7.0) of the protocol. In addition, sites will make a pre-determined choice of either 3750 cGy in 15 fractions or 3000 cGy in 10 fractions (see Section 7.0) for ***all*** patients randomized at that site.

2. In the event of progressive brain metastases or systemic progression, the patient remains in observation for a total of two years and then proceeds to event monitoring for three years (see Section 13.31).

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

1.0 Background

1.1 Treatment

1.11 Study Rationale

The development of brain metastases is an unfortunate and common complication in oncology patients and can occur in 10 to 30 % of cancer patients (Brown *et al*., 2008). Although the standard treatment for most patients with brain metastases remains whole brain radiotherapy (WBRT), surgical resection is commonly utilized for select patients with good performance status and limited disease, since Phase III randomized trials have shown a survival benefit for surgical resection (Patchell *et al*., 1990; Noordijk *et al*., 1994). Due to the high failure rate in the surgical bed (i.e., local failure), Phase III trials were conducted to test the role of adjuvant WBRT after resection of brain metastases (Patchell *et al*., 1998; Kocher *et al*., 2009). Significant improvement in local control was seen, but there was no improvement in overall survival. Because of the lack of a survival benefit and concerns with neurotoxicity with adjuvant WBRT (Chang *et al*., 2009), there have been a number of single institutional studies of stereotactic radiosurgery to the surgical bed (SRS). While some studies have achieved local control similar to WBRT (Quigley *et al*., 2008; Hwang *et al*., 2010; Jensen *et al*., 2010), other studies have found significantly worse local control (Kinhult *et al*., 2005; Narayana *et al*., 2006; Soltys *et al*., 2008). For example local control at one year after SRS has ranged from as low as 35 % (Narayana *et al*., 2006) to as high as 100 % (Hwang *et al*., 2010). In addition due to the lack of rigorous scientific study there is uncertainty of the risk or benefits with SRS to surgical bed in lieu of WBRT. Regardless of the lack of data, there has been acceptance of SRS to the surgical bed as standard practice in many academic and community cancer centers (Vogelbaum, 2009). A poll at the 2006 Congress of Neurological Surgeons Meeting revealed a third of neurosurgeons resect metastasis and follow this with SRS to the surgical bed; it can be safely assumed that this practice has grown since 2006. This change in practice is significant from a societal and medical resources standpoint since the costs of SRS are considerably higher than WBRT (Brown *et al*., 2009). An analysis of 2008 non-Medicare charges in different geographic regions of the United States found WBRT charges ranged from $9,201 to $17,003 while SRS charges ranged from $40,715 to $65,000; essentially the charges for SRS were 4 to 6 fold more than WBRT. With increased financial costs and the lack of clear risk/benefit data, yet growing support in the community for post-operative SRS (instead of WBRT), it is imperative SRS to the surgical bed be studied in a prospective multi-institutional cooperative group trial.

We propose a NCCTG-led phase III trial comparing post-operative SRS with WBRT in patients with resected brain metastases. Having NCCTG lead a multi-institutional trial is a sound decision as NCCTG has shown a strong track record, having nearly completed N0574, the largest brain SRS protocol that includes extensive neurocognitive testing. NCCTG will plan to build on the same model of success as N0574 working in conjunction with other cooperative groups through CTSU.

297 1.12 Current Clinical Trial Relevance and Potential Impact
298 There are ongoing trials comparing observation to post-operative SRS. Although
299 these trials are of great interest, to our knowledge there are no trials that include
300 patients treated with WBRT, the standard of care post-operatively. As outlined
301 above this trial could have significant financial and clinical implications
302 including local control, overall survival, QOL, and neurocognitive function. As
303 an example, if neurocognitive function was significantly worse with post-
304 operative SRS with equivalent survival, this would damper enthusiasm for post-
305 operative SRS and hence decrease utilization of this expensive medical resource;
306 this would also re-establish adjuvant WBRT as the standard of care. If the SRS
307 cohort had a superior outcome in neurocognitive function and equivalent overall
308 survival compared to WBRT it would establish post-operative SRS as the
309 standard of care. If there was a mixed result this issue may remain controversial
310 but at a minimum there would be level I evidence to assist in making therapeutic
311 decisions as well as hypothesis generating data to potentially suggest which
312 groups are best suited for the respective therapy.
313
314 1.13 Treatment Rationale
315
316 1.131 Overall Survival and Tumor Bed Control
317 Below is a table that outlines the previously reviewed series of patients
318 with resected brain metastases observed with serial imaging or treated
319 with either adjuvant WBRT or SRS.
320

Study	Number of patients	1 year local control	Overall survival (months)
Wake Forest SRS (Jensen *et al*., 2010)	106	80%	10.9
Narayana SRS (Narayana *et al*., 2006)	25	35%	12
Soltys SRS (Soltys *et al*., 2008)	72	79%[1]	15.1
Quigley SRS (Quigley *et al.,* 2008)	32	94%[2]	16.4
Hwang SRS (Hwang *et al*., 2010)	25	100%	15
Hwang WBRT (Hwang *et al*., 2010)	18	75%[2]	6.8
Patchell Observe (Patchell *et al*., 1998)	46	36%[3]	10
Patchell WBRT (Patchell *et al*., 1998)	49	85%[3]	11

321 1. 43% for most conformal treatment quartile
322 2. Crude rate
323 3. Taken from figures

1.132 Defining Tumor Bed Control

Tumor bed control is defined as the absence of new nodular contrast enhancement in the surgical bed (Soltys *et al*., 2008).

1.133 Defining Tumor Bed Radiosurgery Target

Although there is no standardized approach to SRS to the surgical bed, most centers apply a 2 mm margin to the surgical bed (Soltys *et al*., 2008; Do *et al*., 2009; Roberge *et al*., 2009; Ryu *et al*., 2009). A review of SRS margins utilized in the treatment of 120 surgical bed cavities found significantly improved 6 month tumor bed control when a 2 mm margin was applied compared to no margin (100 % vs. 87 % respectively) with no increase in toxicity (Soltys *et al*., 2010). Although the largest series in the literature did not define a margin around the tumor bed to which the dose was prescribed (Jensen *et al*., 2010), the treating physician became more likely to prescribe plans with a higher conformality index as the above data emerged. Therefore the treatment volume will be defined as the surgical bed plus a 2 mm margin.

1.134 Impact of SRS on Neurocognitive Function

A review of the available prospective literature of SRS that includes detailed neuropsychologic testing before and after SRS finds little impact of SRS itself on neurocognitive function. A prospective trial of 95 patients with arteriovenous malformation (AVM) who underwent extensive neuropsychologic testing before and up to 3 years after SRS found no cognitive declines and instead found improvement in intelligence, attention, memory over time (Steinvorth *et al*., 2002). Of note the treatment volume and dose of the SRS for the AVMs were similar in size and dose for SRS for typical brain metastases (mean volume 4.7 cm^3 and median dose 20 Gy. Another trial of 10 patients with AVMs who underwent neuropsychologic testing before and after SRS found no differences between pre- and post-radiosurgical (average 11 months after SRS) neuropsychological test scores on any measure (Blonder *et al*., 1999). Although these articles support no negative impact on cognitive function after SRS, they do not address the population of brain metastases treated with SRS. The only prospective trial with detailed neuropsychologic testing before and after SRS for brain metastases was led by Chang *et al* (2009). This trial of patients with 1 to 3 brain metastases found the mean posterior probability of decline for total recall at 6 months to be essentially at baseline function for SRS alone.

1.135 Rationale for Overall Survival Endpoint.
Below is a table that outlines prospective trials of SRS with or without adjuvant WBRT.

Study	Number of patients	Overall survival (months)
Kocher SRS	100	10.9
Kocher SRS + WBRT (Kocher *et al*., 2009)	99	10.9
Aoyama SRS	67	8
Aoyama SRS + WBRT (Aoyama *et al*, 2006)	65	7.5
Chang SRS	30	15.2
Chang SRS + WBRT (Change *et al*, 2009)	28	5.7

Reviewing these data and table in Section 1.131, including the prior outlined study of resected brain metastasis treated with post-operative SRS or WBRT (Hwang *et al*., 2010) (median overall survival 15 vs. 6.8 months respectively), there appears to be a potential survival advantage with SRS compared to adjuvant WBRT.

1.2 Quality of Life (QOL) and Neurocognitive Measures

1.21 Quality of Life and Neurocognitive Tests

The current trial will build on the success of N0574 utilizing the same QOL and neurocognitive tests. There are a number of advantages of such an approach including familiarity and acceptance of these tests by clinical research staff, the well-established use of these tests in CNS research, and the possibility of future post-hoc analyses between studies.

1.22 Quality of Life Questionnaire

The FACT-BR is a validated QOL instrument, comprising a general component (FACT-G, with five subscales (number of questions in parentheses): physical (7), social (7), emotional (6), functional (7), and a disease-specific subscale (BR) of 23 questions (Weitzner *et al*., 1995). As with N0574, the FACT-BR QOL instrument will be used at baseline (after pre-registration, but prior to randomization) and at the same time points as the follow-up brain MRI or CT scans.

1.23 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 (i.e., the inability to work and care for themselves), functional independence will be an important measure of outcome. 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). It also is reliable when administered verbally, as in cases when patients were unable to complete it in writing (Brazil *et al*., 1997). In addition the Eastern Cooperative Oncology Group (ECOG) performance status scale, as a secondary measure of ADL, will allow for comparison to other cancer trials. As with N0574, functional independence will be evaluated at baseline (after pre-registration, but prior to randomization) and at the same time points as the follow-up brain MRI or CT scans.

1.24 Neurocognitive Testing

The prevention and palliation of neurologic problems due to progression are important goals of treatment. Improvement in survival is not ideal as the sole measure of the benefit of a local therapy for brain metastases, because overall survival is often determined by extra cranial disease (Patchell *et al*., 1998; Aoyama *et al*., 2006; Kocher *et al*., 2009; Mehta *et al*., 2009). Measurement of neurocognitive function with an established battery by a qualified examiner is an *objective* measure akin to other objective measures such as imaging or laboratory evaluation. The US Food and Drug Administration has indicated that "improvement in neurocognitive function or delay in neurocognitive progression are acceptable end points" (Meyers and Brown, 2006). Neurocognitive function as a primary endpoint has become an accepted practice and has been utilized in a number of on-going (N0577, N0574) and completed phase III trials (Chang *et al*., 2009; Mehta *et al*., 2009). Therefore as with N0574, neurocognitive progression will be a co-primary endpoint.

The neurocognitive tests to be used in this study, the same tests as N0574, 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 tests selected have either low associated practice effect or include multiple equivalent formats. In addition similar variations of this battery have been utilized in multiple multi-institutional trials including ACOSOG Z0300; ECOG E3F05; NCCTG N0574, N0577, N0874; RTOG 0212, 0424, 0525, 0534, 0614, 0825, and 08342 and the two phase III randomized motexafin gadolinium studies (Mehta *et al*., 2009; Meyers *et al*., 2004).

The neurocognitive tests include:

- ***Memory***: Hopkins Verbal Learning Test (HVLT). (Brandt, 1991)
- ***Verbal Fluency***: Controlled Oral Word Association Test from the Multilingual Aphasia Examination (COWAT). (Benton and Hamsher, 1978)
- ***Visual Attention***: Trail Making Test A. (Reitan, 1958)
- ***Executive Function***: Trail Making Test B. (Reitan, 1958)
- ***Delayed Memory***: Recall and Recognition of Word List encoded from the HVLT.

As with N0574, neurocognitive evaluations will be conducted at baseline (after pre-registration, but prior to randomization) and at the same time points as the follow-up brain MRI or CT scans.

1.25 Fatigue/Uniscale and LASA

In addition to the same QOL and neurocognitive measures used in N0574,

this current trial will utilize two additional QOL tools: the Fatigue/Uniscale Assessment and the Linear Analog Self-Assessment (LASA). These assessments will be collected at the same time points as the FACT-BR QOL instrument described above (see Section 1.22).

1.26 Fatigue/Uniscale Assessment:

The Fatigue/Uniscale Assessment, a QOL tool routinely used in NCCTG treatment studies, will be used to measure QOL. Evidence has arisen indicating that baseline single-item assessments of fatigue and overall quality of life are strong prognostic indicators for survival in cancer patients, independent of performance status. This evidence was derived from two separate meta-analyses presented at ASCO, the first involving 23 NCCTG and Mayo Clinic Cancer Center oncology clinical trials, the second involving 43 clinical trials. Routine inclusion of these measures should be considered similar to that of including performance status, either as stratification or prognostic covariates (Tan *et al*., 2008; Sloan *et al*., 2009).

1.27 The Linear Analog Self-Assessment (LASA)

The LASA will be used to measure overall health-related QOL by assessing overall quality-of-life, mental well-being, physical well-being, and fatigue. LASA items have been validated as general measures of global QOL dimensional constructs in numerous settings (Grunberg *et al*., 1996; Gudex *et al*., 1996; Hyland and Sodergren, 1996; Bretscher *et al*., 1999). A series of LASA items have been constructed and validated for use in multiple studies with similar populations (Bretscher *et al*., 1999). Dr. Sloan and colleagues have done extensive research on the application of single-item LASA measures for assessing a wide variety of patient reported outcomes including fatigue, peripheral neuropathy, hot flash activity, and anxiety. These single-item assessments have become the most-used assessment in all NCI-sponsored cancer control studies (Buchanan *et al*., 2005). Normative data have been obtained from various clinical populations enrolled in NCCTG clinical trials and from healthy participants attending an NCCTG annual meeting. Normative results indicate that, for example, in assessing overall QOL on a 0-100 point scale, healthy volunteers will average about 82, hospice patients will average 78, advanced cancer patients will average somewhere between 60 and 75, newly diagnosed patients will average between 50 and 60, and internal medicine residents will average 44. A score below 50 is indicative of a need for immediate exploration and intervention for the QOL deficit (Sloan *et al*., submitted). Due to recent research by NCCTG investigators, the NCCTG has decided to include LASA measures for overall QOL and fatigue in all future phase II and phase III clinical trials as an independent prognostic factor independent of performance status.

