

RADIATION THERAPY ONCOLOGY GROUP

RTOG BR-0018

A FEASIBILITY STUDY OF NEUROCOGNITIVE EVALUATION IN PATIENTS TREATED FOR BRAIN METASTASES

Study Chairmen

Radiation Oncology

William F. Regine, M.D.
University of Kentucky
Chandler Medical Center
800 Rose Street/Radiation Oncology
Lexington, KY 40536-0293
(859) 323-6486
FAX # (859) 257-4931
wilregi@pop.uky.edu

Neuro-Psychology

Frederick A. Schmitt, Ph.D.
(859) 323-0229
FAX# (859) 323-5943
fas_com@coa.uky.edu

Neuro-Oncology

Roy A. Patchell, M.D.
(859) 323-5672
FAX # (859) 323-6343
rpatchell@aol.com

Quality of Life

Charles B. Scott, Ph.D.
(215) 574-3208
FAX# (215) 928-0153
cscott@phila.acr.org

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**A FEASIBILITY STUDY OF NEUROCOGNITIVE EVALUATION IN PATIENTS
TREATED FOR BRAIN METASTASES**

SCHEMA

R

E

G

I Whole brain RT to 37.5 Gy/15 fractions/2.5 Gy once daily, 5 days/week
Neurocognitive assessments will be done pre and post whole brain RT

S

T

E

R

Eligibility (*See Section 3.0 for details*)

- Histological proof of primary malignancy
- Brain metastases which are measurable by CT or MRI
- Zubrod Status 0-1
- Life expectancy \geq 3 months
- Neurological function status of 0-2
- A certified test administrator is required for administration of neurocognitive assessments
- No prior RT to the brain
- No primary site of hematopoietic origin (*leukemia*) or evidence of leptomeningeal tumor spread
- No major medical illnesses or psychiatric impairments
- Signed study-specific consent prior to registration

Required Sample Size: 50

Institution # _____

RTOG BR-0018

ELIGIBILITY CHECKLIST (11/13/00)

Case # _____

(page 1 of 2)

- _____(Y) 1. Is there histologic confirmation of a primary malignancy?
- _____(N) 2. Is the primary leukemia?
- _____(Y) 3. Does the patient have brain mets which are measurable by CT or MRI?
- _____(N) 4. Does the patient have evidence of leptomeningeal tumor spread?
- _____(Y) 5. Was the CT or MRI done within the last 3 weeks?
- _____(N) 6. Any prior RT to the brain?
- _____(0-1) 7. Report the Zubrod score
- _____(Y) 8. Does the patient have a neurological function status of 0-2?
- _____(Y) 9. Does the patient have a life expectancy of ≥ 3 months?
- _____(Y) 10. Is a Certified Test Administrator (*per Section 11.3*) available to give the neurocognitive assessments/tests to the patient?

The following questions will be asked at Study Registration:

- _____ 1. Name of institutional person registering this case?
- _____(Y) 2. Has the Eligibility Checklist (*above*) been completed?
- _____(Y) 3. Is the patient eligible for this study?
- _____ 4. Date the study-specific Consent Form was signed? (*must be prior to study entry*)
- _____ 5. Patient's Name
- _____ 6. Verifying Physician
- _____ 7. Patient's ID Number
- _____ 8. Date of Birth
- _____ 9. Race

(cont'd on next page)

Institution # _____

RTOG BR-0018

ELIGIBILITY CHECK (11/13/00)

Case # _____

(page 2 of 2)

_____ 10. Social Security Number

_____ 11. Gender

_____ 12. Patient's Country of Residence

_____ 13. Zip Code

_____ 14. Patient's Insurance Status

_____ 15. Will any component of the patient's care be given at a military or VA facility?

_____ 16. Name of Certified Test Administrator

_____ 17. Date of First Test

_____ 18. RT Start Date

Arm 1 _____ 19. Treatment Assignment

Completed by _____

Date _____

1.0 INTRODUCTION

1.1 Background

It has been argued that the standard clinical trial end points of survival and time to progression for patients with primary brain tumors may be inadequate in describing treatment outcomes.¹ Part of the inadequacy of the traditional outcome measures of therapy for brain tumors lies in the fact that the tumor affects brain functioning and the interventions such as chemotherapy and radiation therapy may also impact on brain functions. Therefore, tumor reoccurrence, survival, and time to progression end points in a clinical trial may not fully describe the outcome of an intervention unless added information regarding neurocognitive, neuropsychiatric, and day-to-day functioning are also considered as therapeutic outcomes. These arguments for including neurobehavioral measures as an index for determining treatment outcomes for brain tumor patients have been recently reviewed by Weitzner¹ and will not be repeated here.

Even though the arguments for including neurobehavioral outcome measures in therapeutic trials of brain tumors are convincing, the cost (*time, training, data management, reimbursement*) of adding such cognitive, behavioral, and quality of life measures to any given clinical trial can be prohibitive. In planning a large-scale study of outcomes of brain tumor treatment, cost factors as well as data collection and management must be factored into the consideration of which outcome measures might be beneficial for use in any given trial. As such, a brief review of the literature using neurocognitive data as an outcome measure of therapy for brain tumors is presented and then it is used to develop a rational and potentially cost-effective set of outcome measures for the proposed study.

One of the initial studies of the neurocognitive effects of adjunctive radiation therapy for brain tumors was completed by Taphoorn and colleagues.² They evaluated 60 patients with resected low-grade gliomas. One half of these patients received focal radiotherapy (45-63 Gy) post-resection and the other one half did not receive radiotherapy. Both tumor groups were also compared to a control group of patients with non-Hodgkin's lymphoma. A wide variety of cognitive outcome measures (*45 minute test battery*) were used for evaluating pre- and post-radiotherapy outcomes. These included tests of attention and concentration (*Stroop Test, d2 Test*), eye-hand coordination, problem-solving, and visual search (*Wechsler Intelligence Scale for Children Mazes subtest*), verbal memory (*Rey Auditory Verbal learning Test*), language and semantic retrieval (*Category Fluency*), and visuospatial processing (*Facial Recognition and Judgment of Line Orientation*). Added measures of patient functioning evaluated overall status (*Karnofsky Scale*) and mood (*Profile of Mood States, POMS*). Both groups of low-grade glioma patients showed performance that was below that of the control subjects on all of the neurocognitive measures except Facial Recognition and Line Orientation. The low-grade glioma patients were also more fatigued and depressed based on their POMS scores at follow-up (*mean of 3.5 years post therapy*). No differential effects of radiotherapy were reported for the low-grade glioma patients, however.

Salander and colleagues³ evaluated 30 patients with malignant gliomas following surgical resection and radiotherapy (*2 Gy fractions for 56 Gy total dose*). Each patient's partner was used as a control. Evaluations of cognition included immediate memory span (*Digit Span and Kohs Blocks*), frontal executive functioning and reasoning (*Picture Arrangement, Wisconsin Card Sorting Test, Ravens Progressive Matrices*), verbal memory (*story recall and abbreviated Selective Reminding Test*), speed of processing, mental calculations and vocabulary (*Wechsler Adult Intelligence Scale: Digit Symbol, Arithmetic and Vocabulary subtests*), language and phonemic retrieval (*Controlled Oral Word Association*), and global cognitive functioning (*standardized Mini-Mental State Examination, sMMSE*). Five months post therapy, 11 patients without mortality or tumor reoccurrence were reevaluated. Global mental status was normal in 10 of 11 patients (91%) using the sMMSE. However, group differences were observed between the control group and the tumor group on measures of memory, verbal fluency, and speed of processing suggesting that surgery plus radiotherapy may have contributed to cognitive impairments. Similar data have been presented for the neurocognitive outcomes of whole-brain versus focal radiotherapy. Gregor and colleagues⁴ evaluated 30 patients with clinical and radiological remission of gliomas several years after treatment. Focal radiotherapy patients (*N=14*) were evaluated roughly 4.5 years after therapy (*30 fractions for 54.1 Gy total dose*) and whole-brain radiotherapy patients (*N=16*) were seen 8.7 years post-therapy (*21.8 fractions for 43.2 Gy*). Comparisons of these two groups showed that the whole-brain patients had greater difficulties with tests of constructional praxis (*Block Design and Rey Complex Figure*), scanning and sequencing (*Trailmaking Test*), and abstract reasoning (*Similarities*) when compared to the focal radiotherapy group.

Each of the above summarized studies suffers from methodological limitations including small sample size, lack of carefully selected control groups, variable times for follow-up assessments, different doses of

radiotherapy and variable adjunctive therapies, and patient variability concerning the site of the brain tumor. Nevertheless, the data suggest that tumor resection followed by radiotherapy could impact on brain functioning even in patients with 'good' outcomes such as survival and lack of tumor recurrence. Additionally, the data suggest that there may be differential effects of whole-brain versus focal radiotherapy on treatment outcomes in persons with brain tumors.