1.3 Correlative Research

1.31 Patients Undergoing Brain Irradiation

Little data exists on in vivo methods of measuring neurocognitive decline. Most of the data on this topic is speculative in nature, and primarily are a result of our rapidly growing knowledge of the mechanism of Alzheimer's dementia, which largely resemble the mechanism of radiation induced dementia (Raber, 2010). A variety of measures will be analyzed in this study to better define the mechanism of neurocognitive decline, as well as which patients are most likely to develop

neurocognitive decline after brain irradiation. Pre-operative and post-operative brain MRI or CT scans, as well as a planning MRI or CT scan (see Section 4.0 for timing of this MRI or CT scan) will be submitted. In addition, follow-up brain MRI or CT scans after treatment will be performed at 12 weeks and at 6, 9, 12, 16 and 24 months for imaging studies described below. Serum, buffy coat/DNA, and urine will be collected during this trial at baseline (after pre-registration, but prior to treatment), at 12 weeks post randomization and at 6 and 12 months after randomization. These body fluid biospecimens will be analyzed as described below.

1.32 Imaging

It has been documented that after both external beam and stereotactic radiation to the brain, radiographic changes are noted on brain MRI (Curnes *et al*., 1986; Tomura *et al.*, 2006) Further, brain MRI may reveal radiation changes in the limbic system that may correlate with neurotoxicity (Foster, 2006).

1.33 Genetic Markers

Apolipoprotein E (ApoE) is an important factor in remodeling and repairing neurons in response to injury or stress through its lipid transport function. In fact, recent data suggests that patients having the Apo E4 isoform realize Alzheimer's dementia far earlier than those without it (Caselli *et al*., 2009). This allele is present in 16% of the general population and 50% of patients with late onset Alzheimer's dementia (Teunissen *et al*., 2002). Given the similar mechanisms of dementia between Alzheimer's dementia and radiation induced dementia (e.g. vascular or metabolic), Apo E4 genotyping may prove to be a predictor of radiation induced neuronal damage. The Apo E4 protein binds rapidly and tightly to beta amyloid. Normally beta amyloid exists in a soluble form. However, when bound by Apo E4 protein, beta amyloid becomes insoluble and is more likely to be deposited in plaques which may lead to changes in microvasculature, ultimately leading to neurocognitive decline. Further, patients with just one copy of the Apo E4 allele have demonstrated accelerated hippocampal volume loss which can also compromise neurocognitive function(Helbecque and Amouyel 2004). Recent preclinical mouse data from Crawford and Villasana have shown neurogenesis in the hippocampus and hippocampal dysfunction depending on Apo E status (Crawford *et al*., 2009; Villasana *et al*., 2008). Patients with Apo E2 and Apo E3 alleles, on the contrary, tend to have ¼ the risk of developing Alzheimer's disease. It is felt that the E2 and E3 alleles are able to facilitate repair and protection from neuronal damage. Apo E genotyping will be performed to assess whether a subgroup of patients exists that is genetically predisposed to developing neurocognitive decline (or neuroprotection).

1.34 Inflammatory Markers

Markers of inflammation are elevated with aging and their increase has been associated with cognitive decline (Yaffe *et al*., 2003; Krabbe *et al*., 2004). Epidemiological and retrospective data reveals an improvement in neurocognitive function with the use of NSAID's in patients with Alzheimer's dementia, hence, supporting an inflammatory process involved in neurocognitive decline (Teunissen *et al*., 2002). Chronic inflammation as a result of mass effect from tumor or treatment related inflammation may be associated with neurocognitive deficits and can be measured in plasma. Interleukin 1 (IL-1), Interleukin 6 (IL-6), and Tumor Necrosis Factor alpha (TNF-ά) are pro-

inflammatory cytokines that are a measure of inflammation and have been shown to be elevated in patients with Alzheimer's dementia (Cacabelos *et al*., 1994; Blum-Degen *et al*., 1995; Tarkowski *et al*., 1999; Martinez *et al*., 2000). In this study, inflammatory biomarkers will be measured at baseline (after pre-registration, but prior to treatment) and at the various time points indicated above to assess whether inflammation changed as a result of type of therapy and what impact this has on cognition.

1.35 Oxidative Stress

Considerable circumstantial evidence suggests surrogates for oxidative damage may be ideal biomarkers for radiation-induced neurotoxicity (Beal 1995; Akama *et al*., 1998). Decreased cerebral perfusion results in decreased oxygen and glucose delivery that eventually leads to energy deprivation which is the cause of oxidative stress in the brain (Teunissen *et al*., 2002). Oxidative stress from either tumor or radiation may be a predictor and excellent measure of neurocognitive decline. Isoprostanes are one of the best described indicators of oxidative stress and can be measured *in vivo* (Morrow *et al*., 1992). Our approach to measuring oxidative stress will consist of quantifying protein carbonyl content spectrophotometrically, measuring lipid hydroperoxides, and finally, quantitating isoprostane levels in patient serum.

1.36 Hormone and Growth Factors:

Aging and memory decline is associated with the disruption of hormone regulation, including glucocorticoids, gonadal steroids, and growth hormone (Foster 2006). Cortisol, human chorionic gonadotropin (hCG), insulin-like growth factor-1 (IGF-1), and neuronal growth factor (NGF), have all recently been associated with cognitive decline in Alzheimer's disease (Tuszynski *et al*., 2005; Ding *et al*., 2006). ELISA testing of serum specimens for each hormone and growth factor will be performed at baseline (after pre-registration, but prior to treatment) and at each follow-up visit when neurocognitive testing is performed.

2.0 Goals

2.1 Primary Goals

2.11 Overall Survival

To determine in patients with one to four brain metastases whether there is improved overall survival in patients who receive SRS to the surgical bed compared to patients who receive WBRT.

2.12 Neurocognitive Progression

To determine in patients with one to four brain metastases whether there is less neurocognitive progression post-randomization in patients who receive SRS to the surgical bed compared to patients who receive WBRT.

2.2 Secondary Goals

2.21 Quality of Life (QOL)

To determine in patients with resected brain metastases whether there is improved QOL in patients who receive SRS to the surgical bed compared to patients who receive WBRT.

2.22 Central Nervous System Failure
To determine in patients with one to four brain metastases whether there is equal or longer time to central nervous system (CNS) failure (brain) in patients who receive SRS to the surgical bed compared to patients who receive WBRT.

2.23 Functional Independence
To determine in patients with one to four brain metastases whether there is longer duration of functional independence in patients who receive SRS to the surgical bed compared to patients who receive WBRT.

2.24 Long-Term Neurocognitive Status
To determine in patients with one to four brain metastases whether there is better long-term neurocognitive status in patients who receive SRS to the surgical bed compared to patients who receive WBRT.

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

2.26 Local Tumor Bed Recurrence
To evaluate local tumor bed recurrence at 6 months with post-surgical SRS to the surgical bed in comparison to WBRT.

2.27 Local Recurrence
To evaluate time to local recurrence with post-surgical SRS to the surgical bed in comparison to WBRT.

2.28 CNS Failure Patterns
To evaluate if there is any difference in CNS failure patterns (local, distant, leptomeningeal) in patients who receive SRS to the surgical bed compared to patients who receive WBRT.

2.3 Correlative

2.31 Changes in the Limbic System
To evaluate radiation changes in the limbic system that may correlate with neurotoxicity using brain MRI or CT scans.

2.32 ApoE Subtype
To determine if Apo E (i.e., Apo E2, Apo E3 and Apo E4) genotyping may prove to be a predictor of radiation induced neurocognitive decline (or neuroprotection).

2.33 Inflammatory Markers
To determine if inflammatory markers (i.e., IL-1, IL-6 and TNF- □) may prove to be predictors of radiation induced neurocognitive decline.

2.34 Oxidative Stress Biomarkers
To determine if oxidative stress biomarkers (i.e., protein carbonyl content, lipid hydroperoxides and isoprostane levels) may prove to be predictors of radiation induced neurocognitive decline.

2.35 Hormone and Growth Factors
To determine if hormone and growth factors [i.e., glucocorticoids (i.e. cortisol), gonadal steroids (i.e., estradiol, testosterone, progesterone), growth hormone, human chorionic gonadotropin (hCG), insulin-like growth factor-1 (IGF-1) and neuronal growth factor (NGF)] may prove to be a predictor of radiation induced neurocognitive decline.

3.0 Patient Eligibility

3.1 Pre-registration Inclusion Criteria

3.11 Number of Brain Metastases
Four or fewer brain metastases (as defined on the pre-operative MRI or CT brain scan) and status post resection of one of the lesions.

3.12 Non-CNS Primary Site
Pathology from the resected brain metastasis must be consistent with a non-central nervous system primary site.

Note: Patients with or without active disease outside the nervous system are eligible (including patients with unknown primaries), as long as the pathology from the brain is consistent with a non-central nervous system primary site.

3.13 Size of Metastases
Any unresected lesions must measure < 3.0 cm in maximal extent on the contrasted MRI or CT brain scan obtained ≤ 35 days prior to pre-registration (see Magnetic Resonance Imaging Guidelines, Section 11.2). The unresected lesions will be treated with SRS as outlined in the treatment section (Section 7.4) of the protocol.

Note: The metastases size restriction does *not* apply to the *resected* brain metastasis; with *resected* brain metastases only surgical cavity size determines eligibility.

3.14 Size of Resection Cavity
Resection cavity must measure <5.0 cm in maximal extent on the post-operative MRI or CT brain scan obtained ≤35 days prior to pre-registration.
Note: It is permissible for the resection of a dominant brain metastasis to include a smaller "satellite" metastasis as long as the single resection cavity is less than the maximum size requirements.

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

3.16 Treatment with Gamma Knife or Radiosurgery
Able to be treated with either a gamma knife or a linear accelerator-based radiosurgery system.

3.17 Age
Age ≥ 18 years

3.18 Neurocognitive Testing
Willing and able to complete neurocognitive testing **without assistance from family and companions**. **Note:** Because neurocognitive testing is one of the primary goals of this study, patients must be able to utilize English language booklets (and/or French booklets if enrolled in Canada).

3.19a Quality of Life (QOL) Questionnaires
Willing and able to complete QOL by themselves or with assistance (see Section 4.0)

3.19b ECOG Performance Status
ECOG Performance Status (PS) 0, 1, or 2. See Appendix I.

3.19c SRS Credentialed by IROC Houston Quality Assurance
The site's SRS facility is IROC Houston Quality Assurance approved. See Section 4.4 of the protocol for information on how to obtain this credentialing.

3.19d Neurocognitive Testing Credentialing
The site study team member performing neurocognitive testing of patients must have credentialing confirming completion of the neurocognitive testing training See Section 4.31 of the protocol for information on how to obtain this credentialing.

3.19e Written Informed Consent
Provide written informed consent

3.19f Mandatory Samples for Correlative Tests
Willing to provide mandatory blood and urine samples for correlative research purposes (see Sections 6.154 and 14.0).

3.2 Pre-registration 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 men for up to 3 months after completing treatment.

3.22 Prior Cranial Radiation Therapy

3.23 MRI or CT Scans
Inability to complete a MRI or CT scan with contrast of the head.

3.24 Gadolinium Allergy
Known allergy to gadolinium.

3.25 Cytotoxic Chemotherapy
Planned cytotoxic chemotherapy during the SRS or WBRT.

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

3.27 Leptomeningeal Metastasis
Widespread definitive leptomeningeal metastasis.

3.28 Location of Brain Metastasis
A brain metastasis that is located ≤ 5 mm of the optic chiasm or within the brainstem.

3.3 Randomization Inclusion Criteria

3.31 Number of Unresected Lesions
Post-operative MRI or CT scan confirmed zero, one, two or three unresected lesions. Each unresected lesion must measure ≤ 3.0 cm in maximal extent on the contrasted post-operative MRI or CT brain scan.

Note: The pre-registration, post-operative, brain scan may be used for the randomization scan if obtained ≤ 28 days prior to randomization.

Note: If there are no unresected brain metastases (i.e., all brain metastases have been resected), a post-operative CT brain scan may be used if obtained ≤ 28 days prior to randomization.

3.32 Size of Resection Cavity
Post-operative MRI or CT scan confirms resection cavity measures < 5.0 cm in maximal extent.

Note: The pre-registration, post-operative brain scan may be used for the randomization scan if obtained ≤ 28 days prior to randomization.

Note: If there are no unresected brain metastases (i.e., all brain metastases have been resected), a post-operative CT brain scan may be used if obtained ≤28 days prior to randomization.

3.33 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 Randomization 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

Tests and procedures	≤14 days prior to pre-registration	After pre-registration, but prior to randomization	After randomization	TREATMENT[11]	Follow up/Observation[1, 11]					
					Weeks	Month				
					12	6	9	12	16	24
History and Physical Exam, including Weight, Recording of Medications and ECOG Performance Status	X[2]				X	X	X	X	X	X
Height	X									
Radiation Oncology Consultation (See Section 6.158)	X									
Neuro History and Exam	X				X	X	X	X	X	X
MRI or CT Scan	X[3]	X[4]			X	X	X	X	X	X
Adverse Event Assessment [5]	X				X	X	X	X	X	X
Urine or Serum Pregnancy Test [6]		X								
Mandatory blood samples [7, R] (see Section 14.0)		X			X	X		X		
Mandatory urine samples [7, R] (see Section 14.0)		X			X	X		X		
Optional tissue samples [8] (See Section 17.0)			X							
Mandatory Patient QOL Questionnaire booklet [9] (see Section 4.1)		X[10]			X	X	X	X	X	X[8]
Functional Independence (see Section 4.2)		X[10]			X	X	X	X	X	X
Mandatory Patient Neurocognitive Testing Questionnaire booklet [9] (see Section 4.32)		X[10]			X	X	X	X	X	X[8]

Footnotes for Table 4.0 appear on the following page

Footnotes for Table 4.0

1. Patients will continue to be followed per test schedule [even in the event of progressive disease (PD)] until withdrawal, refusal, death or 24 months from randomization. In the event of PD in the brain or progression of systemic disease, an Evaluation/Observation Form should be completed but patient continues to be followed per the test schedule (i.e., complete neurocognitive testing, MRI or CT scans, etc.). Follow-up visits are required +/- 14 days for week 12, +/- 1 month for months 6, 9, 12, +/- 2 months for month 16, and +/- 4 months for month 24. After 24 months from randomization, an Event Monitoring Form should be completed and thereafter every 6 months until 5 years from randomization.

2. 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.

3. Both pre-operative and post-operative brain scans are required. Pre-operative contrasted MRI or CT brain scans must be obtained ≤ 49 days prior to pre-registration. Post-operative MRI or CT brain scan must be obtained ≤ 35 days prior to pre-registration. In the post-operative, pre-randomization setting, a CT brain scan is allowed although a post-operative MRI is preferred.