Perhaps the best retrospective study in this area is that of Scheibel and colleagues.⁵ They were able to evaluate 106 patients with glioblastoma and 139 patients with anaplastic glioma. Based on such a large sample, they were able to classify patients based on the type of treatment that was received (*116 with resection, 51 with resection and radiotherapy, 78 with resection, radiotherapy, and chemotherapy*) as well as the lateralization of the tumor. Neurocognitive outcome was evaluated with an extensive test battery (*approximately 90 to 120 minutes*). Comparisons of the three types of treatment showed that patients treated surgically, in contrast to surgery plus radiation and/or chemotherapy, tended to show significantly better scores on Digit Symbol (*speed of processing and decoding measure and a global index of brain impairment*). There was also a tendency for the surgery-only patients to outperform the other groups on tests of constructional praxis (*Block Design*) and language (*phonemic verbal fluency*). No group differences were found between the added radiation therapy and radiation plus chemotherapy groups. Perhaps the key findings in addition to the impact of radiation on neurocognition were the findings of performance differences due to tumor site. Patients with right-sided tumors outperformed their counterparts with left-sided tumors on measures of verbal cognition such as Verbal IQ, verbal memory (*Selective Reminding Test*), language comprehension (*Token Test*), visual confrontation naming, and verbal (*phonemic*) fluency. In contrast, left-sided tumor patients' performance was better on one test of visual processing (*Facial Recognition*). Overall, for the purpose of the present proposal, these data suggest that radiotherapy in addition to surgical treatment may result in visuomotor slowing. The lack of data regarding the type and dose of radiotherapy as well as the interval that had elapsed between treatment and evaluation, however, limit the interpretation of these findings. Further, none of these studies has carefully evaluated the impact of preexisting cognitive impairments. Note: it has been reported that cognitive dysfunction may preexist in up to 97% of some cancer patients (*e.g., small cell lung cancer*) before prophylactic cranial irradiation.⁶

The specific cognitive deficits associated with tumor site and radiotherapy as evaluated by the above reviewed studies suggest that patients may experience neurocognitive impairments as a result of their tumor and treatment. Changes due to radiotherapy appear to be specific to visuo-motor skills and global cognition may remain stable over time⁷ although the impact of radiotherapy on memory functions cannot be conclusively determined based on the data in the literature. Experience within the RTOG in patients with brain metastases has demonstrated the feasibility and utility of the MMSE and suggests the potential for improvement in global mental status with brain radiation in this patient population.⁸ Data from the North Central Cancer Treatment Group (*NCCTG*) support the findings of a limited impact of radiation and chemotherapy on neurocognition in patients with high-grade glioma over time.⁹ The NCCTG data using the MMSE, however, suggest that roughly 10% of patients without tumor progression show gross cognitive changes based on evaluations obtained every six months for two years post radiotherapy. Even though the NCCTG data do not show a clear trend toward cognitive impairment, patient functioning at baseline and patient age were thought to be potentially important predictors of neurocognitive changes or outcome following tumor radiotherapy. These data are consistent with the Komaki et al. findings suggesting that preexisting neurocognitive deficits may provide important predictive power in terms of outcome following cranial radiation.⁶ However, the NCCTG data do not provide insights regarding the impact of different dosing regimens of radiotherapy on long-term cognitive outcome and the MMSE does not provide an evaluation of motor or complex memory and learning functions that may change as a result of radiotherapy. Further, the NCCTG data show a relative decrease in the number of patients evaluated with the MMSE from 139 cases at 6 months to 29 cases at 24 months. This change in 'evaluable' cases may have influenced the analyses to some extent.

1.2 Proposed Measures

1.2.1 Given time and resource limitations, selection of the measures used for evaluating cognition focused on brevity, ease of training and use, as well as usefulness as an outcome measure based on the existing literature. Additional evaluations were selected based on their sensitivity to change in other neurologically impaired groups (*e.g., 2&7 Test in HIV*)¹⁰ and the availability of alternate forms of the test procedure (*to reduce practice effects*). A summary and description of the proposed procedures is provided in Table 1.

Table 1: Summary of Measures

Mini-Mental State Exam (MMSE) - most widely used global mental status measure in medical settings (*10 min to complete*) – current version uses standardized instructions and tests for cued recall and recognition.

Hopkins Verbal Learning Test (HVLT) - patient learns 12 words read to them 3 times; immediate recall is tested after each learning trial. Following the third learning and recall trial, the patient completes a recognition test. Delayed recall (*savings or retention*) is evaluated after 15-20 minutes as the final assessment of the battery (*requires about 7 minutes to complete*) indexing learning and short-term memory.

Verbal Fluency/Controlled Word Association Test (COWAT) - patient produces as many words as possible in 1 min. (*each*) for a specific letter (*C, F, L*) 5 min to complete - language & executive/frontal skills

Ruff 2 and 7 Test (2&7) – patient must cancel letters and numbers as rapidly as possible. Test measures neglect, attention, and concentration in less than 6 minutes.

Trailmaking Test (TMT) – This is a measure of visuospatial scanning, attention, sequencing, and speed with two parts (*A & B*). Patients must ‘connect the dots’ either in a numbered sequence or alternating letters and numbers. Generally Part A requires less than 2 minutes to complete and Part B requires less than 5 minutes.

Profile of Mood States Short Form (POMS-SF) – patient select adjectives and rates feelings over past 2-week interval. Provides assessment of depression, anxiety, fatigue, vigor (*self-administered*).

1.2.2 Quality of Life

The POMS Short Form (*POMS-SF*) is a 30 item, six subscales questionnaire with similar reliability and validity data as the long form.¹¹ The subscales of the POMS are tension, depression, anger, vigor, fatigue, and confusion.¹¹ The POMS has previously been used by investigators to measure fatigue in patients receiving radiation therapy and performed quite well in comparison with other measures such as a visual analogue scale and the Beck Depression Index.¹² Nail and King found the POMS to be a sensitive measure and the fatigue subscale to be sufficient to capture the physical symptoms of fatigue.¹³ However, others have felt that the long form was too lengthy with (*65 questions*) to be regularly given to patients.¹⁴

2.0 OBJECTIVES

- 2.1 To test the feasibility of performing a test battery consisting of five neurocognitive measures and a quality of life instrument in patients with brain metastasis.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

- 3.1.1 All patients with a histological proof of a primary malignancy at any site or histology with the exception of leukemias. No biopsy of the brain metastasis is necessary.
- 3.1.2 Patients must have brain metastases which are measurable by computed tomography (*CT*) or MRI. The CT/MRI must be done within three weeks prior to registration. There may be either a solitary brain metastasis or multiple brain metastases.
- 3.1.3 Zubrod performance status of 0-1.
- 3.1.4 Neurological function status of 0-2.
- 3.1.5 The patients must have a life expectancy of at least 3 months.

- 3.1.6 A “certified” test administrator (*Section 11.3*) is required for administration of neurocognitive assessments.
- 3.1.7 Patients must sign a study-specific consent prior to study entry.
- 3.2 Ineligibility Criteria**
- 3.2.1 Prior radiotherapy to the brain
- 3.2.2 Primary site of hematopoietic origin (*leukemia*) or evidence of leptomeningeal tumor spread.
- 3.2.3 Major medical illnesses or psychiatric impairments which in the investigator's mind will prevent administration or completion of protocol therapy/tests.

4.0 PRETREATMENT EVALUATIONS

4.1 General Evaluations

- 4.1.1 A complete history and physical examination including the documentation of all metastatic disease sites. Neurological condition must be evaluated and classified. The histology of the primary should be noted.
- 4.1.2 CT/MRI brain scan must be done within three weeks prior to registration.
- 4.1.3 Completion of neurocognitive tests per Section 11.0 prior to initiation of RT. Forms packets are available from RTOG Headquarters (*fax 215-574-0300*). Request a complete set before beginning to accrue patients.

5.0 REGISTRATION PROCEDURES

- 5.1 The healthcare professional (*e.g., nurse, psychologist*) who is responsible for test administration in this study must be certified by Dr. Schmitt in order to participate in this protocol. Certification will be based on the criteria in Section 11.3.
- 5.2 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday 8:30 am to 5:00 pm ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed and dated Checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

6.0 RADIATION THERAPY

6.1 Whole Brain Radiation Therapy

- 6.1.1 Total Dose: Whole brain radiation therapy (*WBRT*) must begin within one week after registration. One treatment of 2.5 Gy will be given daily, 5 days a week for three weeks for a total of 37.5 Gy. Both lateral portals shall be treated during each treatment session.
- 6.1.2 Physical factors: Treatment will be delivered using megavoltage machines with photon beams ranging from 4 to 8 MV. Electron, particle, or implant therapy is not permissible.
- 6.1.3 Simulation, Immobilization, Localization: The patient will be treated in the supine position. Adequate immobilization and reproducibility of position must be ensured. The target volume will cover the brain and meninges to the foramen magnum.
- 6.1.4 Treatment Planning: Treatments must be delivered through parallel opposed fields that cover the entire cranial contents. There should be beam fall-off of at least 1 cm. The eyes will be excluded from the beam either by field arrangement or shielding.
- 6.1.5 Dose Specification: For the following portal arrangements, the target dose shall be specified as follows: For two opposed coaxial equally weighted beams on the central ray at mid separation of beams.

6.2 Toxicity Reports

- 6.2.1 All fatal toxicities (*grade 5*) resulting from protocol treatment must be reported by telephone to the Group Chairman to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
- 6.2.2 All life-threatening (*grade 4*) toxicities resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
- 6.2.3 Toxicity evaluation will be by the revised NCI CTC version 2.0.
- 6.2.4 Appropriate data forms and, if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

7.0 DRUG THERAPY

Not applicable to this study.

8.0 SURGERY

Not applicable to this study.

9.0 GENERAL MANAGEMENT, CORTICOSTEROID USAGE AND ADDITIONAL THERAPY

9.1 Patients will receive all necessary general medical supportive care.

9.2 Corticosteroids

Corticosteroids will be used as needed and in the smallest dose which will afford the patient satisfactory neurologic function and the best possible quality of life.

9.3 Other Medications

9.3.1 Phenytoin sodium and other antiseizure medication may be used as clinically indicated. All medication doses are to be documented.

9.3.2 Infections are to be treated with appropriate antibiotics that are recorded.

9.3.3 Analgesics and many other medications are to be specified and their dose recorded.

9.4 Additional Treatment for Disease Progression

Disease recurrence or progression should be documented by neurologic examination and CT/MRI scan. Appropriate therapy will then be administered at the discretion of the investigator. Such therapy may consist of chemotherapy, surgery or placement of a shunt, or supportive care. Such therapy shall be documented. Every effort will be made to ensure patient comfort at all times. Patients will be informed that their elective withdrawal from this protocol will in no way jeopardize their follow-up therapy independent of participation in this study.

10.0 PATHOLOGY

Not applicable to this study.

11.0 PATIENT ASSESSMENTS

11.1 General Study Parameters

	Pre RT	At Completion of RT	At 1 month Follow-up
History & Physical, Weight	X	X	X
Neuro & Zubrod Status	X	X	X
Mini Mental Status (<i>MMSE</i>) ^b	X	X	X
Hopkins Verbal Learning Test (<i>HVLT</i>) ^b	X	X	X
Controlled Work Assoc. Test (<i>COWAT</i>) ^b	X	X	X
Ruff 2&7 Test ^b	X	X	X
Trailmaking Test (<i>TMT</i>) ^b	X	X	X
Profile of Mood Status-Short Form (<i>POMS-SF</i>) ^b	X	X	X
CT, MRI Brain Scan	X	X ^a	X ^a

a. CT/MRI scans to measure progression of disease are optional.

b. See Section 1.2 for descriptions.

11.2 Neurocognitive Assessments

Six instruments/tests (*See Section 11.4 and 11.5*) will be used to assess neurocognitive function and quality of life. These are to be filled out by a health care professional (*physician, nurse, or data manager who are certified to administer the tests*), and/or patient.

11.3 CERTIFICATION for Test Administration

The healthcare professional (*e.g., nurse, psychologist*) who is responsible for test administration in this study requires pre-certification by Dr. Schmitt in order to participate in this protocol. Certification will be obtained as follows:

- 11.3.1 The person who will obtain test data must attend a Neurocognitive Assessment Training Workshop that reviews test procedures and data collection. This training session will be held during a RTOG Semi-Annual Meeting(s).
- 11.3.1.1 For persons who are unable to attend an RTOG training meeting, a video tape of test administration and data collection methods will be provided by the RTOG (*upon request by fax: 215-574-0300*) for review and reference during the study. This video tape must be reviewed by all persons who will administer neurocognitive assessments.
- 11.3.2 Test instructions and guidelines are provided in Appendix IV. The instructions must be reviewed and retained for reference. Data forms are available from RTOG (*fax: 215-574-0300*). Please note that there will be two sets of data forms: one for patients assigned to odd-numbered RTOG case numbers, and another for patients assigned to even-numbered RTOG case numbers.
- 11.3.3 Prior to the enrollment of any patient into the study, the healthcare professional who will be evaluating patients must complete two “practice” assessments: One will involve a ‘normal’ healthy individual and the second a volunteer who has undergone radiation treatment for a CNS tumor. Both sessions must be audiotaped.
- 11.3.4 Once all of the above steps have been completed you must complete and sign the Certification Worksheet (*Appendix V*). Submit the signed Certification Worksheet along with your “practice” neurocognitive assessment/test forms and audiotape of both practice sessions to Dr. Frederick A. Schmitt, Ph.D. **Please remember to indicate on your forms and on the audiotape if they are from the assessment of the health individual or previously treated individual.** If certified by Dr. Schmitt, notification of certification will be sent to both the site and to RTOG Headquarters and study enrollment may commence.
- 11.3.5 Finally, at a random point during the study, an audio tape of a testing session may be requested for review and quality control. This audiotape and associated test records will be reviewed by the RTOG and study chairs. For quality control purposes, procedural deviations (*if any*) will be identified and sites will be notified of the results of the review. If significant procedural variations are noted, re-training (*‘recertification’*) of the test administrator will be requested.
- 11.3.6 Completed test forms must be signed by the certified test administrator prior to submission to the RTOG. Dr. Schmitt and colleagues will be available by telephone and e-mail if questions arise about the testing procedures.

11.4 Instructions for Administration of Neurocognitive Exams

- 11.4.1 MMSE – is an eleven item form designed to assess cognitive mental performance. The examination requires 5-10 minutes to administer. See Appendix IV for sample exam and instructions for administration.
- 11.4.2 HVLT - patient learns 12 words read to them 3 times; immediate recall is tested after each learning trial. Following the third learning and recall trial, the patient completes a recognition test. Delayed recall (*savings or retention*) is evaluated after 15-20 minutes as the final assessment of the battery (*requires about 10 minutes to complete*). Note: for each individual patient, different HVLT versions are used at each test/assessment session (*e.g., Form 1 at registration, Form 2 at completion of treatment, and Form 3 at first follow-up*).
- 11.4.3 COWAT – patient produces as many words as possible in 1 min. (*each*) for a specific letter (*P, R, W*) (*C,F,L*)(*5 min to complete*) – language & executive/frontal skills. See Appendix IV for sample exam and instructions for administration.
- 11.4.4 Ruff 2&7 – patient must cancel letters and numbers as rapidly as possible. Test measures neglect, attention, and concentration in less than 6 minutes. See Appendix IV for sample exam and instructions for administration.
- 11.4.5 TMT – a measure of visuo-spatial scanning, attention, sequencing, and speed with two parts (*A & B*). Patients must ‘connect the dots’ either in a numbered sequence or alternating letters and numbers. Generally Part A requires less than 2 minutes to complete and Part B requires less than 5 minutes.

11.5 Administration of Quality of Life Exam

- 11.5.1 POMS-SF - patient selects adjectives and rates feelings over past 2-week interval. Provides assessment of depression, anxiety, fatigue, vigor (*self-administered*). See Appendix IV for sample exam and instructions for administration. Only original (*blue*) forms must be used. These will be available in the patient-specific forms packets at patient entry or contact RTOG for an advance set (*fax 215-574-0300*). See Section 12.2.2.

11.6 Timing of Administration

All neurocognitive tests and the POMS-SF must be administered sequentially (*See Appendix IV*) and completed during the testing session on the same (*single*) day.

11.7 Reporting Neurocognitive Test Results

Except for the MMSE and the POMS-SF, results of all other neurocognitive tests are recorded on the Neurocognitive Assessment Summary Form. Except for the MMSE and the POMS-SF, individual patient tests/forms will not be submitted to RTOG Headquarters but will be kept on file at the institution as part of the patient's study file for submission upon request.

The completed MMSE (*MS*) and POMS-SF (*PM*) forms must be attached to and submitted with Neurocognitive Assessment Summary Form (*CS*). Study/case specific labels must be applied to each page.

12.0 DATA COLLECTION

(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX#215/928-0153)

12.1 Summary of Data Submission

<u>Item</u>	<u>Due</u>
Demographic Form (A5)	Within 2 weeks of study entry
Initial Evaluation Form (I1)	
Pretreatment CT/MRI Report (C3/ME)	
Neurocognitive Assessment Summary Form (CS)	
Mini Mental Status Evaluation (MS)	
Profile of Moods State-SF (PM)	
Radiotherapy Form (T1)	Upon completion of treatment
Follow-up Form (FS)	
Neurocognitive Assessment (CS)	
Mini Mental Status Evaluation (MS)	
Profile of Moods State-SF (PM)	At one month post RT
Follow-up Form (FS)	
Neurocognitive Assessment (CS)	
Mini Mental Status Evaluation (MS)	
Profile of Moods State-SF (PM)	

12.2 Special Forms Processing

- 12.2.1** Each completed assessment of the Mini Mental Status Evaluation (*MS*) or the Profile of Moods States-SF (*PM*) must be attached to and submitted to the Neurocognitive Assessment Summary Form (*CS*). Study/case labels must be affixed to all forms. The PM form code must be recorded in the form type box on the label.
- 12.2.2** The POMS-SF is covered by copyright. **Only original (*blue*) forms will be accepted.**
- 12.2.3** Except for the MS, PM, and CS forms, test results are not submitted to RTOG Headquarters. Test results will remain on file at the institution as source documentation pending request for submission by RTOG or study chair.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

- 13.1.1** Feasibility of performing a test battery of neurocognitive and quality of life measures.

13.2 Sample Size

The primary objective of this trial is to establish whether patients can and will complete a battery of neurocognitive and quality of life measures. In order to participate in this study, patients must complete the battery prior to the initiation of therapy. The battery will also be completed at the end of radiation therapy and at the one-month follow-up point. The RTOG Recursive Partitioning Analysis (*RPA*) Classes for brain metastases patients estimates the median survival time (*MST*) to range from 2.3 to 7.1 months. Since the radiation therapy schedule is three weeks and additional follow-up is another four weeks, the percent of patients alive at the study endpoint ranges from 55% to 82%. A sample size of 25 evaluable patients would provide a 95% two-sided confidence interval that would extend 17%. It is estimated that 75% of the evaluable patients will complete the battery at all three-time points. If the completion rate is lower then the confidence interval will be wider, and if it is higher then the interval will be shorter. In the worst case scenario of only 54% of the patients living to the one-month follow-up then 47 patients will be required in order to have 25 patients available at that time point. In the best case scenario, at least 39 patients will be alive at the one-month follow-up time point. Under the best case, the confidence interval will extend 13.6%.