4. A MRI or CT contrasted brain scan must be obtained ≤ 28 days before randomization. Sometimes this scan will be used for SRS planning purposes. A pre-randomization MRI scan is not required in two circumstances:
    a) The post-operative MRI or CT scan may be used for the randomization scan if obtained ≤ 28 days prior to randomization.
    b) There are no unresected brain metastases (i.e., all brain metastases have been resected). A post-operative CT brain scan is sufficient in those circumstances if obtained ≤ 28 days prior to randomization.

5. Report **all** adverse events that have occurred since the prior visit including late effects of radiation.

6. Patient, if female of childbearing potential, must have a negative urine or serum pregnancy test result ≤ 7 days prior to randomization.

7. Mandatory blood draws and mandatory urine samples will be collected at baseline (after pre-registration, but any time prior to treatment), at 12 weeks post randomization, and at 6 and 12 months following randomization. Kits are required for this collection. (Mayo Clinic Rochester will use Special Studies Refer Cards.)

8. Optional tissue should be submitted ≤ 30 days after randomization.

9. Patient Quality of Life and Neurocognitive Testing questionnaire booklets **must** be used; copies are not acceptable for this submission. Please obtain a supply of all necessary booklets before registering patients. Booklets should be ordered from CTSU by completing the CTSU Supply Request Form on the CTSU website. Questionnaire booklets are to be completed during the scheduled clinic visits indicated in the table above and returned to study staff.

10. If the patient Quality of Life questionnaires and/or the neurocognitive testing questionnaires were completed ≤ 14 days prior to randomization for clinical reasons, and comply with the standards of the testing outlined in the protocol, these results will be allowed (as per protocol, proper documentation is required and booklets need to be forwarded) and do not need to be repeated after pre-registration, prior to randomization.

11. **Treatment:**
    Cycle 1 = starts day 1 of treatment and ends at week 12 follow up.
    Follow up/Observation:
    Cycle 2 = starts at 12 weeks and ends at 6 month follow up.
    Cycle 3 = starts at 6 months and ends at 9 month follow up.
    Cycle 4 = starts at 9 months and ends at 12 month follow up.
    Cycle 5 = starts at 12 months and ends at 16 month follow up.
    Cycle 6 = starts at 16 months and ends at 24 month follow up.

R Research funded (see Section 19.0).

4.1 Patient Quality of Life (QOL) Questionnaire Booklets

The Patient Quality of Life (QOL) Questionnaire Booklet contains the FACT-Br, Fatigue/Uniscale and the LASA questionnaires (Appendix III).

Please obtain a supply of all necessary booklets before registering patients. Booklets should be ordered from CTSU by completing the CTSU Supply Request Form on the CTSU website.

Questionnaire booklets are to be completed during the scheduled clinic visits and returned to study staff. Patient and Examiner Questionnaire Booklets **must** be used; copies are not acceptable for this submission. Instructions for the administration of the QOL patient questionnaire booklets are provided in Appendix II. Briefly, the patient is to complete the Patient QOL Questionnaire Booklet, this will require about 10 to 15 minutes to complete. Since the patient may experience cognitive deterioration during treatment, 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

The QOL booklet will be administered at baseline (after pre-registration and prior to randomization) and at the beginning of each scheduled study visit after treatment (i.e., at 12 weeks and at 6, 9, 12, 16 and 24 months post randomization).

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, Attention: QAS for N107C. Northwest 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. At baseline (after pre-registration and prior to randomization) and at the beginning of each scheduled study visit after treatment (i.e., at 12 weeks and at 6, 9, 12, 16 and 24 months post randomization), 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 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 form at the treating institution and mail the ***original*** completed form to NCCTG Operations Office, Attention: QAS for N107C, Northwest Clinic 3-24 CC, 200 First Street SW, Rochester, MN 55905.

4.3 Neurocognitive Testing

4.31 Neurocognitive Testing Certification

Note: Patients **<u>may not</u>** 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. Jane Cerhan, Mayo Clinic Rochester or 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;
NCCTG N0574, N0577 or N0874;
RTOG BR-0018, 0212, 0424, 0525, 0534, 0614, 0834, 0825, 1125
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 N107C 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 N107C 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 N107C 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..

Complete the "Neurocognitive Booklet for Certification Use Only." The booklet includes a brief quiz and a practice test. Complete the practice test with a colleague **(not** a patient).

Scan and email a copy of the ***entire booklet*** to Dr. Cerhan. as she will review the certification booklet. 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.. The Alliance Regulatory Affairs 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 N107C in the search boxes and clicking 'Go'.

If there are questions about testing procedures, please contact Dr. Cerhan 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 Neurocognitive Certification and Patient Neurocognitive Testing Booklets

The study site should obtain all necessary neurocognitive certification and neurocognitive patient testing questionnaire booklets ***before pre-registering patients***. Booklets should be ordered from CTSU by completing the CTSU Supply Request Form on the CTSU website. Note: CTSU will not send questionnaire booklets until the site has submitted a copy of their IRB approval excerpt to the CTSU Regulatory Office. Neurocognitive certification and

neurocognitive patient testing questionnaire booklets must be used; copies are not acceptable for submission. Neurocognitive patient testing questionnaire booklets are to be completed and returned to site study staff during the scheduled clinic visits.

4.33 Timing of Neurocognitive Testing

Baseline neurocognitive testing will be performed following the surgical procedure but before beginning treatment and thereafter as outlined in Table 4.0.

4.34 Neurocognitive Tests Format

The credentialed site study team member will administer the neurocognitive tests to the patient using the patient questionnaire titled "Neurocognitive Examiners Booklet". There are six different versions of the questionnaires labeled form 1, form 2, form 3, form 4, form 5 and form 6. Each questionnaire has a unique version of the Hopkins Verbal Learning Test (HVLT) to prevent patient recall from a prior test. The questionnaire booklet requires approximately 20 to 30 minutes to complete and includes the following tests:

Memory: Hopkins Verbal Learning Test (HVLT) (Brandt 1991).
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 Trail Making Test A and B, please contact Dr. Cerhan as adjustments may be made depending on the patient's situation.

4.35 Submission of the Completed Neurocognitive Test Questionnaires

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 the Neurocognitive Booklet. Retain ***a copy*** of the completed neurocognitive booklet at the treating institution and ***mail the original*** of the completed booklet to NCCTG Operations Office, Attention: QAS for N107C, NW Clinic 3-24 CC, 200 First Street SW, Rochester, MN 55905

Please be sure to fax the Neurocognitive Evaluations Submission Fax Form (Appendix VI) to the QAS for N107C at (507) 266-7240.

4.36 Quality Control for Patient Neurocognitive Testing Booklets

Throughout the study, Dr. Cerhan will review all patient questionnaire booklets for quality control purposes. 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 NCCTG 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 IROC Houston's website at http://irochouston.mdanderson.org 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 IROC Houston Quality Assurance Center electronically from the IROC Houston's website for review. The questionnaire is available on the IROC Houston's website, http://irochouston.mdanderson.org , under 'Credentialing.'

4.42 SRS Phantom Study

An SRS phantom study with the IROC Houston Quality Assurance must be successfully completed. 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 IROC Houston's website at http://irochouston.mdanderson.org ; select 'Credentialing' then 'NCCTG'. Upon review and successful completion of the phantom irradiation, the IROC Houston Quality Assurance Center will notify the Alliance Regulatory Affairs Manager at thaynes2@uchicago.edu of the site's SRS credentialing. The Alliance Regulatory Affairs Manager will record and then forward this information 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 N107C 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 N0574 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 IROC Houston's website at http://irochouston.mdanderson.org; 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
< 60 years vs. ≥ 60 years

5.2 Extra-Cranial Disease Controlled
≤ 3 months vs. > 3 months.

5.3 Number of Pre-operative Brain Metastases
1 vs. 2 to 4

5.4 Histology
Lung vs. Radioresistant vs. other
Note: Radioresistant is defined as brain metastases from a sarcoma, melanoma, or renal cell carcinoma histology.

5.5 Resection cavity maximal diameter
≤ 3cm vs. > 3cm

6.0 Registration/Randomization Procedures

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

6.1 Pre-Registration (Step 1)

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 N107C 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 IROC Houston 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 updates have occurred at the facility. A copy of the RTFI may be downloaded from the CTSU website and submitted to the CTSU Regulatory Office.

6.14 Access Requirements for Oncology Patient Enrollment Network (OPEN)

6.141 Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.

6.142 To perform pre-registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.

6.143 To perform pre-registrations on protocols for which you are a member of the Lead Group (i.e.,Alliance), you must have an equivalent 'Registrar' role on the Lead Group (i.e., Alliance) roster. Role assignments are handled through the Groups in which you are a member.

6.144 To perform pre-registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group pre-registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

NOTE: *The OPEN system will provide the site with a printable confirmation of pre-registration and treatment information. Please print this confirmation for your records.*

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

6.15 Patient Pre-Registration (Step 1)

6.151 Patient pre-registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

6.152 All site staff will use OPEN to enroll patients to this study. Each site will need to credit their existing affiliated Cooperative Group for the enrollment. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

6.153 Prior to accessing OPEN, site staff must verify the following:

- All eligibility criteria must have been met within the protocol stated timeframes. Site staff should use the pre-registration forms provided on the Alliance or CTSU web site as a tool to verify eligibility.

- All patients must have signed an appropriate consent form and HIPAA authorization form (if applicable).

6.154 Correlative Research
Mandatory Urine and Blood Samples
A mandatory correlative research component for blood and urine is part of this study, the patient will be automatically registered onto this component (see Sections 3.19f and 14.0).

6.155 Patient Permission for Biospecimen Use
At the time of randomization, the following will be recorded:

- Patient has/has not given permission to store and use his/her **blood sample(s)** for use in future research to learn about, prevent, or treat cancer.

- Patient has/has not given permission to store and use his/her **blood sample(s)** for use in future research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

- Patient has/has not given permission for Alliance to give his/her stored **blood sample(s)** for use in future research to outside researchers.

- Patient has/has not given permission to store and use his/her **urine sample(s)** for use in future research to learn about, prevent, or treat cancer.

- Patient has/has not given permission to store and use his/her urine sample(s) for use in future research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

- Patient has/has not given permission for Alliance to give his/her stored urine sample(s) for use in future research to outside researchers.

- Patient has/has not given permission to store and use his/her tissue sample(s) for use in future research to learn about, prevent, or treat cancer.

- Patient has/has not given permission to store his/her tissue sample(s) for use in future research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

- Patient has/has not given permission for Alliance to give his/her stored tissue sample(s) for use in future research to outside researchers.

6.156 Completion of Pre-treatment Tests/Procedures
Pretreatment tests/procedures must be completed prior to pre-registration within the guidelines specified on the test schedule (see Section 4.0).

6.157 Grading of Baseline Symptoms
All required baseline symptoms (see Section 10.51) must be documented and graded.

6.158 Confirmation of Eligibility
A radiation oncologist has seen the patient and confirms the patient is a suitable candidate for this study.

6.159a Blood and Urine Kits
Blood and urine kits available on site.

6.159b Patient Questionnaire Booklets
Quality of Life (QOL) questionnaire booklets and Patient Neurocognitive Testing questionnaire booklet – Neurocognitive Evaluations are available on site; copies are not acceptable for this submission.

6.2 Registration/Randomization (Step 2)

6.21 Randomization Using OPEN
If the randomization scan has been obtained, sites should access OPEN to randomize (Step 2) the patient. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

6.22 Verification of Registration Requirements
Prior to accepting the registration/randomization, the registration/randomization application 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 (*USA institutions only*)

6.23 Stratification Factors
The factors defined in Section 5.0, together with the registering membership, will be used as stratification factors.

6.24 Randomization Groups
The patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups (Pocock and Simon 1975).
Arm A: WBRT
Arm B: SRS to surgical bed

6.25 Start of Treatment
Treatment cannot begin prior to randomization and must begin ≤ 21 days after randomization.

6.26 Treating Physician and Site
Treatment on this protocol must commence at the accruing membership under the supervision of an Alliance or CTSU member physician.

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.

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 registering the patient as long as treatment guidelines are followed and the site delivering the SRS has been credentialed for SRS by the IROC Houston Quality Assurance Center.
Note: Please inform IROC Houston Quality Assurance Center and Alliance that your site will register the patient and perform SRS at another site; please include the sites' names and CTEP site codes. Without this information, CTSU may delay the registration of the patient as it would have no SRS credentialing on file for the registering site.

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. The SRS dose is decreased modestly for larger lesions in order to account for the volume effect on complication rates.

7.14 Cytotoxic Chemotherapy Prohibited During SRS and WBRT
Cytotoxic chemotherapy is not allowed during the SRS or during the WBRT. Chemotherapy may start immediately following SRS and/or WBRT.

7.15 Timing of SRS and WBRT
Patients must initiate radiotherapy/radiosurgery treatment ≤ 21 days after registration.

7.2 Whole Brain Radiation Therapy (WBRT) Guidelines (For **ARM A Only**)

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

For unresected brain metastases see Section 7.4.

7.21 Equipment

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

7.212 Calibration
The calibration of therapy machines to deliver WBRT used in this study shall be verified by the IROC Houston Quality Assurance Center.

7.22 Target Volume

7.221 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.

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

7.23 Target Dose

7.231 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).

7.232 Dose Definition
The absorbed dose is specified below in Gy to muscle (or water).

7.233 Tissue Heterogeneity
Corrections for tissue heterogeneity are allowed.

7.234 Prescribed dose and fractionation

Sites performing radiation therapy must predetermine one of the two fractionation schedules that will be utilized for N107C for ***all*** patient randomized at the site. A site may choose a total dose to the prescription point is 3750 cGy. This dose is delivered in 15 fractions of 2.5 Gy. The alternative choice for a site is a total dose to the prescription point of 3000 cGy delivered in ten fractions of 3 Gy each. All radiation fields shall be treated once each day. If possible, the treatment shall be given 5 days a week.

7.235 Dose Uniformity

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

7.236 Treatment Interruptions

No corrections shall be made for treatment interruptions less than or equal to seven days. For interruptions greater than seven days, please contact Dr. Paul Brown (See title page).

7.24 Treatment Technique

7.241 Patient Position

It is recommended that the patient be treated supine.

7.242 Beam Configuration

The cranial volume is typically 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. In addition, forward planned field in field radiotherapy is allowed to decrease hot spots. However intensity modulated radiotherapy which by definition involves inverse planning is not allowed.

7.243 Field Shaping

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

7.25 Treatment Timing

7.251 No Unresected Brain Metastases

Patients must initiate radiotherapy ≤ 21days after randomization.