The change from baseline will be estimated at each time point for each test in the battery. At the end of therapy the percent of patients alive could range from 74 to 91%. Indicating that 35-43 patients will be available for testing. If at least 75% of the available patients complete the battery at that time point then 27-33 patients will be analyzable. A 95% confidence interval around the change scores will be computed and will extend approximately 4%. This assumes a standard deviation of 10%. The confidence interval will be wider at the one-month follow-up based upon a reduced number of analyzable tests.

Assuming a 5% ineligibility rate, **then 50 total patients will be required to be enrolled in this study.**

13.3 Patient Accrual

The patient accrual is projected to be 10 cases per month. At that rate, it will take 5 months to reach the required total accrual of 50 cases. If the average monthly accrual rate is less than 4 patients, the study will be re-evaluated with respect to feasibility.

13.4 Analyses Plans

13.4.1 Interim Analyses

Interim reports with statistical analyses are prepared every six months until the initial manuscript reporting the treatment results has been submitted. In general, the interim reports will contain information about:

- a) the patient accrual rate with a projected completion date for the accrual phase;
- b) the quality of submitted data with respect to timeliness and completeness.

13.4.2 Analysis for Reporting the Initial Results

This analysis will be undertaken when each patient has been potentially followed for a minimum of one month. The usual components of this analysis are:

- a) tabulation of all cases entered, and any excluded from the analysis with reasons for the exclusion;
- b) reporting institutional accrual;
- c) distribution of important prognostic baseline variables;
- d) observed results with respect to the endpoints described in Section 13.1. Further subgroup analyses will not be undertaken due to the small sample sizes.

13.5 Inclusion of Women and Minorities

In conformance with the National Institute of Health (*NIH*) Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we make the following observations. The recursive partitioning analysis of the RTOG database for patients entered into brain metastases trials failed to show any treatment interaction with gender.¹⁵ Furthermore, there is no indication that compliance rates for the neurocognitive and quality of life battery will differ by race or gender. The estimate distribution of patients is as follows.

Planned Gender and Minority Inclusion

	American Indian or Alaskan Native	Asian	Black or African American	Hispanic or Latino	Native Hawaiian or Pacific Islander	White	Other or Unknown	Total
Female	0	0	0	0	0	20	0	20
Male	0	0	0	0	0	30	0	30
Total	0	0	0	0	0	50	0	50

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APPENDIX I

RTOG BR-0018

SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE

A FEASIBILITY STUDY OF NEUROCOGNITIVE EVALUATION IN PATIENTS TREATED FOR BRAIN METASTASES

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. You are being asked to take part in this study because you have cancer that has spread to the brain.

Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, *Taking Part in Clinical Trials: What Cancer Patients Need To Know*, is available from your doctor.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find out how easy or hard it is for patients whose cancer has spread to the brain to complete a series of six tests that measure neurocognitive (memory) skills and quality of life issues.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 50 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

- All patients will receive:

Radiation Therapy: Radiation therapy to the brain will be given once a day, five days per week for three weeks. Radiation therapy treatments will be given at your institution.

Neurocognitive and Quality of Life Testing:

Six tests will be administered by a health care professional (physician, nurse, or research associate). These tests will each take from three to ten minutes for a total of approximately 45 to 90 minutes of testing. There will be additional time for instructions and a break between tests. During these tests you will be asked to answer some general knowledge questions, recall words from a list that is read to you, match numbers and symbols, think of

words that begin with a specific letter, cross out certain numbers from a list of numbers, and describe your feelings over the last two weeks. You may be audiotaped during the session.

If you take part in this study, you will have the following tests and procedures:

- Procedures that are part of regular cancer care and may be done even if you do not join the study:

Procedures

Physical Exam

CT or MRI of Brain

Schedule

At study entry, when radiation therapy is finished, and one month after treatment

At study entry and as medically indicated

- Procedures being done because you are in this study:

Procedure

Neurocognitive and Quality of Life Testing

Audiotape of Test Session

Schedule

At study entry, when radiation therapy is finished, and one month after treatment

May be done to make sure tests are being performed correctly.

HOW LONG WILL I BE IN THE STUDY?

You will receive radiation therapy for three weeks. One month after your treatment ends you will complete the neurocognitive testing.

The researcher may decide to take you off this study if it is in your medical best interest, your condition worsens, or new information becomes available and this information suggests the treatment will be ineffective or unsafe for you. It is unlikely, but the study may be stopped early due to lack of funding or participation.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Drugs may be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the radiation therapy is stopped, but in some cases side effects can be serious or long-lasting or permanent.

Risks Associated with Radiation Therapy

Very Likely

Reddening and tanning of skin
Temporary hair loss in the treatment area
Skin blistering
Dry mouth or altered taste
Fatigue, sleepiness
Headaches, nausea

Less Likely But Serious

Permanent hair loss
Hearing loss
Cataracts or eye injury resulting in
blindness
Mental slowness, behavioral changes

Reproductive risks: Because radiation can affect an unborn baby, you should not become pregnant or father a baby while on this study. You should not nurse your baby while on this study. Ask your doctor about counseling and more information about preventing pregnancy.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with cancer in the future.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) radiation therapy; (2) chemotherapy; (3) surgery; or (4) no treatment except medications to make you feel better. With the latter choice, your tumor would continue to grow and your disease would spread. These treatments could be given either alone or in combination with each other.

Another option may be to get the treatment plan described in this study at this center and other centers even if you do not take part in the study.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments. Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (*RTOG*). Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (*FDA*), the National Cancer Institute (*NCI*), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A Data Safety and Monitoring Board, an independent group of experts, may be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

For information about your disease and research-related injury, you may contact:

Name

Telephone Number

For information about this study, you may contact:

Name

Telephone Number

For information about your rights as a research subject, you may contact:

(OPRR suggests that this person not be the investigator or anyone else directly involved with the research)

Name

Telephone Number

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

Visit the NCI's Web sites for comprehensive clinical trials information
<http://cancertrials.nci.nih.gov> or for accurate cancer information including PDQ
<http://cancernet.nci.nih.gov>.

SIGNATURE

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (*full study plan*).

Patient Signature (*or legal Representative*)

Date

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

ZUBROD PERFORMANCE SCALE

0	Fully active, able to carry on all predisease activities without restriction (<i>Karnofsky 90-100</i>).
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (<i>Karnofsky 70-80</i>).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (<i>Karnofsky 50-60</i>).
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (<i>Karnofsky 30-40</i>).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (<i>Karnofsky 10-20</i>).

NEUROLOGIC FUNCTION (NF) STATUS

<u>NF</u>	<u>Definition</u>
0	No neurologic symptoms; fully active at home/work without assistance.
1	Minor neurologic symptoms; fully active at home/work without assistance.
2	Moderate neurologic symptoms; fully active at home/work but requires assistance.
3	Moderate neurologic symptoms; less than fully active at home/work and requires assistance.
4	Severe neurologic symptoms; totally inactive requiring complete assistance at home or in institution-unable to work.

APPENDIX III

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. **When a protocol toxicity requires more intense, special handling, study-specific reporting procedures supersede the General Guidelines.**

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.
 - a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.
2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.
3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).
4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.
5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

A copy of all correspondence submitted to NCI, or to another Cooperative Group (in the case of RTOG-coordinated intergroup studies) must also be submitted to RTOG Headquarters when applicable.

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.
7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.
8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
2. All life-threatening (grade 4) toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. ADVERSE DRUG REACTIONS DRUG AND BIOLOGICS

An adverse reaction is a toxicity or an undesirable effect usually of severe nature. Specifically, this may include major organ toxicities of the liver, kidneys, cardiovascular system, central nervous system, skin, bone marrow, or anaphylaxis. These undesirable effects may be further classified as "known" or "unknown" toxicities.

Known toxicities are those which have been previously identified as having resulted from administration of the agent. They may be identified in the literature, the protocol, the consent form or noted in the drug insert.

Unknown toxicities are those thought to have resulted from the agent but have not previously been identified as a known side effect.

Commercial and Non-Investigational Agents

- i. Any fatal (*grade 5*) or life threatening (*grade 4*) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.
- ii. Unknown adverse reactions (\geq *grade 2*) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.
- iii. All neurotoxicities (\geq *grade 3*) from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.
- iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

Reactions definitely thought not to be treatment related should not be reported, however, a report should be made of applicable effects if there is a reasonable suspicion that the effect is due to protocol treatment.

Investigational Agents

Prompt reporting of adverse reactions in patients treated with investigational agents is mandatory. Adverse reactions from NCI sponsored drugs are reported to:

Investigational Drug Branch (*IDB*)
P. O. Box 30012
Bethesda, MD 20824
Telephone number available 24 hours
(301) 230-2330 FAX # 301-230-0159

i. Phase I Studies Utilizing Investigational Agents

- | | |
|--|--|
| - All deaths during therapy with the agent. | Report by phone within 24 hours to IDB and RTOG Headquarters.
**A written report to follow within 10 working days. |
| - All deaths within 30 days of termination of the agent. | As above |

- All life threatening (*grade 4*) events which may be due to agent. As above
 - First occurrence of any toxicity (*regardless of grade*). Report by **phone within 24 hours** to IDB drug monitor and RTOG Headquarters. ****A written report may be required.**
- ii. *Phase II, III Studies Utilizing Investigational Agents*
- All fatal (*grade 5*) and life threatening (*grade 4*) known adverse reactions due to investigational agent. Report **by phone** to RTOG Headquarters and the Study Chairman within 24 hours ****A written report must be sent to RTOG within 10 working days with a copy to IDB. (*Grade 4 myelosuppression not reported to IDB*)**
 - All fatal (*grade 5*) and life threatening (*grade 4*) unknown adverse reactions resulting from or suspected to be related to investigational agent. Report **by phone** to RTOG Headquarters, the Study Chairman and IDB within **24 hours**. ****A written report to follow within 10 working days.**
 - All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent. ****Report in writing** to RTOG Headquarters and IDB within 10 working days.