7.252 Unresected Brain Metastases Present

Patients must initiate radiosurgery or radiotherapy ≤ 21days after randomization. The preferred approach is radiosurgery to unresected brain metastases followed by WBRT. Regardless completion of one treatment dictates initiation of the other treatment within 14 days. For example after SRS to unresected brain metastases, WBRT must start within 14 days of completion of SRS.

7.253 Quality Control and Definitions of Deviations
Quality control and deviations will be done according to the guidelines in Appendix VII. All plans and associated materials as per NCCTG standards will be reviewed by 2 radiation oncologists and the IROC Houston Quality Assurance Center.

7.3 Stereotactic Radiosurgery (SRS) to Surgical Bed Guidelines (For **ARM B Only)**
Radiosurgery for patients on this protocol can only be performed at IROC Houston Quality Assurance Center credentialed facilities. See protocol Section 4.4 for details.

For unresected brain metastases see Section 7.4.

If all lesions cannot be treated on the same day, all lesions MUST be treated ≤ 7 days of treatment of the first lesion. The radiosurgery can be delivered at a different site than the site registering the patient (see Section 7.12).

7.31 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.

7.32 Equipment

7.321 Modality
Gamma knife or X-rays with nominal energy of 4 megavoltage (MV) or greater for accelerator-based treatments, including isocentric conical collimators, mini-multi-leaf (5 mm or less) technology or linear accelerators mounted on robotic arms.

7.322 Calibration
The calibration of linear accelerators used in this study shall be verified by the IROC Houston Quality Assurance Center.

7.33 Target Volume Definitions
The volumes shall be defined by a planning MRI or CT brain scan. ICRU-50 and supplement (ICRU-62) nomenclature target volumes are defined as follows:

7.331 Clinical Tumor Volume (CTV2)
This is defined as the surgical cavity (CTV1) with a 2 mm margin as seen on planning MRI or CT scan. However this 2 mm margin does not need to expand into structures that typically are not at risk of tumor infiltration from brain metastases such as bone. The surgical access track for deep lesions will not be specifically targeted. The maximal cross-sectional diameter of the surgical cavity must be < 5.0 cm.

7.34 Target Dose

7.341 Prescription Specification
The dose should be prescribed to the highest isodose line encompassing the CTV2 (surgical cavity plus 2 mm – see Section 7.331), which can range from 50% to 90% of the maximum dose.

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

7.343 Prescription Dose
The total prescribed dose is determined by surgical cavity volume (CTV1). The volume determines dose due to the often irregular shape of surgical cavities:

Arm B (SRS):
Lesions < 4.2 cc receive 20 Gy
Lesions ≥ 4.2 to < 8.0 cc receive 18Gy
Lesions ≥ 8.0 to < 14.4 cc receive 17 Gy
Lesions ≥ 14.4 to < 20 cc receive 15 Gy
Lesions ≥ 20 to < 30 cc receive 14 Gy
Lesions ≥ 30 cc to < 5cm max 12 Gy

7.344 Dose Conformity
The ratio of the prescription isodose volume to the target volume (CTV2) 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. See Radiation Therapy Quality Control Guidelines (Appendix VII).

7.35 Treatment Technique
An immobilization/patient localization system is mandatory for this study. Multiple isocenter and non-isocentric techniques are permitted.

7.36 Normal Tissue and 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 maximum point dose to the optic chiasm should be less than 9 Gy. No more than 1cc of the brain stem should exceed 12 Gy.

7.37 Dose Calculation and Reporting

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

7.372 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).

7.373 Conformity Index
The PITV, defined as the ratio of the prescription isodose volume to the target volume (CTV2), shall be calculated and reported. If the prescription isodose volume is calculated from a DVH, that DVH shall be submitted (see Section 18.0 Records and Data Collection Procedures) and Radiation Therapy Quality Control Guidelines (Appendix VII).

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

7.375 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 Section 18.0 Records and Data Collection Procedures) and Radiation Therapy Quality Control Guidelines (Appendix VII).

7.376 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.

7.4 Guideline for ***Unresected*** Brain Metastases

For BOTH ARMS A and B; however SRS doses to **unresected** brain metastases will be different between treatment arms.

Radiosurgery for patients on this protocol can only be performed at IROC Houston Quality Assurance Center credentialed facilities. See protocol Section 4.4 for details.

If all lesions cannot be treated on the same day, all lesions MUST be treated ≤7 days of treatment of the first lesion. The radiosurgery can be delivered at a different site than the site registering the patient (see Section 7.12).

7.41 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.

7.42 Equipment

7.421 Modality
Gamma knife or X-rays with nominal energy of 4 megavoltage (MV) or greater for accelerator-based treatments, including isocentric conical collimators, mini-multi-leaf (5 mm or less) technology or linear accelerators mounted on robotic arms.

7.422 Calibration
The calibration of linear accelerators used in this study shall be verified by the IROC Houston Quality Assurance Center.

7.43 Target Volume Definitions

7.431 The volumes shall be defined by a planning MRI or CT brain scan. ICRU-50 and supplement (ICRU-62) nomenclature target volumes are defined as follows:

7.432 Gross Clinical Tumor Volume (CGTV)
This is defined as the contrast enhanced tumor seen on planning MRI or CT scan. The maximal cross-sectional diameter must be < 3.0 cm.

7.433 Clinical Target Volume (CTV)
This is defined as the GTV for this study. Typically there will be no expansion of GTV to create CTV, but an optional 1mm expansion of GTV is allowed when defining the CTV.

7.44 Target Dose

Prescription Specification
The dose should be prescribed to the highest isodose line encompassing the CTV, which can range from 50% to 90% of the maximum dose.

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

Prescription Dose
The total prescribed dose is determined by treatment arm and tumor size (maximal diameter).

Arm A (WBRT):
SRS for unresected brain metastases:
Lesions <1.0 cm receive 22 Gy
Lesions ≥1– <2.0 cm receive 20 Gy
Lesions ≥2 – <3.0 cm receive 18 Gy
WBRT: Refer to prescribed dose and fractionation in Whole Brain Radiation Therapy (WBRT) Guidelines section.

Arm B (SRS only):
SRS for unresected brain metastases:
Lesions <1.0 cm receive 24 Gy
Lesions ≥1– <2.0 cm receive 22 Gy
Lesions ≥2 – <3.0 cm receive 20 Gy

Dose Conformity
The ratio of the prescription isodose volume to the target volume (CTV) 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. See Radiation Therapy Quality Control Guidelines (Appendix VII).

Planning MRI or CT scan
If at the time of planning MRI or CT scan for SRS more than 3 unresected brain metastases are noted, the patient should remain on study. If SRS is performed, the dosing guidelines 7.443 should be followed. Also see Section 13 and contact Study Chairs for guidance as needed.

7.45 Treatment Technique

An immobilization/patient localization system is mandatory for this study. Multiple isocenter and non-isocentric techniques are permitted.

7.46 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 maximum point dose to the optic chiasm should be less than 9 Gy. No more than 1cc of the brain stem should exceed 12 Gy.

7.47 Dose Calculation and Reporting

Treatment Time

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

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).

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 Section 18.0 Records and Data Collection Procedures) and Radiation Therapy Quality Control Guidelines (Appendix VII).

Prescription Isodose Line

The total dose delivered to the prescription isodose line shall be calculated and reported.

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 Section 18.0 Records and Data Collection Procedures)and Radiation Therapy Quality Control Guidelines (Appendix VII).

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.

8.0 Dosage Modification Based on Adverse Events: None

9.0 Ancillary Treatment/Supportive Care

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 Event Characteristics

CTCAE term (AE description) and grade**:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. 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 v 4.0. 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 submission of 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 Section 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).

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 serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected

- The determination of whether an AE is expected is based the 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 Myeloctyic 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: Studies using Commercial Agent(s) ONLY:

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]

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>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

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.

[1]Serious 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

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.
Effective Date: May 5, 2011

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 re-connection.

10.41 Contact Information for NCI Safety Reporting

Website for submitting expedited reports	https://eapps-ctep.nci.nih.gov/ctepaers/
AEMD Help Phone (for CTEP)*	301-897-7497 Monday through Friday, 7:00 AM to 7:00 PM (US Eastern Time)
CIP Help Phone for SAE reporting*	301-897-1704 Monday through Friday, 7:00 AM to 7:00 PM (US Eastern Time)
Fax for expedited report supporting Medical Documentation for CTEP trials	301-230-0159 (back-up FAX: 301-897-7404)
Fax for expedited report supporting Medical Documentation for CIP trials	301-897-7402
AEMD Help Email:	aemd@tech-res.com
CIP SAE Reporting Email	CIPSAEReporting@tech-res.com
Technical (e.g., IT or computer issues ONLY) Help Phone*	1-888-283-7457
CTEP-AERS Technical Help Email	ncictephelp@ctep.nci.nih.gov.
CTCAE v4 Help/Questions Email	ncictcaehelp@mail.nih.gov
CTEP-AERS FAQs link	https://eapps-ctep.nci.nih.gov/ctepaers/help/webhelp/CTEP-AERS%20FAQ.htm
CTEP-AERS Computer Based Training link	http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

*Office phone and fax are accessible 24 hrs per day 7 days a week (The AEMD 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

EVENT TYPE	REPORTING PROCEDURE
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 electronically via the NCCTG Remote Data Entry System within 5 working days 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 CTCAE v4.0 grading unless otherwise stated in the table below:

System Organ Class (SOC)	Adverse event	Baseline	Each evaluation
Ear and labyrinth disorders	Hearing impaired	X	X
	External ear inflammation	X	X
Eye disorders	Retinopathy	X	X
Gastrointestinal disorders	Nausea	X	X
	Vomiting	X	X
Injury, poisoning and procedural complications	Dermatitis radiation	X	X
	Wound dehiscence	X	X
Nervous system disorders	Cognitive disturbance	X	X
	Peripheral motor neuropathy	X	X
	Central nervous system necrosis	X	X
Skin and subcutaneous tissue disorders	Alopecia	X	X

10.52 Adverse Event Submission Using Case report Forms (CRFs)

Submit via appropriate North Central Cancer Treatment Group (NCCTG) Case Report Forms (i.e., paper or electronic, as applicable) the following AEs 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 or procedure.

10.523 Grade 5 AEs (Deaths)

10.5231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5232 Any death more than 30 days after 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

11.1 Response criteria

The neurologic examination and the MRI and/or CT at each evaluation will be scored as follows:

11.11 Unresected Brain Metastases

The response score will be rated as one of the following (follow-up MRI or CT brain scans will be compared to the prior MRI or CT 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 developed outside the radiosurgical bed (in the brain or meninges).

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.

11.12 Resected Brain Metastasis (i.e. surgical cavity)

Note: Tumor bed control is defined as the absence of new nodular contrast enhancement in the surgical bed. By definition a post-operative MRI or CT brain scan is required as a baseline study. If there is *questionable* development of nodular enhancement in the surgical bed than this should be graded as stable disease recognizing follow-up studies will make this determination more certain (e.g. questionable area of nodular enhancement continues to grow and should therefore be coded as disease progression).

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

Stable disease: Absence of new nodular contrast enhancement in the surgical bed.

Disease progression: Development of new nodular contrast enhancement in the surgical bed.

Note: Tumor progression of the treated cavity bed 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 four categories (see Section 4.0): pre-registration (pre-operative and post-operative), randomization (prior to randomization), planning if SRS is performed (typically after randomization, prior to treatment) and follow-up (observation). The pre-registration MRI brain scans will be used to determine preliminary patient eligibility. The pre-registration and pre-randomization MRI brain scans are without parameters since they are performed prior to study entry. The pre-randomization MRI brain scan will be used to determine final eligibility. If SRS is performed there will typically be a planning scan

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

- Axial post-contrast images
- 5mm or less slice thickness
- Scanner should be at least a 1.0 Tesla magnet

Note: It is recommended the same technique be used for each of the diagnostic MRI brain scans at follow-up.

Note: The (pre-registration) post-operative MRI scan may be used for the randomization (prior to randomization) scan if the scan was obtained ≤ 28 days prior to randomization.

11.3 Patient Monitoring during Active Treatment

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 or CT brain scan at baseline (after pre-registration, but prior to randomization) and post-treatment at week 12 post randomization and at months 6, 9, 12, 16 and 24. Follow-up visits are required +/- 14 days for week 12, +/- 1 month for months 6, 9, 12, +/- 2 months for month 16 and +/- 4 month for month 24. At each scheduled study visit, a QOL booklet (FACT-BR, Fatigue Uniscale, and LASA), functional independence (Barthel ADL Index and ECOG performance status), and neurocognitive evaluations will be completed.

11.4 Patient Monitoring during Observation

Patients will be in observation phase and assessed for local recurrence, progression in the surgical bed, distant brain recurrence and progression until death or 24 months from study entry. Patients will continue to be monitored after progression and should continue to be followed using the test schedule for observation (Section 4.0).

11.5 Response Rate

11.51 MRI or CT scans

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

Central Review: In addition to the review and response evaluation of the MRI or CT scans by the local investigators there will also be a parallel central review of all MRI and CT scans by Drs. Brown and Parney. This central review will be *only* for the surgical cavity and will not be for distant brain failure or other aspects of the scans. Drs. Brown and Parney will perform readings at different sessions to ensure that the interpretations will remain independent. If readings are discordant, a third PI (Dr. Laack) will adjudicate and determine the surgical bed control for the dataset. The readers will be blinded to the treatment arm and will interpret the data from all time points available. These reviews will be ongoing and performed either at the semi-annual group meetings or at Headquarters.

11.511 As part of the central review there will also be a determination of gross total resection by central review. This will follow the same procedures as outlined above in 11.51. The pre-operative and post-operative, pre-randomization brain scans will be utilized to make these determinations.

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. Autopsy reports should be obtained, whenever possible, and sent by fax to the 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). **All MRI or CT brain scans are to be submitted ≤ 1week of completion (Note: this applies to ALL participating sites).** This includes pre-registration (both pre- and post-operative), randomization, planning scans, and follow-up. These scans will be essential for central review of brain control.

Images on CDs are preferred to film but must be DICOM compatible. Send all images to NCCTG Operations Office, Attn: QAS for N107C, NW Clinic 3-24 CC, 200 First Street SW, Rochester, MN 55905

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 Five New Lesions

Patients who develop recurrence to the brain following study treatment should be retreated with SRS alone **if one to five 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 Five 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. If more than five new metastases, repeat WBRT should be considered, as outlined below, if there has been an extended period of time since the first course of WBRT, generally 6 months or more.

The salvage WBRT dose guidelines are as follows:

Arm A: Repeat WBRT 25 Gy in 10 fractions.

Arm B: Initial WBRT of 30 Gy in 10 fractions.

If needed repeat WBRT of 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 Evaluation/Observation 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. 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. The patient will go to Event Monitoring.

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. 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

14.1 Body Fluid Biospecimen Submission

Table 14.11 Summary of Body Fluid Biospecimens for This Protocol

Biospecimen to submit	Mandatory or optional	When to submit	Reason for submission (methodology section)	Protocol section with specific details for specimen submission
Blood/blood products (EDTA whole blood)	Mandatory	Multiple draws (see Section 14.24 for schedule)	Correlative studies (Section 14.4)	Section 14.2
Blood/blood products (serum from no additive whole blood)	Mandatory	Multiple draws (see Section 14.24 for schedule)	Correlative studies (Section 14.4)	Section 14.2
Urine	Mandatory	Multiple collections (see Section 14.34 for schedule)	Correlative studies (Section 14.4)	Section 14.3

14.2 Blood/Blood Products Handling

14.21 Blood Collection, Processing and Shipping Kits
Kits are required for this study.

14.211 The kit contains supplies and instructions for collecting, processing, and shipping serum, whole blood, and urine (see Section 14.3) specimens.

14.212 Participating institutions may obtain kits by completing and faxing the Supply Order Form (found in the Forms Packet) to the number listed on the form. Fill out the site address to where the kits will be shipped on the Fax Supply form. Because we are now being charged for all outgoing kits, a small, but sufficient, supply of the specimen collection kits should be ordered prior to patient entry. Do not send the unused kits back to Biospecimen Accessioning and Processing (BAP) Receiving or the BAP Shared Resource.

14.213 Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. Allow up to two weeks to receive the kits. Kits may arrive inside the shipping boxes or as second shipment box.

14.214 Kits will not be sent via rush delivery service unless the participating institution provides their own FedEx® account number or alternate billing number for express service. NCCTG will not cover the cost for rush delivery of kits.

14.22 Sample Collections During Weekdays Only
All samples must be collected Monday-Thursday ONLY.

14.23 Labeling of Tubes
Label specimen tube(s) with protocol number, patient study ID number, and time and date blood is drawn.

14.24 Collection and Processing
Collect and process all blood/blood products according to specific kit instructions and table below.

Table 14.241 Summary of Research Blood/Blood Products to Be Collected for This Protocol

Mandatory or optional	Collection tube and additive (Color of tube top)	Volume to collect per tube (Number of tubes collected)	Blood product	Baseline [1]	12 weeks [2]	6 months [2]	12 months [2]	Process at site?	Storage/ shipping conditions [3]
Mandatory	None (red)	10 mL (2)	Serum	X	X	X	X	Yes	Freeze/ dry ice
Mandatory	EDTA (purple)	10 mL (1)	Whole Blood	X	X	X	X	No	Refrigerate or cold pack DO NOT FREEZE

1 After randomization, but prior to treatment;
2 After randomization;
3 After all samples have been processed according to kit instructions, ship all specimens according to shipping instructions (See Section 14.25 for detailed shipping instructions).

14.25 Shipping

14.251 Verify ALL sections of the Research Blood Submission Form (see Forms Packet), BAP Requisition Form (provided in kit), and specimen collection labels are completed and filled in correctly. Enter information from the Research Blood Submission Form into the remote data entry system ≤ 7 days after specimen collection (see Forms Packet).

14.252 Specimens must be shipped the same day they are drawn.

14.253 Specimens will be shipped in a dual-temperature shipping container. Place the refrigerated EDTA tubes with a properly prepared cold pack in one compartment. See kit instructions for specific details for cold pack preparation (i.e., frozen or refrigerated) and proper packing of blood and cold pack to avoid freezing of specimen. Place the frozen serum samples with dry ice in the other compartment of the dual-temperature shipping container.

14.254 Ship specimens via Priority Overnight service, Monday – Thursday ONLY, to BAP Receiving according to kit instructions. Do not send samples on weekends or just prior to federal holidays.

14.255 The BAP kits will include a smart shipper label (3 x 5 white barcoded label) affixed to the shipping boxes. The smart shipper label is a pre-addressed return label, which replaces the need for an airbill. Shipping costs will be covered by NCCTG if the shipping box provided with the BAP kit is used for shipping specimens to BAP Receiving

14.256 BAP Freezer will receive the samples and immediately forward specimens to the NCCTG Research Base BAP Shared Resource, Hilton SL-21, Attn: BAP Supervisor.

14.3 Urine Handling

14.31 Kits

Kits are required for this study. The supplies and instructions for collecting, processing, and shipping urine specimens are combined with the blood collection kit

14.32 Sample Collections During Weekdays Only

All samples must be collected Monday-Thursday ONLY.

14.33 Labeling of Tubes

Label specimen tube(s) with protocol number, patient ID number, and time and date specimen is collected.

14.34 Collection and Processing

Collect and process urine according to specific kit instructions and table below.

Table 14.341 Summary of Research Urine to Be Collected for This Protocol

Mandatory or optional	Collection container description	Volume to collect (Number of containers collected)	Baseline[1]	12 weeks[2]	6 months[2]	12 months[2]	Process at site?	Storage/ shipping conditions[3]
Mandatory	Urine (no additive)	50 mL (1)	X	X	X	X	No	Refrigerate or cold pack DO NOT FREEZE

1 After randomization, but prior to treatment;
2 After randomization;
3 After all samples have been processed according to kit instructions, ship all specimens according to shipping instructions (see Section 14.35 for detailed shipping instructions).

14.35 Shipping

14.351 Verify ALL sections of the Research Urine Submission Form (see Forms Packet), BAP Requisition Forms (provided in the blood/urine kits), and specimen labels are completed and filled in correctly. Enter information from the Research Urine Submission Form into the remote data entry system ≤ 7 days after specimen collection (see Forms Packet).

14.352 Urine Shipping

14.3521 Urine specimens must be shipped the same day they are drawn.

14.3522 Urine specimens will be shipped in the same dual-temperature shipping container as the whole blood and serum. Place the urine container with a properly prepared cold pack in the same compartment as the EDTA whole blood. See kit instructions for specific details for cold pack preparation (i.e., frozen or refrigerated) and proper packing of blood and cold pack to avoid freezing of specimen.

14.353 Ship specimens via Priority Overnight service, **Monday – Thursday ONLY,** to BAP Receiving according to kit instructions. **Do not send samples on weekends or just prior to federal holidays.**

14.354 The BAP kits will include a smart shipper label (3 x 5 white barcoded label) affixed to the shipping boxes. The smart shipper label is a pre-addressed return label, which replaces the need for an airbill. Shipping costs will be covered by NCCTG if the shipping box provided with the BAP kit is used for shipping specimens to BAP Receiving.

14.355 BAP Receiving will receive the samples and immediately forward specimens to the NCCTG Research Base BAP Shared Resource, Stabile 13-10A, Attention: BAP Supervisor.

14.4 Correlative Study Methodology and Storage Information

A variety of measures will be analyzed in this study (see Section 1.3 for additional details) to better define the mechanism of neurocognitive decline as well as which patients are most likely to develop neurocognitive decline after brain irradiation. Serum (collected in a no additive red top tube) and DNA or buffy coat and plasma (collected in an EDTA purple top tube) will be collected during this trial at baseline (after pre-registration, but prior to treatment), after treatment at week 12 and at 6 and 12 months post randomization. These body fluid biospecimens will be analyzed as described below. The assays described below will be performed at the NCCTG Research Base (Mayo Clinic campus in Rochester), Dr. Deepak Khuntia will serve as the correlative research chair and will be available for any communications.

14.41 Genetic markers

DNA will be extracted from baseline blood in the BAP Shared Resource at the NCCTG Research Base. Apo E (i.e., Apo E2, Apo E3, and Apo E4) genes will be analyzed for single nucleotide polymorphisms (SNPs) either by Taqman or direct sequencing in the Genotyping Shared Resource at the NCCTG Research Base.

14.42 Inflammatory Markers

Serum specimens collected at baseline and at each follow-up visit (see Section 14.4) will be analyzed using commercially-available ELISAs from R&D Systems, Inc. for the following inflammatory biomarkers: interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF). These markers will be assayed at the NCCTG Research Base.

14.43 Oxidative Stress

Our approach to measuring oxidative stress will consist of quantifying protein carbonyl content spectrophotometrically (Protein Carbonyl Assay Kit, Cayman Chemical Company), measuring lipid hydroperoxides (Lipid Hydroperoxide Assay Kit, Cayman Chemical Company), and finally, quantitating isoprostane levels (8-Isoprostane EIA Kit, Cayman Chemical Company) in patient serum collected at baseline (after pre-registration, but prior to treatment), after treatment at week 12 and at 6 and 12 months post randomization. These assays will be performed at the NCCTG Research Base.

14.44 Hormone and Growth Factors

Serum specimens collected at baseline and at each follow-up visit will be analyzed using commercially available ELISAs for the following hormone and growth factors: glucocorticoids (e.g., cortisol), gonadal steroids (e.g., estradiol, testosterone, progesterone), growth hormone, human chorionic gonadotropin (hCG), insulin-like growth factor-1 (IGF-1), and neuronal growth factor (NGF). These assays will be performed at the NCCTG Research Base.

14.45 Metabolic Studies

Urine specimens will be collected at the same time points that the blood specimens are collected (i.e., at baseline and at each follow-up visit). Urine will be stored at −70º C at the BAP facility at Mayo Clinic Rochester for future metabolic studies. Specific metabolic studies will be identified at the conclusion of the main study, depending on the state of the science at that time. These studies will be performed at the NCCTG Research Base.

14.46 Future Studies

A portion of the serum and DNA will initially be analyzed as described above. According to patient consent information (see Sections 6.154-6.155), remaining body fluid biospecimens will be stored frozen at −70º C at the BAP facility at Mayo Clinic Rochester until specific analyses are identified. As protocols are developed, they will be presented for Alliance and IRB review and approval. (This collection is part of a general strategy of investigation for the majority of NCCTG studies.)

14.5 Specimen Registration and Tracking

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: http://bioms.allianceforclinicaltrialsinoncology.org using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS web page to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: 1-855-55-BIOMS or Bioms@alliancenctn.org. For assistance in using the application or questions or problems related to specific specimen logging, please contact: 1-855-55-BIOMS or Bioms@alliancenctn.org.

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

All submitted specimens must be labeled with the protocol number (N107C), patient ID, patient's initials and date and type of specimen collected (e.g., serum, whole blood).

A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens.

Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

14.6 Return of Genetic Testing Research Results

Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians.

If at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

15.0 Radiation Therapy Risks and Nursing Guidelines

15.1 Whole Brain Radiotherapy (WBRT)

15.11 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

15.12 Nursing Guidelines

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

15.122 Instruct patient in corticosteroid use per MD order.
Note: corticosteroid use not required per protocol.

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

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

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

15.126 Assess for increased fatigue; instruct patient in energy–saving life–style.

15.127 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 Stereotactic Radiosurgery (SRS)

15.21 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

15.22 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.

16.0 Statistical Considerations and Methodology

16.1 Study Overview

This study will be a randomized phase III trial for patients with one to four brain metastases. Upon registration, patients will be randomly assigned to one of the two arms: Arm A – whole brain radiotherapy (WBRT) arm and Arm B – stereotactic radiosurgery (SRS) arm. A dynamic allocation procedure will be used to allocate an equal number of patients to each arm. This procedure will balance the marginal distributions of the stratification factors between arms, and the stratification factors that will be used are: extra cranial disease controlled (≤ 3 vs. > 3 months), age (< 60 vs. ≥ 60 years), number of brain metastases (1 vs. ≥ 2), resection cavity maximal diameter (≤ 3 vs. > 3 cm) and histology (lung vs. radioresistant vs. others, where radioresistant is defined as brain metastases from a sarcoma, melanoma, or renal cell carcinoma histology).

16.2 Primary Goals

The primary goals of the study are to detect whether there is less neurocognitive progression post-randomization in patients who receive SRS compared to patients who receive WBRT and whether the overall survival with post-surgical SRS is marginally superior to WBRT.

16.3 Primary Endpoints

16.31 Neurocognitive Progression

Neurocognitive progression is defined as a drop of at least one standard deviation from baseline in one of the six neurocognitive tests (all tests are standardized based on published norms) at post-randomization evaluation. If patient dies prior to a post-randomization neurocognitive evaluation, they will be considered as a neurocognitive progression at that time point. In addition, if a patient does not complete all the neurocognitive tests, they will be considered a progression at the time of the first missed neurocognitive evaluation they missed. Details of neurocognitive tests are listed in Section 4.3.

16.32 Overall Survival

Overall survival defined as the time from randomization to death from any cause.

16.4 Accrual Time and Study Duration

The total number of eligible patients to be accrued is 174 (87 per arm). Based on the accrual of the ongoing NCCTG trial N0574, we anticipate the accrual rate for this trial will be approximately 48-72 eligible patients per year (4-6 per month). The estimated accrual period will be a maximum of 4 years and the total study duration will be a maximum of 5 years. A total of 192 patients, including an extra 18 to accommodate losses due to cancellations, ineligibility, or major protocol violations, will be entered into this trial unless undue toxicity is encountered.

16.5 Sample Size Derivation for the Primary Goal

16.51 The Null Hypothesis I

The null hypothesis I in this study is that SRS is equivalent to WBRT in terms of the neurocognitive progression free rate at 6 month post-randomization versus the alternative that SRS is superior to WBRT. Based on the literature, we assume that the proportion of patients with neurocognitive progression at the 6 month post-registration evaluation is 0.65 for patients undergoing WBRT(Li, Bentzen et al. 2007). In other words, we assume the 6-month neurocognitive progression free rate is 35% in the WBRT group. Under a 1:1 randomization, a sample size of 174 will give us at least 85% power to detect a 20% difference of 6-month neurocognitive progression free rate between the two treatment groups, assuming a one-sided type I error rate of 0.05 (EAST5, calculation method for "difference of proportions with multiple looks"). Our primary analysis will be based on an intention to treat principle where by all randomized patients to the trial will be considered evaluable and we will do a time-to event analysis using Kaplan-Meier curves and a log-rank test. Patients who die before 6-months or are alive and do not complete all the neurocognitive tests will be considered as having a neuro-cognitive progression at the time of death or at the time they missed their first neuro-cognitive evaluation (and there were no subsequent neuro-cognitive evalutions). The time-to-event analysis will have more power than determined using the proportion of patients who are neurocognitive progression-free at 6 months. As a secondary sensitivity analysis, we will analyze the 6-month neurocognitive progression free rate endpoint rather than using a time-to-event analysis as will be done for the primary analysis. We will also do a time to event analysis where patients are censored for neuro-cognitive progression at the time of death (if they have not progressed prior to death) and are censored at the time of their last neuro-cognitive evaluation (if they had not progressed prior to that).