**** See attached (*if applicable to this study*) NCI Adverse Drug Reaction Reporting Form**

APPENDIX IV

RTOG-WBI Pilot Study – Instructions and Procedures

STEP 1 - Administer MMSE Registration, Attention Concentration (serial sevens or world spelled backwards), and 3-item recall tasks per previous RTOG procedures and scoring sheets. Note: the recommended order of items can be found starting on page 6 of this appendix. This order is suggested to minimize interference between the HVLTL and MMSE memory tasks. For this purpose, a forms packet will be issued for each individual case number. Forms cannot be used across the patient population.

STEP 2 - Hopkins Verbal Learning Test (HVLTL) - INSTRUCTIONS

Trial 1: *“Listen carefully while I read a list of 12 words. Try your very best to memorize as many of these words as you can. When I stop, you are to say back as many of the words as you can, in any order that you wish. Ready?”*

- Read the words at the rate of one word per 2 seconds. Then have the patient recall them.
- Record those words that are repeated on the form (3) or number order of recall (*preferred*, see example).
- If a word is said that is not in the list (*intrusion*), write it on the form and tell the patient: “that word was not in the list”.
- If no more words are produced within 10-15 seconds, ask the patient if they can remember any more words.
- If not, record the number of words that were correctly repeated on the answer sheet and move on to trial 2.

Trial 2: *“That was a good beginning. Now, I’m going to read the same list again. When I stop, I want you to tell me as many words as you can remember, including the words you said the first time. It does not matter in what order you say them. Just say as many words as you can remember whether or not you said them before. Ready?”*

- Record those words that are repeated on the form (3) or numbered order of recall.
- If a word is said that is not in the list, write it on the form and say: “that word was not in the list”.
- If no more words are produced within 10-15 seconds, ask the patient if they can remember any more words.
- If not, record the number of words correctly recalled and move on to trial 3.

Trial 3: *“Very good. I’m going to read the list again. Again, listen carefully and try to remember as many words as you can whether or not you said them before. Ready?”*

Continue to follow recording procedures from previous trials. Note that each learning and recall trial should last about 1 minute.

Trial 4-Recognition: *“Now I am going to read a list of 24 words to you. Some of these words are from the list that you learned and just tried to remember. Other words are new words and I have not read them to you before. After each word, I want you to say ‘YES’ if you think the word was in the previous list and ‘NO’ if it was not.”*

- Record YES/NO answers by marking the Y/N boxes next to each word.
- Guessing is allowed.

I Record the 24-hour time on the scoring form when trial 4 is completed.

STEP 3 - Administer the remaining **MMSE** tasks per RTOG procedures and scoring sheets.

STEP 4 - Ruff 2&7 TEST ADMINISTRATION (I timed test I you will need a stopwatch)

Instructions – *“This procedure is called the twos & sevens. This is the practice section (show patient practice page).*

What you are to do is find all of the 2’s and all of the 7’s and cross them out like this. (Demonstrate: patient should put a short slash through the target numbers. Circling numbers or putting “X’s” through them is not allowed)

Go from the left to the right in order and then drop to the next line and keep doing the same thing (crossing out 2’s and 7’s).

Now you probably will not finish this whole thing; that’s okay. After you have been working for a little while, I am going to say “NEXT”. When I say “NEXT”, I want you to stop wherever you are and drop under the solid line (point out solid line) to the next part starting again at the left marking out only 2’s and 7’s.”

Administer the Practice trial observing the patient’s performance. The examiner should allow 15 seconds to elapse for the first block, then say “NEXT” and allow 15 seconds for the second block.

“Good. Now here is the longer version. You are going to start up here at the top and find all of the 2’s and all of the 7’s. Every time I say “NEXT”, you drop down to the next section and do the same thing.

I want you to go as fast as you can without missing any of the 2’s or 7’s.”

- Each section/block is 15 seconds long.
- It is important that the patient works from left to right and does not skip around between lines.
- Should the patient start marking on an incorrect segment, the examiner redirects him/her to the appropriate spot without restarting the 15 second interval.

Every effort should be made to make each interval exactly 15 seconds long. If there is an examiner’s error and one section is under- or over-timed, the following interval should be increased or decreased an amount of time that will bring the total test time back to normal. A note should be made to indicate which two sections were affected.

The total test time should always be exactly 5 minutes.

SCORING:

1. Count the number of 2’s and 7’s crossed out per section.
2. Circle and count any omissions that occur prior to the last 2 or 7 that was marked by the patient in any given block.

3. Enter the number of correctly crossed out 2's and 7's as well as errors and omissions onto the summary data form.

STEP 5 – POMS – Short Form; per RTOG procedures and scoring sheets (5 minutes).

STEP 6 – Allow the patient a 5 – 10 minute break. Review the answers for the mood scale (POMS-SF) to insure completeness.

STEP 7 - HVLT Delayed Recall Trial 5:

I Record the 24-hour clock time on the scoring sheet.

I Note that at least 20 minutes should have elapsed between the clock time for HVLT Trial 7 and this time.

Say: *“Now tell me as many words as you remember from the original list of words that you learned.”* **Do not read the list again.**

- Record those words that are repeated on the form (3) or record numbers for order in which words are recalled.
- If a word is said that is not in the list, write it on the form and say: “that word was not in the list”.
- If no more words are produced within 10-15 seconds, ask the patient if they can remember any more words.
- If not, record the number of words correctly recalled on the data sheets and then move on to step 7.

STEP 8 – Trail Making Test (I timed testI)

Part A: 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).

Say: *“I want you to connect the dots in order as fast as you can. Start here at number 1 and go from 1 to 2 to 3 and so on until you reach the end. You should connect the dots in a continuous movement without lifting your pencil from the paper. Work as fast as you can without making any mistakes. If you make a mistake, just trace back to where you made the error and try again. Ready...go!”*

If the patient makes a mistake on Sample A, quickly point out the mistake and explain it. If the patient still cannot complete Sample A, take his/her hand and guide him/her through it, using the opposite end of the pen, lightly touching the worksheet to avoid making marks on the copy. If the patient completes Sample A correctly and appears to understand what to do, proceed immediately to Part A.

After the practice trial, move on to Part A and say: *“I have some more of these. Start here at number 1 (point out start) and go from 1 to 2 to 3 and so on until you reach the end (point to end). Again, work as fast as you can. Ready...go!”* Begin timing.

- Start timing as soon as the instruction to begin is given.
- Watch closely to catch any errors as soon as they are made.
- If an error is made, call it to the patient's attention and have him/her start again from the error point.
- Do not stop timing until the patient reaches the circle marked END.
- Record the time to completion on the test sheet in seconds, and say: *"That's fine. Now we'll try another one."*

Part B: Show the practice section for Part B and say: *"This time I want you to do something a little different. I want you to alternate numbers with letters of the alphabet. So, for example, you would go from 1 to A to 2 to B and so on. Do you understand? Again, I want you to work as fast as you can without making any mistakes. You should connect the dots in one continuous movement. Ready...go!"*

Again, if the patient makes a mistake on Sample B, point out the error and explain it. If the patient still cannot complete Sample B, take his/her hand and guide him/her through it, using the opposite end of the pen, lightly touching the worksheet to avoid making marks on the copy. If the patient completes Sample B correctly and appears to understand what to do, proceed immediately to Part B.

After the practice trial, move on to Part B and say: *"I have some more of these. Again, go from 1 to A to 2 to B and so on (point to circles) until you reach the end (point to end). Work as fast as you can. Ready...go!"* Begin timing.

- Start timing as soon as the instruction to begin is given.
- Watch closely to catch any errors as soon as they are made.
- If an error is made, call it to the patient's attention and have him/her start again from the error point.
- Do not stop timing until the patient reaches the circle marked END.
- Record the time to completion on the test sheet in seconds.

STEP 9 – Controlled Oral Word Association Test (COWAT) (I-timed testI)

Say: *"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', 'Eats' and 'Eating'".

For example, if I say "s", you could say "sit", "shoe", or "show". 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, terminate 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:

“That is fine. Now I am going to give you another letter. Again, 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 one minute.

- If the patient discontinues before the end of the time period, encourage him/her to try to find more words.
- If he/she is silent for 15 seconds, repeat the basic instruction and the letter.
- No extension on the time limit is made in the event that instructions are repeated.
- Continue the evaluation with the remaining two letters, allowing for one minute each.

Recording and Scoring. The record sheet 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. However, **ALL** incorrect responses should be recorded verbatim.

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.

Comments on scoring. 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 admissible responses.

Patients often give both a verb and the substantive derived from the verb or adjective (e.g., fun-funny; sad-sadness). These are not admissible responses.

On the other hand, if the substantive 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.

Slang terms are OK if they are in general use.

Foreign words (e.g., pasta; Lebensraum; passé; lasagna) are admissible if they can be considered part of the English lexicon (e.g., found in the dictionary).