16.52 The Null Hypothesis II

The null hypothesis II in this study is that SRS is inferior to WBRT in terms of overall survival versus the alternative hypothesis that SRS is marginally superior to WBRT. The estimated median OS in patients with adjuvant WBRT is 9 months and the median OS for patients with post-surgical SRS is approximately 11 months (Patchell *et al*., 1998; Aoyama *et al*., 2006; Kocher *et al.,* 2009). Thus, there is some preliminary evidence that SRS would result in a marginal improvement in OS, with approximately a 20% reduction in hazard over WBRT. Using the design proposed by Freidlin *et al* (2007) and using EAST version 5.0 for the calculations, a sample size of 174 patients will give us at least 90% power at a 0.05 one-sided significance level for targeting a hazard ratio of 1.3 (in favor of WBRT) versus 0.8 (in favor of SRS), assuming a 2.8 years accrual and a minimum of 10 months follow-up. In other words, the trial will have 0.95

probability of rejecting the alternative hypothesis of marginal superiority of SRS with respect to OS if the true hazard ratio is 1.3 (in favor of WBRT), and 0.90 probability of concluding the marginal superiority of SRS if the true hazard ratio is 0.8 (in favor of SRS). This is equivalent of concluding that SRS is inferior to WBRT if the median OS in SRS is 7 months compared to 9 months in WBRT, and marginal superiority of SRS over WBRT if the median OS is 11.25 months versus 9 months. The total expected event of death is 134.

16.6 Analysis Plan for the Primary Goal

Efficacy analysis will be based on the intention-to-treat principle with all eligible patients belonging to the treatment arm to which they were randomized. The Cox proportional hazards model will be used to assess whether the distributions of overall survival times differ with respect to treatment regimen having adjusted for all stratification factors. The corresponding p-value associated with the treatment covariate will be compared to the nominal p-value to make the conclusion regarding the primary goal.

The distribution of overall survival for Arm A and B will be estimated using the Kaplan-Meier method. The hazard ratios and median survivals will be estimated with their 95% confidence intervals. The final analysis will take place once 134 total events (deaths from any cause) have been observed in the trial, and the last patient has been followed for at least 6 months post-radiation, whichever comes later. Hypotheses I and II will be considered jointly in making the conclusion for this study:

For Null Hypothesis I, the distribution of neurocognitive progress-free survival for Arm A and B will be estimated using the Kaplan-Meier method. The curves will be compared with a log rank test. The hazard ratios and median survivals will be estimated with their 95% confidence intervals. If the Null Hypothesis I is rejected indicating superiority of SRS in the neurocognitive progression free and the Null Hypothesis II is rejected indicating marginal superiority of SRS in OS , this study would establish post-operative SRS as the standard of care.

If the Null Hypothesis I is rejected indicating superiority of SRS in the neurocognitive progression free survival and the Null Hypothesis II is not rejected indicating SRS is inferior to WBRT in terms of OS, then SRS may still have clinical use due to its clear advantage in neurocognitive progression free survival. This study will provide level I evidence to assist in making therapeutic decisions.

If the Null Hypothesis I is not rejected indicating no identified difference between SRS and WBRT in the neurocognitive progression free survival and the Null Hypothesis II is not rejected indicating SRS is inferior to WBRT in terms of OS, then this study would re-establish adjuvant WBRT as the standard of care.

16.7 Interim Analysis for the Primary Goal

Interim analyses for hypothesis I will be performed at the time when 50% of the evaluable patients have been followed for 6 months, and 50% events have been observed for hypothesis II. Since we are testing two hypotheses simultaneously, each of the two co-primary endpoints will be tested independently at the interim analysis, and for each co-primary endpoint, early rejection of the null hypothesis will be considered.

16.71 Neurocognitive Progression Free Survival

We use the conservative Lan-DeMets spending function (corresponding to the O'Brien-Fleming boundary) (O'Brien and Fleming 1979) for early termination to reject the null hypothesis in favor of the alternative. The interim analysis will use 6-month neurocognitive free survival rate (NFP6). The efficacy boundary for NPF6 is 0.0056 at the interim analysis.

16.72 Overall Survival

We use the Lan-Demets spending function (corresponding to the O'Brien-Fleming boundary) (O'Brien and Fleming 1979) for early termination to reject the null hypothesis in favor of the alternative. Specifically, the boundary for declaring marginal superiority of SRS for OS is 0.0056 at the interim analysis and the marginal superiority boundary for SRS is 0.0482 at the final analysis.

16.73 Interim Analysis

If the observed p-value for NPF6 is smaller than 0.0056 indicating superiority of SRS in NPF6 and the observed p-value for OS is smaller than 0.0056 indicating marginal superiority of SRS in OS, we may close the study and recommend the SRS as the standard of care. For all other scenarios of the interim analysis, we would recommend continue the accrual and wait till the final analysis to draw the conclusion.

16.8 Secondary Endpoints and Analysis

Secondary endpoints include local control of the surgical bed, time to CNS failure and various quality of life.

16.81 Local Control of Surgical Bed

Local control of surgical bed is defined as the absence of the development of recurrent tumor in the surgical bed. There will be an evaluation of local control of the surgical bed both locally by the local investigators and centrally; however the central review will have precedence in the analyses. There will also be an analysis of the impact of gross total resection or less than gross total resection as defined by central review on local control of the surgical bed.

16.82 Time to CNS Failure

Time to CNS failure is defined as the date the patient is randomized on this study to the date of diagnosis of disease progression. Notice the development of new lesions in the brain outside the surgical bed will be counted as a disease progression thus an event of CNS failure. Time to recurrent tumor in the surgical bed and time to CNS failure will be estimated using Kaplan-Meier methods for each arm and be compared between arms using Cox proportional hazard models with all stratification factors adjusted. Hazard ratios and median of the distributions will be estimated with their 95% confidence intervals.

16.83 Quality of Life

The primary QOL objective is to ascertain at 6 months (24 weeks) post-randomization whether patients assigned to SRS have better QOL than patients on WBRT. One-sided null hypotheses for improvement on SRS will be used. The 6 month time point is proposed as being late enough to capture mor treatment effects, but early enough to avoid a substantial difference between-arm morbidity and mortality.

The QOL booklet will be administered at baseline, (after pre-registration, but prior to any treatment) and at the beginning of each scheduled study visit after treatment (i.e., at 12 weeks and at 6, 9, 12, 16 and 24 months post randomization). 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 6, using two-sample t-tests and associated confidence intervals. To explore any long-term difference between the two arms, score changes from baseline to each time point after month 6 will also be compared graphically and using two sample t-tests. The Bonferroni adjustment will be used to adjust the α level (Type I error). In addition, a mixed effect model may also be applied to data collected at all time points to explore any trend difference between arms.

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

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 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 who's 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.

16.9 a Correlative Endpoints and Analysis

Correlative endpoints include radiation changes in the limbic system and all kinds of biomarkers specified in Section 2.3. To explore the correlation between radiation changes in the limbic system and neurotoxicity, descriptive and graphical methods will be used. To explore the predictive effect of different biomarkers on neurocognitive decline, continuous biomarkers will be evaluated between the NPF6 success vs. failure groups using two-sample t-tests (or Wilcoxon rank sum tests as needed) as well as side-by-side boxplots. Categorical biomarkers will be evaluated between the NPF6 success vs. failure groups using Fisher exact tests (or Chi-squared tests as appropriate) as well as bar graphs.

16.9b Monitoring:

16.9b1 This study will be monitored by the Clinical Data Update System (CDUS) version 4.0. An abbreviated report containing cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

16.9b2 This study will be monitored by the NCCTG External Data Monitoring Committee (DMC), an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DMC every six months as per NCI guidelines.

16.9c Inclusion of Women and Minorities

This study will be available to all eligible patients regardless of race, gender, or ethnic group.

There is no information currently available regarding differential agent effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analyses will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for such subset analyses. A total of 192 patients may be enrolled. Based on prior studies involving similar disease sites, we expect about 7% of patients will be classified as minorities by race and about 40% of patients to be women. Expected sizes of racial by gender subsets are shown in the following 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**

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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.

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Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	5	+	8	=	13
Not Hispanic or Latino	72	+	107	=	179
Ethnic Category: Total of all Subjects	77	+	115	=	192
Racial Category					
American Indian or Alaskan Native	1	+	2	=	3
Asian	2	+	2	=	4
Black or African American	1	+	1	=	2
Native Hawaiian or other Pacific Islander	1	+	3	=	4
White	72	+	107	=	179
Racial Category: Total of all subjects	77	+	115	=	192

551 **Accrual**
552 **Rate:** 4-6 pts/month
553 **Projected Start Date of Study: 07/12/2011**
554

555 **Total Expected**
556 **Accrual:** 174 Min 192 Max

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Tissue Biospecimen Submission

Note: It is optional that patients consent to submission of the tissue(s) listed in the following table. For optional paraffin-embedded tissues, the site must submit tissue being requested, if tissue is available.

Note: As outlined below submission of tissue below requires tissue from *both* the primary cancer and brain metastasis.

17.11 Summary Table of Tissue Biospecimens for This Protocol

Tissue	Mandatory or optional	When to submit	Reason for submission	Protocol section with specific details
Formalin-fixed paraffin-embedded (FFPE) tissue blocks with corresponding H&E **OR** unstained slides with two corresponding H&Es from primary cancer tissue	Optional	≤ 30 days following randomization	Tissue Banking	Section 17.2
Formalin-fixed paraffin-embedded (FFPE) tissue blocks with corresponding H&E **OR** unstained slides with two corresponding H&Es from brain metastasis	Optional	≤ 30 days following randomization	Tissue Banking	Section 17.2

17.2 Paraffin Embedded Tissue Blocks/Slides

At time of submitting slides or tissue blocks, the following materials below are required for shipment (please include the ***patient study ID number*** on all materials):

- All H&E slides, slides and/or blocks from primary caner tissue and metastatic cancer tissue
- Research Tissue Submission Form
- Surgical Pathology Report
- Operative Report *(optional)*

17.21 FFPE Tissue Block and H&E Slide Submission

Submit one formalin fixed paraffin-embedded (FFPE) tumor tissue block with representative tumor from the primary cancer and brain metastasis. **A corresponding H&E slide for each submitted block must be provided to permit quality assurance (QA) of each tissue block**. Once the QA is completed, all stained slides will be returned. If a block is not available a tissue punch (2 mm) of the block is acceptable.

Alternatively**, if the institution is unable to provide a tissue block**, submit 15 five micron sections mounted on charged glass slides and 5 ten micron sections mounted on uncharged glass slides. **Label the slides with patient study ID number, accession number, and order of sections cut (i.e., 1-15 for the five micron slides), and thickness of section (i.e., five microns).** H&E stain every 10th 5 micron slides that is cut (i.e., slides labeled 1 and 15). These slides will be reviewed centrally under the research base's quality assessment protocol. For samples containing less than 7 square millimeters of tumor tissue, multiple sections should be mounted onto each slide to ensure that the appropriate amount of tumor tissue is available. Ideally, each slide must have a minimum of 75% tumor tissue on the slide to be deemed adequate for study. **Do not bake or place covers slips on the slides.**

17.22 Shipping Instructions and Precautions

17.221 The block/slides must be appropriately packed to prevent damage (e.g., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, patient initials and patient study ID number.

17.222 Tissue specimens should be shipped ≤ 30 days after registration.

17.223 Verify that the appropriate sections of the Research Tissue Submission Form are completed and filled in correctly. Enter information from the Research Tissue Submission Form into the remote data entry system on the same day the specimen is submitted (see Forms Packet).

17.23 Shipping Address

Ship all block/slide tissue specimens and accompanying materials to the NCCTG Research Base at the following address:

NCCTG Operations Office
Attn: PC Office
RO_FF_03_24-CC/NW Clinic
200 First Street SW
Rochester, MN 55905

17.3 Tissue Banking Procedures

If corresponding H&E slides were not submitted with the tissue specimen, the NCCTG Operations Office will request a slide to be processed (i.e., cut and H&E stained) from the tumor tissue block. Processing will be performed in the NCCTG Research Base Pathology Resource Core (PRC), formerly Tissue and Cell Molecular Analysis (TACMA) Shared Resource, Mayo Clinic Rochester.

The NCCTG Operations Office will forward the blocks and/or H&E slide(s) to Dr. Giannini and/or associates, Mayo Clinic Rochester, to be reviewed under the research base's protocol for assessing tissue quality for the proposed banking.

After the pathologist assesses the tissue quality, the block and appropriate paperwork will be returned to the NCCTG Operations Office.

At the completion of the study, material will be banked in the NCCTG Operations Office (Attn: Pathology Coordinator) for future research according to the patient consent permission (see Section 6.155). Potential future research may include immunohistochemistry (IHC) analyses, DNA extraction, and/or tissue microarray (TMA) construction to analyze predictive biomarkers, changes in expression pattern with therapy, and correlation with response and/or adverse events. When a protocol is developed, it will be presented for IRB review and approval.

17.4 Specimen Registration and Tracking

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: http://bioms.allianceforclinicaltrialsinoncology.org using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS web page to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: 1-855-55-BIOMS or Bioms@alliancenctn.org. For assistance in using the application or questions or problems related to specific specimen logging, please contact: 1-855-55-BIOMS or Bioms@alliancenctn.org.

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

All submitted specimens must be labeled with the protocol number (N107C), patient ID, patient's initials and date and type of specimen collected (e.g., serum, whole blood).

A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens.

Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Pre-Registration Material(s)

Case Report Form (CRF)	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)
Pre-Registration Screening Failure Form	Complete only if patient is NOT randomized after he/she is pre-registered

Initial Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)
Response Review Material1	Submit ≤ 14 days after randomization if withdrawal/refusal occurs prior to beginning protocol therapy
End of Active Treatment /Cancel Notification Form	
On-Study Form	≤ 14 days after randomization
Baseline Adverse Event Form	
Pretreatment Measurement Form	
Research Blood Submission Form (See Section 14.0)	
Research Urine Submission Form (See Section 14.0)	
Patient Questionnaire Booklet Quality of Life (QOL)2,3	
Functional Independence3	
Neurocognitive Testing Booklet 2,4	
Patient Questionnaire Booklet Quality of Life (QOL) Compliance Form 5	
Neurocognitive Testing Booklet Compliance Form	
Concomitant Steroid and Anticonvulsant Treatment Form	
CRF	**Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)**
Pathology materials (For optional tissue submission)	≤ 30 days after randomization
Research Tissue Submission Form	≤ 30 days after randomization

1. Submit the following to **NCCTG Operations Office, Attn: QAS for N107C, 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 N107C 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 12, month 9 or month 24). As outlined below *all* pre-randomization and completion of therapy MRI or CT scans should be submitted. See Section 11.8 for additional details.

a. Pre-randomization MRI or CT scans 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 N107C.**
b. Post-treatment MRI or CT scans at week 12 and at 6, 9, 12, 16, and 24 months. These studies will be reviewed by the NCCTG PIs for central review of <u>local control of surgical bed.</u>

2. Original questionnaire booklets **must** be used; copies are not acceptable for this submission.

3. Submit original Patient QOL Questionnaire Booklet and Functional Independence form to the NCCTG Operations Office, Attn: QAS for N107C NW Clinic 3-24 CC, 200 First Street SW, Rochester MN 55905

4. Submit ***original*** Patient Neurocognitive Testing Questionnaire Booklet to NCCTG Operations Office, Attn: QAS for N107C, NW Clinic 3-24 CC, 200 First Street SW, Rochester MN 55905

5. This form must be completed **only** if the Patient QOL Questionnaire Booklet contains absolutely **<u>NO</u>** patient provided assessment information.

Test Schedule Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)	
	At end of treatment[10] (week 12 follow up)	**At each evaluation during observation[10] (6, 9, 12, 16, and 24 month follow ups)**
Evaluation/Treatment Form	X[1]	
Evaluation/Observation Form		X
End of Active Treatment/Cancel Notification Form	X	
Adverse Event Form	X	X
Active Monitoring Measurement Form (Resected Surgical Cavity Form or Unresected Brain Metastases Form, whichever is appropriate)	X[2]	X[2]
Radiation Therapy Material	X[3]	
Response Review Material	X[4]	X[4]
Research Blood Submission Form	X[5]	X[5]
Research Urine Submission Form	X[5]	X[5]
Patient QOL Questionnaire	X[6,7]	X[6,7]
Functional Independence	X[7]	X[7]
Neurocognitive Testing Booklet	X[6,8]	X[6,8]
Patient QOL Questionnaire Booklet Compliance Form	X[9]	X[9]
Neurocognitive Testing Booklet Compliance Form	X	X
Concomitant Steroid and Anticonvulsant Treatment Form	X	X
Notification Form – Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form	At each occurrence (see Section 10.0)	
ADR/AER		
Late Adverse Event		

1. Cycle 1 only.

2. Submit copy of documentation of response or progression to the NCCTG Operations Office, Attn: QAS for N107C, NW Clinic 3-24 CC, 200 First Street SW, Rochester MN 55905

3. **All participating 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 A only).
   b. SRS reporting forms for both SRS plan to surgical bed and if applicable SRS to unresected brain metastases:
      - For 1 unresected lesion complete SRS reporting Form Site 1

- For 2 unresected lesions complete SRS reporting Form Site 1 and Site 2.
- For 3 unresected lesions complete SRS reporting Form Site 1, Site 2 and Site 3.

c. Daily treatment records (Arm A Only).

d. Dosimetry calculations (Arm A only), monitor unit calculations (Arm A only), and color copies of the required isodose curves.

e. Color copies of required DVH's (as applicable and including CTV).

f. Copies of representative simulation (and/or Beams Eye View, BEV) films of all treated fields (Arm A only).

g. Copies of representative port (and/or Digitally Reconstructed Radiographs, DRR) films of all treated fields (Arm A only).

h. Copies of pre-randomization and planning contrasted MRI or CT brain scans. **Separate copies of the CD must be sent to the Radiation Coordinator and the QAS for N107C.** Note: When images are submitted on CD(s), they **must** include a viewing tool.

4. Submit the following to NCCTG Operations Office, Attn: QAS for N107C NW Clinic 3-24, 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 N107C 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 12, month 9 or month 24). As outlined below *all* pre-randomization and completion of therapy MRI or CT scans should be submitted. See Section 11.8 for additional details.

   a. Pre-randomization MRI or CT scans 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 N107C**

   b. Post-randomization MRI or CT scans at week 12 and at months 6, 9, 12, 16, and 24. These studies will be reviewed by the Alliance PIs for central review of local control of surgical bed.

5. Submit for the 12 week, 6 month, and 12 month post-randomization visits only.

6. Original questionnaire booklets **must** be used; copies are not acceptable for this submission.

7. Submit original Patient QOL Questionnaire Booklet and Functional Independence form to the NCCTG Operations Office, Attn: QAS for N107C, NW Clinic 3-24, 200 First Street SW, Rochester MN 55905

8. Submit ***original*** Patient Neurocognitive Testing Questionnaire Booklet to NCCTG Operations Office, Attn: QAS for N107C, NW Clinic 3-24, 200 First Street SW, Rochester MN 55905

9. This form must be completed **only** if the Patient QOL Questionnaire Booklet contains absolutely **NO** patient provided assessment information.

10. **Treatment:**

    Cycle 1 = starts day 1 of treatment and ends at week 12 follow up.

Follow up/Observation:

Cycle 2 = starts at 12 weeks and ends at 6 month follow up.
Cycle 3 = starts at 6 months and ends at 9 month follow up.
Cycle 4 = starts at 9 months and ends at 12 month follow up.
Cycle 5 = starts at 12 months and ends at 16 month follow up.
Cycle 6 = starts at 16 months and ends at 24 month follow up.

Follow-up Material(s)

CRF	Event Monitoring Phase[1]		
	Every 6 months	Death	New primary
Event Monitoring Form	X[2]	X	At each occurrence
Autopsy Reports		X[3]	At each occurrence

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

2. An Event Monitoring Form should be completed for patient withdrawal/refusal, adverse event/side effects/complications, off-treatment for other complicating disease, and death. Patients should also go to event monitoring after 24 months from randomization. Patients in event monitoring should complete an event monitoring form every 6 months until 5 years from randomization.
Note: Patients should *not* go to event monitoring in the event of progressive disease and should continue to be followed using the test schedule for observation (e.g. complete neurocognitive testing, MRI or CT scans, etc.) even in the event of progressive disease (PD) until withdrawal, refusal, death or 24 months from randomization. Submit copy of documentation of progression to the NCCTG Operations Office, Attn: QAS for N107C, NW Clinic 3-24, 200 First Street SW, Rochester MN 55905

3. Submit if available.

18.2 Additional Submission Instructions

18.21 Non-NCCTG CTSU Sites

18.211 CTSU sites will fax forms (except Patient and Examiner Questionnaire Booklets, see Section 18.0) to NCCTG Operations Office, Attn: N107C 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 N107C, NW Clinic 3-24, 200 First Street SW, Rochester MN

18.213 CTSU sites will submit original Patient Neurocognitive Testing Questionnaire Booklet to NCCTG Operations Office, Attn: QAS for N107C, NW Clinic 3-24CC, 200 First Street SW, Rochester MN 55905

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 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

Correlative research tests of submitted blood and urine specimens.

19.3 Paired Tissue Submission Payment

NCCTG will reimburse sites up to $300 for the costs associated with contributing the paired tissue specimens. Tissue from ***both*** the primary cancer and brain metastasis ***are required for this reimbursement.***

19.4 Other Budget Concerns

There will be no charges associated with QOL or neurocognitive assessments.

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Appendix I: ECOG Performance Status Criteria

ECOG Performance Status Criteria
Description
Grade 0 Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
Grade 1 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).
Grade 2 In bed <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.
Grade 3 In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
Grade 4 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
Grade 5 Dead.

Appendix II: Administration of Quality of Life (QOL) Patient Questionnaire Booklet

Instructions for Study Staff

The instructions given below are intended to serve as a guide for the administration of the Quality of Life (QOL) questionnaire booklet. This booklet contains three QOL assessment tools: FACT-BR, Fatigue/Uniscale, and Linear Analogue Self-Assessment (LASA) Scale. The QOL questionnaire 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 QOL questionnaire 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 QOL questionnaire 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.

Appendix III: Patient Quality of Life (QOL) Questionnaire Booklet

You have been given a booklet to complete for this study. The booklet contains some questions about your quality of life and health status as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel and tolerate treatment.

1. The booklet contains three sets of questions:
    a. FACT-BR (50 questions)
    b. Fatigue/Uniscale Assessments (2 questions)
    c. Linear Analogue Self-Assessment Scale (4 questions)

2. Directions on how to complete each set of questions are written on the top of each set.

3. Please complete the booklet during your scheduled clinic visit and return it to your nurse or your physician.

Thank you for taking the time to help us.

Appendix IV: Administration Procedures for the Neurocognitive Tests

1. Testing should be completed in one session. Test instructions must be followed verbatim with every patient at every study visit. All tests should be completed in black pen. On follow-up visits, it is preferred that patients complete the neurocognitive test battery before seeing the physician since the emotional impact of the results of their follow-up brain scan may influence the patient's performance on the neurocognitive assessments.

2. Two of the tests to be administered have alternate forms or versions in order to reduce the effects of practice. These versions will be alternated in the testing booklets provided. Always try to use the correct booklet labeled for the patient's visit number (this number is identified on the title page of each booklet).

3. You may fill the delay interval between COWA and HVLT-R Part B (Delayed Recall) with QOL questionnaires.

4. ***Originals*** of the test booklets should be mailed to NCCTG Operations Office, Attn: QAS for N107C, , NW Clinic 3-24 CC, 200 First Street SW, Rochester, MN 55905.

5. Please keep copies of all completed original test booklets. In the event of questions, contact Dr. Cerhan at the telephone number and email address listed on the Protocol Resources page of the protocol.

6. Patients should ***not*** be given copies of their tests to avoid learning the material between test administrations.

7. Before dismissing the patient, thank the patient for his/her cooperation. Remind the patient of his/her next appointment and that these tests will be repeated

Setting up for Neuropsychological Testing

- 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
- Desk for you both to write on (clipboard works in a pinch)
- Stopwatch
- 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**

Test Instructions

Administer the tests in the following order to every patient at every visit

1. **HOPKINS VERBAL LEARNING TEST - REVISED (HVLT-R)**

   This test has three parts and six alternate forms:

   1. **Part A – Learning Trials:** Complete the three learning trials first

   2. **Part B - Delayed Recall:** Complete after a 20-minute delay that includes administration of Trail Making Tests and COWA.

   3. **Part C - Delayed Recognition:** Complete immediately after Delayed Recall

   Part A – Learning Trials: Trial 1

   Examiner*: "I am going to read a list of words to you. Listen carefully, because when I am through, I'd like you to tell me as many of the words as you can remember. You can tell them to me in any order. Are you ready?"*

   - Read the words at the rate of one word every 2 seconds.
     Examiner: "OK. Now tell me as many of those words as you can remember."
   - Check off the words the patient recalls on the form.
   - If a word is said that is not in the list (*for example, "intrusion"*), do not write that word on the form and say nothing to the patient about the word not being on the list.
   - There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
   - If not, move on to trial 2.
   - Never tell the patient whether a word is correct, and don't tell them how many words are left on the list (e.g., don't say "there are three more.").

   Part A – Learning Trials: Trial 2

   Examiner*: "Now we are going to try it again. I am going to read the same list of words to you. Listen carefully, and tell me as many of the words as you can remember, in any order, including the words you told me the first time."*

   - Read the words at the rate of one word every 2 seconds.
   - Check off the words the patient recalls on the form.
   - If a word is said that is not in the list (*for example, "intrusion"*), do not write that word on the form and say nothing to the patient about the word not being on the list.
   - There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
   - If not, move on to trial 3.

Part A – Learning Trials: Trial 3

Examiner*: "I am going to read the list one more time. As before, I'd like you to tell me as many of the words as you can remember, in any order, including all the words you've already told me."*

- Read the words at the rate of one word every 2 seconds.
- Check off the words the patient recalls on the form.
- If a word is said that is not in the list (for example, "intrusion"), do not write that word on the form and say nothing to the patient about the word not being on the list.
- There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
- Do not tell the respondent that recall of the words will be tested later.
- Record the time on the clock that you complete 'Part A – Free Recall' (for example, 10:00 am) on the designated space on the HVLT-R form.

2. TRAIL MAKING TEST [Timed Test]

Part A – Sample*:* The Sample for Part A must be completed/attempted by each patient at every assessment. Place the Sample A worksheet flat on the table, directly in front of the patient *(the bottom of the worksheet should be approximately six inches from the edge of the table).*Give the patient a black pen and say:

Examiner*: "On this page* (point) *are some numbers. Begin at number 1* (point to 1) *and draw a line from 1 to 2* (point to 2), *2 to 3* (point to 3), *3 to 4* (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. Ready, begin."*

If the patient completes Sample A correctly and in a manner demonstrating that s/he understands what to do, proceed immediately to Test A. If the patient makes a mistake on Sample A, point out the error and explain it.

The following explanations of mistakes serve as illustrations:

- ***"This is where you start (point to number 1)"***
- ***"You skipped this circle (point to the circle omitted)"***
- ***"You should go from number 1 to 2, 2 to 3, and so on, until you reach the circle marked END"***

If it is clear that the patient intended to touch a circle but missed it, do not count it as an omission. Remind the patient, however, to be sure to touch the circles. If the patient still cannot complete Sample A, take his/her hand and guide him/her through the trail using the opposite end of the pen, lightly touching the worksheet to avoid making marks on the copy. Then say:

Examiner*: "Remember, begin at number 1 (*point to 1*) and draw a line from 1 to 2 (*point to 2*), 2 to 3 (*point to 3*), 3 to 4 (*point to 4*) and so on, in order, until you reach the circle marked END (*point*). Do not skip around, but go from one number to the next in proper order.*

Remember to work as fast as you can. Ready, begin."

If the patient does not succeed, or it becomes evident that s/he cannot do the task, DISCONTINUE testing and indicate the corresponding reason on the Trail Making A & B Scoring (TMABS) sheet. If the patient completes Sample A correctly and appears to understand what to do, proceed immediately to Part A.