The number of correct words should be indicated below each column on the recording sheet and on the summary data form that is sent to the RTOG.

TEST FORM USE / ORDER

Several of these tests have alternate forms or versions in order to reduce the effects of practice. In the Table below, those tests with alternate forms are listed. The order of form use will be determined using the patient's RTOG case number. If the case number is ODD, use the forms in the order listed under ODD. Similarly, if the case number is EVEN, refer to the EVEN columns in determining test order.

TEST	ODD-1 st visit	ODD-2 nd visit	EVEN-1 st visit	EVEN-2 nd visit
HVLT				
2&7				
Trailmaking B				
COWAT	'C-F-L'	'P-R-W'	'P-R-W'	'C-F-L'

The forms packet will contain alternate versions of the neurocognitive tests. It will match the case number of your patient (odd or even) in conjunction with each time frame indicated for testing. Baseline neurocognitive testing must take place prior to the start of any protocol treatment. Please remember to not use these forms across your patient population that is accrued to this study.

Additional comments:

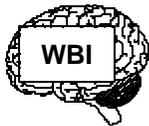
1. Testing should be completed in one session.
2. **Request a sample forms packet** from RTOG Headquarters to have on hand before beginning to accrue patients.

Follow the **instructions on the Forms Packet Index** before submission of forms to RTOG.

3. Please keep all original test records. In the event of questions, they should be FAXed to Dr. Schmitt. Except for the items specified below, test results are not submitted to RTOG Headquarters. Results remain on file at the institution as **source documentation** pending request for submission by RTOG or a Study Chair.

4. **Except for the MMSE (MS Form) and the POMS-SF (PM), all test results are recorded on the Neurocognitive Assessment Summary Form (CS)** all of which are found in the Forms Packet. The POMS-SF is covered by copyright, therefore, only original forms can be used, i.e., do not use copies. Original POMS-SF Forms (PM) are provided in the form packet. Additional original forms will be supplied upon request from the RTOG Registrar. The completed original POMS may be kept on site with a copy submitted to RTOG. Results of the MMSE must be recorded on the MS form for submission along with the relevant date of assessment and calendar due date. Both the MS and PM forms must be submitted as **attachments** to the Neurocognitive Assessment Summary Form (CS). Study/case specific labels must be applied to all forms. The PM form type must be recorded in the form type box on the label.
5. Patients should not be given copies of their tests to avoid learning the material between test administrations.
6. Before dismissing the patient, thank him/her for their cooperation: Remind the patient of their next appointment and that these tests will be repeated.

In the event that a patient cannot complete a given test, please write the reason(s) on the test form AND the data summary form.



RTOG WBI Neurocognitive Outcome Pilot Study
Mental Status Exam

RTOG ID# _____

DATE: _____

Visit #: _____

Level of Consciousness:

Alert _____

Lethargic _____

Fluctuating _____

MMSE Items	Patient Response	MAX	SCORE
Registration	_____	3	
Serial Sevens or WORLD 'backwards'	_____	5	
Recall of 3 objects	_____	3	

Results must be recorded on the MS Form found in the RTOG Forms Packet

Hopkins Verbal Learning Test (HVLТ Form 1)

Words	Trial 1	Trial 2	Trial 3
Lion			
Emerald			
Horse			
Tent			
Sapphire			
Hotel			
Cave			
Opal			
Tiger			
Pearl			
Cow			
Hut			
Number Correct:			

Trial 4-Recognition

HORSE	<table border="1"><tr><td>Y</td><td>N</td></tr><tr><td></td><td></td></tr></table>	Y	N			EMERALD	<table border="1"><tr><td>Y</td><td>N</td></tr><tr><td></td><td></td></tr></table>	Y	N			balloon	<table border="1"><tr><td>Y</td><td>N</td></tr><tr><td></td><td></td></tr></table>	Y	N			apartment	<table border="1"><tr><td>Y</td><td>N</td></tr><tr><td></td><td></td></tr></table>	Y	N		
Y	N																						
Y	N																						
Y	N																						
Y	N																						
house	<table border="1"><tr><td></td><td></td></tr></table>			mountain	<table border="1"><tr><td></td><td></td></tr></table>			boat	<table border="1"><tr><td></td><td></td></tr></table>			COW	<table border="1"><tr><td></td><td></td></tr></table>										
HUT	<table border="1"><tr><td></td><td></td></tr></table>			CAVE	<table border="1"><tr><td></td><td></td></tr></table>			dog	<table border="1"><tr><td></td><td></td></tr></table>			LION	<table border="1"><tr><td></td><td></td></tr></table>										
TENT	<table border="1"><tr><td></td><td></td></tr></table>			TIGER	<table border="1"><tr><td></td><td></td></tr></table>			HOTEL	<table border="1"><tr><td></td><td></td></tr></table>			PEARL	<table border="1"><tr><td></td><td></td></tr></table>										
ruby	<table border="1"><tr><td></td><td></td></tr></table>			SAPPHIRE	<table border="1"><tr><td></td><td></td></tr></table>			coffee	<table border="1"><tr><td></td><td></td></tr></table>			Penny	<table border="1"><tr><td></td><td></td></tr></table>										
OPAL	<table border="1"><tr><td></td><td></td></tr></table>			Cat	<table border="1"><tr><td></td><td></td></tr></table>			scarf	<table border="1"><tr><td></td><td></td></tr></table>			diamond	<table border="1"><tr><td></td><td></td></tr></table>										

Record 24 hour clock time trial 4 ended: _____

RTOG ID# _____

DATE: _____

Visit #: _____

MMSE Orientation

TIME	Response	SCORE	PLACE	Response	SCORE
Day of Week		<input type="checkbox"/> 0 <input type="checkbox"/> 1	Name of Place		<input type="checkbox"/> 0 <input type="checkbox"/> 1
Date		<input type="checkbox"/> 0 <input type="checkbox"/> 1	City/Town		<input type="checkbox"/> 0 <input type="checkbox"/> 1
Month		<input type="checkbox"/> 0 <input type="checkbox"/> 1	State		<input type="checkbox"/> 0 <input type="checkbox"/> 1
Year		<input type="checkbox"/> 0 <input type="checkbox"/> 1	County		<input type="checkbox"/> 0 <input type="checkbox"/> 1
Season		<input type="checkbox"/> 0 <input type="checkbox"/> 1	Floor		<input type="checkbox"/> 0 <input type="checkbox"/> 1

MMSE Items	Patient Response	MAX	SCORE
3 STEP Command	Right hand Folds ½ Place on Floor	3	
Repetition	NO IFS ANDS OR BUTS	1	
Close Your Eyes	Reads and follows command	1	
Write a Sentence		1	
Naming	Pencil Watch	2	
Copy Pentagons		1	<input type="checkbox"/> 0 <input type="checkbox"/> 1

Results must be recorded on the MS Form found in the RTOG Forms Packet

ADMINISTER 2&7 TEST to the patient

ADMINISTER POMS Short Form to the patient

Give patient a 5-10 minute break (can use this time to review answers to POMS)

ADMINISTER HVLIT DELAYED RECALL

ADMINISTER Trailmaking Tests A and B

ADMINISTER Verbal Fluency (COWAT)

RTOG ID # _____

DATE: _____

Visit #: _____

2&7 TEST Practice

The 2 and 7 Test

2	G	O	X	C	7	M	J	7	H	Z	R	N	G	A	S	2	Y	W	Q	2	L	H	B	Z	G	J	N	V	7	E	T	2	P	R	V	M	J	H	S	T	Q	2	C	7	K	L	W	C	7
X	M	T	7	K	T	R	2	A	V	P	I	W	O	C	2	G	J	7	L	S	2	B	N	V	W	7	T	O	X	R	2	P	H	7	F	D	A	B	M	2	W	H	K	A	S	T	2	O	P
H	W	E	D	2	T	R	N	E	Q	X	2	P	K	L	7	P	K	7	Z	C	V	7	2	Z	7	E	T	G	H	L	K	S	D	I	N	7	S	2	W	I	S	N	7	T	B	M	O	P	W
3	1	0	7	8	9	4	4	7	0	5	3	7	6	3	8	1	5	2	3	6	5	6	9	7	0	8	9	1	5	7	8	4	3	6	2	8	6	3	2	8	6	1	5	4	2	8	0	9	1
2	9	1	8	9	2	8	1	3	7	6	4	5	3	7	8	0	4	6	7	9	6	2	9	1	2	8	3	9	1	8	3	7	8	9	4	6	5	9	1	4	7	0	8	6	7	1	3	0	3
9	1	0	2	3	3	8	9	4	1	2	6	5	5	3	5	7	6	8	9	5	7	0	5	9	6	1	7	3	2	8	5	9	2	8	3	1	2	8	3	3	1	4	3	8	9	4	6	2	5

RTOG ID# _____

DATE: _____

Visit #: _____

2&7 TEST

6 5 1 4 7 0 3 3 5 7 3 0 5 8 2 6 0 3 7 5 8 6 2 6 2 4 9 3 1 5 6 3 0 8 9 4 2 4 7 8 1 3 6 1 7 9 1 2 8 9
 0 3 8 1 4 7 3 2 8 3 9 8 4 3 2 7 1 8 6 7 1 5 8 7 1 8 5 3 2 0 0 5 1 6 7 9 1 3 4 1 1 5 3 5 2 9 4 2 1 4
 6 4 2 8 3 0 6 7 9 0 2 9 5 1 5 0 5 7 6 3 3 7 5 8 5 8 0 9 4 7 5 8 3 4 7 0 8 9 5 4 6 3 7 0 3 9 2 3 7 3