Part A – Test: After the patient has completed Sample A, place the Part A test worksheet directly in front of the patient and say:

Examiner*: "Good! Let's try the next one. On this page are numbers from 1 to 25. Do this the same way. Begin at number 1 (*point*) and draw a line from 1 to 2 (*point to 2*), 2 to 3 (*point to 3*), 3 to 4 (*point to 4*) and so on, in order, until you reach the circle marked END (*point*). Do not skip around, but go from one number to the next in proper order. Remember to work as fast as you can. Ready, begin."*

- Start timing as soon as the instruction is given to "begin."
- Watch closely in order to catch any errors as soon as they are made. If the patient makes an error, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred.
- The patient must complete the test in 3 minutes or less
- DO NOT STOP TIMING UNTIL HE/SHE REACHES THE CIRCLE MARKED "END."
- If the patient does not complete the test within 3 minutes terminate the testing. The test can also be discontinued if the patient is extremely confused and is unable to perform the task. Complete the Trail Making A & B Scoring (TMABS) sheet indicating the reason the test was terminated and the last correct number reached on the test.
- If the patient successfully completes the test, record the time to completion on the Trail Making A & B Scoring (TMABS) sheet in minutes and seconds. Then say, **"*That's fine. Now we'll try another one.*"**

Part B – Sample: The Sample for Part B must be completed/attempted by each patient at every assessment. Place the Sample B worksheet flat on the table, directly in front of the patient (the bottom of the worksheet should be approximately six inches from the edge of the table) and say:

Examiner: "*On this page (*point*) are some numbers and letters. Begin at number 1 (*point to 1*) and draw a line from 1 to A (*point*), A to 2 (*point to 2*), 2 to B (*point to B*), B to 3 (*point to 3*), 3 to C (*point to C*) and so on, in order, 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."*

If the patient completes Sample B correctly, and in a manner demonstrating that s/he understands what to do, proceed immediately to Part B. If the patient makes a mistake on Sample B, point out the error and explain it.

The following explanations of mistakes serve as illustrations:

- ***"You started with the wrong circle. This is where you start (point to number 1)"***
- ***"You skipped this circle (point to the circle omitted)"***
- ***"You should go from number 1 (*point*) to A (*point*), A to 2 (*point to 2*), 2 to B (*point to B*), B to 3 (*point to 3*) and so on, until you reach the circle marked END (*point*)"***

If it is clear the patient intended to touch a circle but missed it, do not count it as an omission. Remind the patient, however, to be sure to touch the circles. If the patient still cannot complete Sample B, take their hand and guide them through the trail using the opposite end of the pen, lightly touching the worksheet to avoid making marks on the copy. Then say:

Examiner*: "Now you try it. Remember, begin at number 1 (*point to 1*) and draw a line from 1 to A (*point to A*), A to 2 (*point to 2*), 2 to B (*point to B*), B to 3 (*point to 3*) and so on, in order, until you reach the circle marked END (*point*). Ready, begin."*

If the patient does not succeed or it becomes evident that s/he cannot do the task, DISCONTINUE testing and indicate the corresponding reason on the Trail Making A & B Scoring (TMABS) sheet. If the patient completes Sample B correctly and appears to understand what to do, proceed immediately to Part B.

Part B – Test: After the patient has completed Sample B, place the Part B Worksheet directly in front of the patient and say:

Examiner*: "Good! Let's try the next one. On this page are both numbers and letters. Do this the same way. Begin at number 1 (*point*) and draw a line from 1 to A (*point to A*), A to 2 (*point to 2*), 2 to B (*point to B*), B to 3 (*point to 3*), 3 to C (*point to C*) and so on, in order, until you reach the circle marked END (*point*). 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. Do not skip around, but go from one circle to the next in the proper order. Draw the lines as fast as you can. Ready, begin."*

- Start timing as soon as the instruction is given to "begin."
- Watch closely in order to catch any errors as soon as they are made. If the patient makes an error, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred.
- The patient must complete the test in 5 minutes or less.
- DO NOT STOP TIMING UNTIL HE/SHE REACHES THE CIRCLE MARKED"END."
- Record the time to completion on the Trail Making A & B Scoring (TMABS) in minutes and seconds.
- If the patient does not complete the test within 5 minutes terminate the testing. The test can also be discontinued if the patient is extremely confused and is unable to perform the task. Complete the Trail Making A & B Scoring (TMABS) sheet indicating the reason the test was terminated and the last correct number or letter reached on the test.
- If the patient successfully completes the test, record the time to completion on the Trail Making A & B Scoring (TMABS) sheet in minutes and seconds.

3. CONTROLLED ORAL WORD ASSOCIATION (COWA) [Timed Test]

This test has three parts (letters).

Examiner*: "I am going to say a letter of the alphabet, and I want you to say as quickly as you can all of the words that you can think of that begin with that letter. You may say any words at all, except proper names such as the names of people or places. So 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 it is a correct response, say ***"good"***, and ask for another word beginning with the letter "s." If a second appropriate word is given, proceed to the test itself.

If the patient gives an inappropriate word on either occasion, correct the patient, and repeat the instructions. If the patient then succeeds, proceed to the test.

If the patient fails to respond, repeat the instructions. If it becomes clear that the patient does not understand the instructions or cannot associate, stop the procedure, and indicate the reason(s) on the scoring sheet.

If the patient has succeeded in giving two appropriate words beginning with the demonstration letter, say:

Examiner*: "That is fine. Now I am going to give you another letter and again you say all of 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 and I say STOP."*

"You will have a minute for each letter. The first letter is '___' (see scoring sheet).

Allow exactly one minute for each letter

- If the patient discontinues before the end of the time period, encourage him/her to try to think of more words.
- If he/she is silent for 15 seconds, repeat the basic instruction and the letter (e.g., **"Tell me all the words you can think of that begin with a "c"**).
- No extension on the time limit is made in the event that instructions are repeated.
- Continue the evaluation with the remaining two letters, allowing one minute for each.

Recording and Scoring:

- The COWA provides lines on which the patient's responses can be entered *(e.g., write in the word that is said by the patient)*. If his/her speed of word production is too fast to permit verbatim recording, a "+" should be entered to indicate a correct response.
- Incorrect responses should be struck through with a line. It is usually easiest to record each response and incorrect responses can be crossed out later during scoring.

- If the patient provides more responses than there are lines on the record sheet, place check marks in the boxes to indicate correct responses only.• Count all the correct responses. The number of correct words should be indicated below each column.

Comments on scoring:

- Note: It can be helpful for the first several patients and for patients known to be fast with their word production to tape record the session for transcription at a later time.
- The instructions include a specific prohibition against giving proper names or different forms of the same word. Therefore, inflections of the same word *(e.g., eat-eating; mouse-mice; loose-loosely; ran-run-runs)* are not considered correct responses.
- Patients often give both a verb and a word derived from the verb or adjective *(e.g., fun-funny; sad-sadness)*. These are not considered correct responses. On the other hand, if the word refers to a specific object *(e.g., foot-footstool; hang-hanger)*, it would be counted as a correct answer.
- Many words have two or more meanings *(e.g., foot; can; catch; hand)*. A repetition of the word is acceptable IF the patient definitely indicates the alternative meaning to you.
- Slang terms are OK if they are in general use.
- Foreign words can be counted as correct if they can be considered part of the lexicon *(for example, pasta; passé; lasagna)*, the criterion being their listing in a standard dictionary. All incorrect and repeated responses MUST be crossed out with one single line. Additionally, all duplicate entries that have been verified to have different meanings must be marked "ok" Refer to the descriptions above for guidelines for acceptability. Add the total number of correct responses in each column and input the totals where indicated on the COWA worksheet.
- If the test is discontinued or omitted, please mark this on the bottom of the test form.

HOPKINS VERBAL LEARNING TEST - REVISED (HVLT-R)

Part B – Delayed Recall

DO NOT READ THE WORD LIST AGAIN.

Record the time on the clock that you *start* 'Part B – Delayed Recall' (for example, 10:20 am) on the designated space on the HVLT-R form.

Administer 'Part B – Delayed Recall' after completing all Trail Making Tests and the COWA.

There should be at least 20 minutes between 'Part A' and 'Part B' of the HVLTR. If the time is too short, allow the patients to complete a questionnaire.

Examiner: "*Do you remember that list of words you tried to learn before? Tell me as many of those words as you can remember."*

- Check the box on the corresponding line of the HVLT-R worksheet for each word the patient accurately recalls.
- If a word is said that is not in the list (*for example, "intrusion"*), do not write that word on the form and say nothing to the patient about the word not being on the list.

- There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
- If not, record the number of words that were correctly recalled on the summary form.

Part C – Delayed Recognition

Examiner*: "Now I'm going to read a longer list of words to you. Some of them are words from the original list, and some are not. After I read each word, I'd like you to say "Yes" if it was on the original list or "No" if it was not. Was [word] on the list?"*

- Read the words from the top of the columns down.
- Check either the "**Y"** (Yes) or "**N"** (No) box next to each word to indicate the patient's response.
- Guessing is allowed.
- If the test is discontinued or omitted, please mark this on the bottom of the test form and indicate the reason.
- The score for this portion of the HVLT-R is the number of list words (i.e., words that in CAPS) correctly identified ("yes" response) minus the number of non-list words (i.e., words in lower case) incorrectly identified ("yes" response). Therefore, the actual score can range from –12 *(no list words identified and all non-list words identified)* to +12 *(all list words identified and no non-list words identified)*.

Appendix V: Patient and Examiner Neurocognitive Testing Questionnaire Booklet

This booklet is to be completed by the certified test administrator on behalf of the patient. This booklet also contains two tests (Trail Making Test A and B), which will be administered by the certified test administrator to the patient during the neurocognitive evaluations.

1. The tests and battery format that will be done in this booklet includes the following and will take approximately 20 to 30 minutes to complete:
    a. *Memory* (4.5 minutes): Hopkins Verbal Learning Test (HVLT) (Brandt 1991).
    b. *Verbal Fluency* (3.5 minutes): Controlled Oral Word Association Test from the Multilingual Aphasia Examination (COWAT) (Benton and Hamsher 1978).
    c. *Visual Attention* (5 minutes): Trail Making Test A (Reitan 1958)
    d. *Executive Function* (5 minutes): Trail Making Test B(Reitan 1958)
    e. *Delayed Memory* (1.5 minutes): Recall and Recognition of Word List encoded from the HVLT (Brandt 1991).

2. Directions on how to complete these tests is provided in the Administration Procedures for the Neurocognitive Test Battery (see Forms Packet).

3. The certified test administrator will provide verbal instruction to the patient for completing the patient completed portion of the neurocognitive evaluations (i.e., Trail Making Test A and B).

Thank you for taking the time to help us.

Appendix VI: Neurocognitive Testing Submission Fax Form

Fax completed form to:
QAS for N107C
Telefax (507) 266-7240

From: _____

Date: _____

Re: Neurocognitive Evaluations Booklet Submission

Attention: 2 Completed Neurocognitive Evaluations booklets (completed Patient and Examiner Questionnaire Booklets) have been sent to you via surface mail, as of _____(date).

Contact Information:	
Person administering test:	
Name of site:	
Phone:	
Email:	
Patient's study ID #:	

Appendix VII: Radiation Therapy Quality Control Guidelines for SRS and WBRT

SRS Guidelines

1. SRS Compliance Criteria

A final review of the stereotactic radiotherapy treatment will be performed by the community NCCTG Radiation Oncology co-Chair and the study chair. The review process will include all Response Review Materials as outlined in Section 18.0. Based on the evaluation and verification of data submitted, the Quality Assurance scores will be assigned to each case.

2. SRS Target Coverage QA

The 'target" as outlined below is by definition the CTV (regarding SRS to surgical cavity, target is defined as CTV2).

95% of the prescribed dose should completely encompass the target. For example if 18 Gy is prescribed to the 50 % isodose then the minimum dose to the target should be 17.1 Gy.
Minor Deviation: 90% of the prescribed dose completely encompasses the target.
Major Deviation: < 90% of the prescribed dose completely encompasses the target.

3. SRS Dose prescription

If the prescribed dose is not within 90% of the dose corresponding with the maximum dimension of the target as outlined in the protocol is a Major Deviation.

4. SRS Dose Conformity QA

For lesions 5 mm or greater, the ratio of the prescription isodose volume to the target volume (CTV) should be between 1.0 and 2.0.
Minor Deviation: If the ratio is ≥ 0.9 but < 1.0 or >2.0 but ≤ 3.0.
Major Deviation: If the ratio is above 3.0 it is a major deviation.

For lesions less than 5 mm, a ratio up to 3.0 is acceptable.
Minor Deviation: If the ratio is >3.0 but ≤ 3.5.
Major Deviation: If the ratio is above 3.5.

5. SRS Normal Tissue/Critical Structures

Minor Deviation: If maximum point dose to the optic chiasm is >9 Gy but <12 Gy.
If 1cc of the brain stem is >12 Gy but <14 Gy.

Major Deviation: If maximum point dose to the optic chiasm is 12 Gy or greater.
If 1cc of the brain stem is 14 Gy or greater.

WBRT Guidelines

1. Target Volume Coverage

No deviation: Coverage + < 1 cm of specified.
Minor deviation: Coverage + > 1 to 2 cm of specified or failure to cover tumor volume + > ½ specified margin.
Major deviation: > 2 cm of specified or failure to cover the target (i.e. brain) as defined in the protocol.

2. Isodoses

Initial volume isodose plots are required on a minimum of three contours; one at central axis (CA), one superior to CA (2 cm below the superior field edge) and one inferior to CA (2 cm above the inferior field edge).

No deviation: Isodoses submitted as required, and inhomogeneity across the target volume shall be no greater than + 10%.

Minor deviation*: Isodose information incomplete or inhomogeneity across the target volume >10 but < 15%.

Major deviation*: No isodoses submitted or inhomogeneity across the target volume > 15%.

* Deviations would occur only if isodose information is incomplete or not submitted after there has been a request to submit complete isodose information.

3. Normal Tissues

Normal structures are only to be included within the radiation field in as much as this is necessary to treat the primary tumor volume. A minor deviation will result when normal structures are unnecessarily included, but this is not felt to result in unacceptable toxicity that would interfere with the scientific aims of the protocol. A major deviation will result when normal structures are unnecessarily included in the radiation therapy field and such inclusion is felt likely to result in a major increase in toxicity which would potentially compromise the scientific goals of the study.

4. Other Parameters

Dose per fraction, total dose, overall treatment time and portal films unless there are extraordinary circumstances such as significant patient illness requiring hospitalization, etc.

No deviation: +/- < 5% of protocol specification.

Minor deviation: +/- > 5% to 10% of protocol specification.

Major deviation: +/- > 10% of protocol specification or incomplete data (i.e. no portal or sim films, etc.) available for review (after additional request has been made).

5. Scoring of Deviations

Any individual minor deviation will result in an overall score of minor deviation; any major deviation will result in an overall score of a major deviation. Multiple minor deviations will not add up to a major deviation.