C S O 7 S C W Y 7 Z C R I 2 Y P L W 2 O S Y 7 C 2 H M X C W T M A 2 E J 7 H B 2 B M C P C R U 2 D N
 W P J 2 E H X Y B S 7 E T Y X B M P 2 H 7 J T 2 C K L L Q 2 O T L C H G 2 Z U Y Z 7 X C V 7 I B R 7
 P F 2 N W M O 7 C C H J 2 M W I O P S 7 T D K L 7 U I D S 2 L I O C F 7 D O W M S 2 D W Q 7 C H 2 T

C G H F P I T R A C M W 7 E W S 2 S L Y M Q 7 Y O X T P Q 7 D K 2 C K V 2 N Y 2 P N 7 C H L 7 2 P S
 J H S Y O 7 B L U D 7 I H 2 K Y T 7 G S Q P 7 L V C K 2 S C 3 Z P Y Z W U 7 X U L 2 M X R 2 Z W M O
 U P 2 S P T O X Y B 7 L U 2 Z E I R N K J 2 S P X Z Y L 7 D T P Y 7 V P W X 7 L 2 E V 7 I 5 X Y 2 D

5 7 0 3 3 5 5 6 4 5 9 7 5 2 5 6 3 0 7 1 9 1 2 1 5 3 2 3 1 9 7 4 1 4 0 6 8 9 8 7 3 5 2 4 6 5 5 0 3 2
 0 6 7 6 9 2 0 1 4 8 4 2 6 4 5 5 7 3 0 9 1 2 4 6 8 7 3 1 8 5 0 4 6 6 1 0 9 3 2 1 7 4 4 6 3 7 9 2 8 1
 0 3 2 9 1 0 9 1 4 2 8 9 4 1 4 0 2 6 8 7 7 8 4 3 1 9 9 8 0 2 4 6 5 3 9 1 4 3 7 1 0 7 4 5 9 2 6 4 7 1

7 3 0 9 9 3 4 1 5 9 7 3 1 2 4 8 3 4 5 0 9 1 4 7 9 0 4 3 1 2 0 4 2 4 3 3 5 9 3 2 1 7 8 3 2 9 4 0 1 3
 2 4 7 0 1 9 7 8 3 3 0 9 1 3 4 7 4 3 9 2 8 1 7 0 0 7 3 1 2 9 8 2 8 4 4 3 1 0 3 8 4 2 4 0 2 1 0 9 8 4
 6 7 9 8 8 1 5 6 8 7 1 9 3 9 3 8 3 9 2 3 7 2 1 6 3 6 1 2 9 0 3 7 8 8 3 2 7 1 0 8 8 3 1 3 0 4 3 2 4 1

Y G S I S Q W 7 Z 2 J 7 X U T 7 T O E U 2 W L I Y R F H V C Q P I H 1 7 O T H 2 7 F M 2 S L A R J 2
 P 7 W E B S Y T 7 V M H W Q G 7 D 2 L N E J P 7 R C F 2 S 7 S G 2 L W X P X B R I C M 2 C 7 I W T R
 X D Z Y 2 8 C T 7 L I M T Y 2 S Q 2 X C E Y 7 W U J J E 2 K Y C V X 2 A R Y 7 L V B I Y 7 U Q T 7 J

5 5 9 0 1 3 9 4 6 4 2 0 0 3 1 2 3 4 6 9 7 0 2 1 2 7 8 9 2 4 6 7 7 0 3 1 8 0 0 5 3 7 8 1 9 4 3 0 1 8
 9 9 2 3 2 0 3 2 1 4 0 9 3 2 6 3 7 8 0 9 1 4 6 4 5 7 6 4 0 6 1 4 4 8 2 0 9 7 8 7 6 4 3 9 8 1 4 7 4 3
 4 7 3 1 0 9 3 1 8 7 4 1 2 5 9 6 3 7 2 2 4 6 4 9 8 2 1 0 7 9 5 7 8 5 6 0 9 5 2 5 1 4 2 0 3 3 9 0 1 8

2 F J I A S 2 W 7 N B V 7 X B N R 2 O P E 7 C H I O 2 T R P P O Y L R W 2 V 7 D L F L R 7 X F T K Y
 P T B R U 7 Q 5 B Y H J K W 7 B 2 R 7 F Y W 7 I M D O X 7 M N 2 G 7 I J L 2 T N 7 C S H I E S K P F
 7 G R O E 1 7 T R P X 2 F J K 2 T R P N C X N 2 R 7 L I B 2 G R O Y D 2 O E U 2 X P K 2 W E D E Z A

2 C H I K I 7 P L T W N Y B 2 Z Q X 0 2 N E 7 M 2 T Y 2 S K S Z Q Y R S 2 K I E D C I O A 7 P L W 7
 M Y P Z 7 U W E O R 7 S 1 2 A S B 1 7 Q P 2 F G H H W O P W 2 Z V T E 7 H L I 2 U H G 7 X C H V 7 J
 H J U 2 K S W G 2 J P O 7 Q R 1 2 8 P J H G 7 E E S Q 2 V P L S 7 M S 2 N V X Z U Q F 2 F Y 7 V E O

6 9 7 3 2 6 8 4 4 2 8 9 1 1 9 5 2 9 6 7 8 3 4 9 8 1 8 2 4 9 7 6 4 0 2 9 8 4 4 0 1 7 3 9 2 0 8 7 3 1
 3 8 1 2 9 4 8 9 3 7 3 6 6 2 8 1 7 6 5 3 2 6 3 9 3 6 5 4 7 3 8 1 8 2 4 9 5 2 0 6 1 7 3 0 2 4 9 4 6
 8 3 9 8 7 6 1 3 9 8 7 1 4 8 6 5 9 2 0 4 4 8 2 3 1 6 7 4 2 1 6 0 0 2 9 5 2 4 6 9 1 7 9 0 9 7 8 9 3

RTOG ID # _____

DATE: _____

Visit #: _____

2&7 TEST

3 6 6 9 2 5 8 5 0 2 3 5 3 8 0 1 8 9 2 1 7 6 5 3 3 0 4 2 9 5 5 1 7 8 9 5 7 3 4 0 8 5 9 2 3 4 0 7 8 8
3 2 3 3 7 9 5 1 2 5 0 5 1 6 6 1 1 0 3 4 2 4 8 0 5 3 8 7 6 4 3 3 0 8 7 3 2 1 1 9 6 5 3 7 0 9 7 4 2 3
5 3 9 2 1 0 3 2 4 6 9 7 3 1 6 5 1 7 0 0 9 5 3 4 9 3 4 2 7 4 7 4 8 8 4 2 1 4 1 9 2 1 5 2 3 5 9 0 1 4

G U V Q P S T 2 X G 7 H W Q S 2 H J 2 I C 7 O 2 P E C Y Z 7 A P W 7 K D N I U M 7 E C V H D T 2 O C
K Q 7 X A S B I O 7 P F H M 2 N Y 2 X J H 2 E E S V P L S M N V 7 X L K A 2 P T 7 K J C 2 C 7 E G P
R R T 7 Z X C N 2 T Y F 7 F Y K A S U M 2 D 7 J H 2 Y Y I E 2 G W O P M D K D 7 U Q F I 7 O E I Z 7

7 1 3 0 4 9 2 1 7 8 2 9 4 3 1 7 4 4 1 0 9 8 7 3 2 3 1 6 6 0 9 1 4 8 5 7 6 3 5 1 7 9 4 8 1 2 4 1 3 9
2 9 5 9 8 3 6 2 5 6 0 1 3 0 8 6 5 4 7 4 3 1 8 2 3 4 1 7 3 6 9 9 2 1 7 3 0 0 3 4 2 0 8 9 2 3 9 7 4 1
0 9 1 2 4 0 7 1 1 4 6 5 3 7 1 9 0 4 5 2 3 5 7 9 8 7 1 2 0 8 2 8 4 8 6 7 3 8 9 0 1 8 4 0 7 3 9 8 1 0

X H P S Q 2 E B M W E S 7 P O C 2 X 2 S E I P V 7 E T Y P B N 7 L P A B 2 V P W 7 M 2 M E 7 S R P Z
I K H 7 P R X B R C M N Y T C 2 A R 7 S 7 C 2 H L T 2 O C Y 7 H L W 2 E X Z 7 T L P B 2 W L Q Y A B
Y 2 N S N T S L 7 E W 7 G P X 2 T V N I S 7 P L K R C N U S A P T R A 7 G H 2 J K 2 J C G 7 Q P J 2

I W R Y Q Z 2 E B W O I 2 H L 7 L V B W M N R 7 S T U E Y L D Q M 2 X 7 Z 2 C G Y T 7 D 2 A P I 2 G
B Y D Q 2 P F U F Y 7 E I Y L A Z T 7 2 E H J 2 J R K 7 2 R N 7 S U S W 7 P C X 2 1 E J G H T M V Z
S 2 B T E I 7 X 2 U Q E Y I P A 7 D G J L Z C B 7 G J D A S G L E C 7 N I 2 W C 7 T M 2 L P A Q 2 S

8 6 8 2 1 2 1 9 6 0 1 6 4 5 3 7 1 0 4 1 9 6 7 9 9 6 5 3 0 4 2 4 7 2 8 7 8 4 8 7 3 5 2 3 0 8 8 9 4 5
2 6 8 9 7 8 1 7 3 8 5 5 8 2 6 8 7 6 8 5 0 6 5 5 1 2 4 8 2 1 9 5 3 7 6 5 3 9 7 9 0 5 6 6 1 8 4 3 2 8
7 0 9 5 1 6 7 9 4 3 4 7 1 9 9 4 8 2 5 9 1 5 2 5 4 7 0 8 3 9 5 1 5 0 5 2 6 3 3 5 3 2 5 8 1 7 9 5 0 7

U 7 W R S F D 7 F H R V C 7 2 R E Y I 2 A H S H J 2 D E 7 B E R N I M W 7 P I Y 2 P E J G H 7 O Q W
W P U N O 2 H F G Z H 2 H J L 2 S L Q 1 7 E U C 7 N E J D R U S S 7 L K Y 2 P F S T A 2 1 7 1 2 B T
M T O V 2 B 7 S T 2 K E U 2 L X C V Q 1 T 2 X Z P I G O L 2 W T C 2 M Q 7 Z C X O Y 1 7 W S 7 A V W

0 0 1 4 5 7 6 8 8 7 3 5 8 2 1 8 9 3 4 4 7 8 4 0 9 1 8 7 3 1 5 9 0 7 3 8 9 8 2 4 5 6 0 7 0 1 7 2 1 4
3 2 5 6 1 3 0 7 8 3 2 8 1 4 6 5 2 6 6 4 0 0 7 1 4 6 9 2 9 6 6 4 3 1 2 9 5 8 7 1 2 0 0 4 8 3 0 1 2 9
2 5 6 8 9 1 4 9 3 0 7 0 1 2 4 4 5 3 8 9 5 0 2 1 1 4 2 8 0 1 8 3 7 4 8 1 9 2 1 3 6 9 0 7 4 3 7 9 8 7

H M W I O P S 2 T G H W V J K 7 S 2 D R U 7 U N K S 7 A R H C F I 7 P W B X O 2 A 7 G 7 E S 2 P N X
Q I H J W 2 I C R K 2 R R P S K J 7 N S C 2 N I Q O X V U 7 E S T F 7 I 2 P O L 2 U Y 7 C X 7 Z A E
L 2 U E U 2 L W O 7 F J D 7 I D S O 7 N B X N S 3 B I 7 F 2 K A R R 7 O A W 7 C K B E S O T W I Y D

2 1 3 1 4 7 9 6 6 5 7 4 1 0 2 0 4 3 5 5 8 1 4 3 3 8 4 7 9 3 6 8 2 1 0 3 2 5 5 1 2 8 9 0 3 4 2 5 1 6
4 5 1 3 5 8 8 9 2 3 3 6 1 4 7 5 6 2 4 3 7 0 5 4 1 1 0 0 7 9 3 9 7 6 8 5 2 3 1 2 1 3 2 9 0 1 7 5 6 8
0 0 1 8 7 9 3 4 5 2 3 6 1 0 7 8 3 9 1 4 8 4 5 6 7 9 3 9 3 1 6 0 6 4 7 8 9 0 7 0 2 9 8 1 7 3 2 8 9 8

Instructions for Administration of Mini-Mental Status Examination (MMSE)

The Mini-Mental Status Exam could be administered by the physician, a nurse or an assistant trained in the administration of such tools. The person administering the Mini-Mental Status Exam needs to be sensitive when the patient shows embarrassment about their inability to answer these questions. Patients should be assured by telling them that this is another way of telling how the treatment is affecting their brain tumor. It also needs to be made clear to the patient that it is very important to get this type of information directly from them. The person administering the test needs to understand that either the correct answer is given or not. There should be no partial credit for answers short of the mark.

The MMSE begins with a graded assessment of orientation to place and time, for which a maximum of 10 points is possible. This is followed by testing two aspects of memory. The first is the immediate recall for three objects presented orally, followed by a serial sevens task which is interposed to assess attention, concentration, and calculation, and also to prevent the individual from rehearsing the three objects previously learned. A maximum of 11 points may be obtained in this section of the test.

The final section surveys aphasia by testing functions of naming, repetition, understanding a three-stage command, reading, writing and copying a drawing. There is a maximum of 9 points which may be obtained on this section, for a total possible MMSE score of 30 points.

1. Orientation

1. Ask for: the year, season, date, day, month. Then ask specifically for parts omitted, e.g., "Can you also tell me what season it is?" One point for each correct.
2. Ask in turn, "Can you tell me the name of this department?" (state, county, town, hospital, floor.) One point for each correct.

2. Registration

Ask the patient if you may test his memory. Then say the names of 3 unrelated objects, clearly and slowly, about one second for each. After you have said all 3, ask him to repeat them. This first repetition determines his score (0-3) but keep saying them until he can repeat all 3, up to 6 trials. If he does not eventually learn all 3, **recall** cannot be meaningfully tested.

3. Attention and Calculation

Ask the patient to begin with 100 and count backward by 7. Stop after 5 subtractions (93, 86, 79, 72, 65). Score the total number of correct answers. If the patient cannot or will not perform his task, ask him to spell the word "world" backward. The score is the number of letters in correct order, e.g., dlrow=5, dlrow=3.

4. Recall

Ask the patient if he can recall the 3 words you previously asked him to remember in the registration section. Score 0-3.

5. Language

NAMING: Show the patient a wrist watch and ask him what it is. Repeat for pencil. Score 0-2.

REPETITION: Ask the patient to repeat the sentence "No ifs, ands, or buts" after you. Allow only one trial. Score 0-1.

Instructions for Administration of Mini-Mental Status Examination (MMSE)

3 STAGE COMMAND: Give the patient a piece of plain blank paper and ask him to follow your instructions: "Take the paper in your right hand, fold it in half and put it on the floor." Score 1 point for each part correctly performed.

READING: On a blank piece of paper, print the sentence, "Close your eyes," in letters large enough for the patient to see clearly. Ask him to read it and do what it says. Score 1 point only if he actually closes his eyes.

WRITING: Give the patient a blank piece of paper and ask him to write a sentence for you. Do not dictate a sentence. It is to be written spontaneously. It must contain a subject and a verb and be sensible. Correct grammar and punctuation are not necessary.

COPYING: On a clean piece of paper, draw two intersecting pentagons, each side about 1 inch, and ask him to copy it exactly as it is. All 10 angles must be present and 2 must intersect to score 1 point. Tremor and rotation are ignored.

Estimate the patient's level of sensorium along a continuum, from alert on the left to coma on the right, by drawing a vertical line at the appropriate point in the horizontal line. Record the coded assessment.

SPECIAL CONSIDERATIONS

The examination is conducted so as to minimize stress for the patient. Errors are not indicated to the subjects and, in general, mistakes are not corrected. Refusals are considered to be errors after a minimum of encouragement. Individuals with peripheral impairment such as blindness or restriction of the hands due to arthritis or other peripheral disorders are scored the number correct out of the possible items they could answer given their other noncognitive impairments. Please note these exceptions on the MMSE form. It is important not to allow your administration of this test to be affected by your perception of why the patient may have responded incorrectly or not at all. That is, the examination should be conducted without the examiner modifying the scoring by assumptions of whether or not the individual was motivated, paying attention, or could understand. For the purpose of the exam, the score indicates a failed performance, not necessarily a failed performance under all conceivable circumstances.

Spencer MP, and Folstein MF. The Mini-Mental State Examination. In: PA Keller and LG Ritt (Eds). Innovations in Clinical Practice: A Source Book. Vol 4. Sarasota, FL: Professional Resource Exchange, Inc., 307-308, 1985.

APPENDIX V

Certification Worksheet for Test Administrator

RTOG BR-0018

**A FEASIBILITY STUDY OF NEUROCOGNITIVE EVALUATION IN PATIENTS
TREATED FOR BRAIN METASTASES**

This worksheet must be completed and signed by the person requesting certification and submitted to Dr. Schmitt prior to the registration of any patients to RTOG BR-0018. Refer to protocol Section 11.3 for details.

- _____ (Y/N) 1. Have you attended a Neurocognitive Assessment Training Workshop at an RTOG meeting? If yes, date? _____
- _____ (Y) 2. If you have not attended a training session, have you watched the Neurocognitive Assessment Administration video available from RTOG Headquarters? *(fax request to 215-574-0300)*
- _____ (Y) 3. Have you reviewed the Neurocognitive Assessment Administration Instructions and Procedures in Appendix IV of the protocol?
- _____ (Y) 4. Have you completed the two "practice" Neurocognitive Assessments discussed in Section 11.3.3 of the protocol?

Signature of test administrator _____
Date
(person who performed "Practice" Neurocognitive Assessments and attended training session or watched video)

Printed name of test administrator _____
RTOG Institution number/Name

Telephone number of test administrator _____
Fax number of test administrator

If you have any questions regarding the certification, please contact Dr. Schmitt. Once you have completed this form, please attach the Neurocognitive Assessment forms from both "practice" individuals and submit along with the audiotape to:

Frederick A. Schmitt, Ph.D.
University of Kentucky
Department of Neurology
L445 Kentucky Clinic
Lexington, KY 40536-0284
Phone: (859) 323-0229 or (859) 257-1412 ext. 322 (research assistants)
e-mail: fas_com@coa.uky.edu

For Dr. Schmitt's Use Only <i>(to fax to 215-574-0300, RTOG HQ)</i>	
_____ (Y/N)	The above individual has been certified for administering the neurocognitive assessments for this study.
Signature _____	Date _____