

North Central Cancer Treatment Group

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

Addendum 1 – July 6, 2007

Summary

Scientific Changes:

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

Administrative/Editorial Changes:

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

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

Title page

Reflects the addition of Addendum 1 and revised NCI version date.

The phone number for the NCCTG Study Chair has been updated as follows:
507/284-2511 **3559**

NCI Version Date has been updated.

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

ECOG

Co-chair: Lawrence Kleinberg, M.D.

RTOG

Co-chair: Anthony L. Asher, M.D.

Protocol Resource Page

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

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

Marcia Salayi
NCCTG *Research Base* Nurse
Phone: 507-284-2459
Email: salayi.marcia@mavo.edu
Beverly L. Kowbel
NCCTG Member Nurse
Phone: 306-766-2681
Email: bev.kowbel@scf.sk.ca

Cancer Trials Support Unit (CTSU) Address and Contact Information

Page 4: The first sentence under the section “Patient Eligibility or Treatment Related Questions” has been corrected as follows:
Contact the NCCTG Quality Control Specialist (listed under NCCTG Contacts **below on page 3**).

Index Page

Page 5: Title of Appendix VI revised as follows to match form:
Neurocognitive ~~Evaluations~~ **Booklet** Submission Fax Form

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

~~Appendix VII – Neurocognitive Booklet Order Form~~

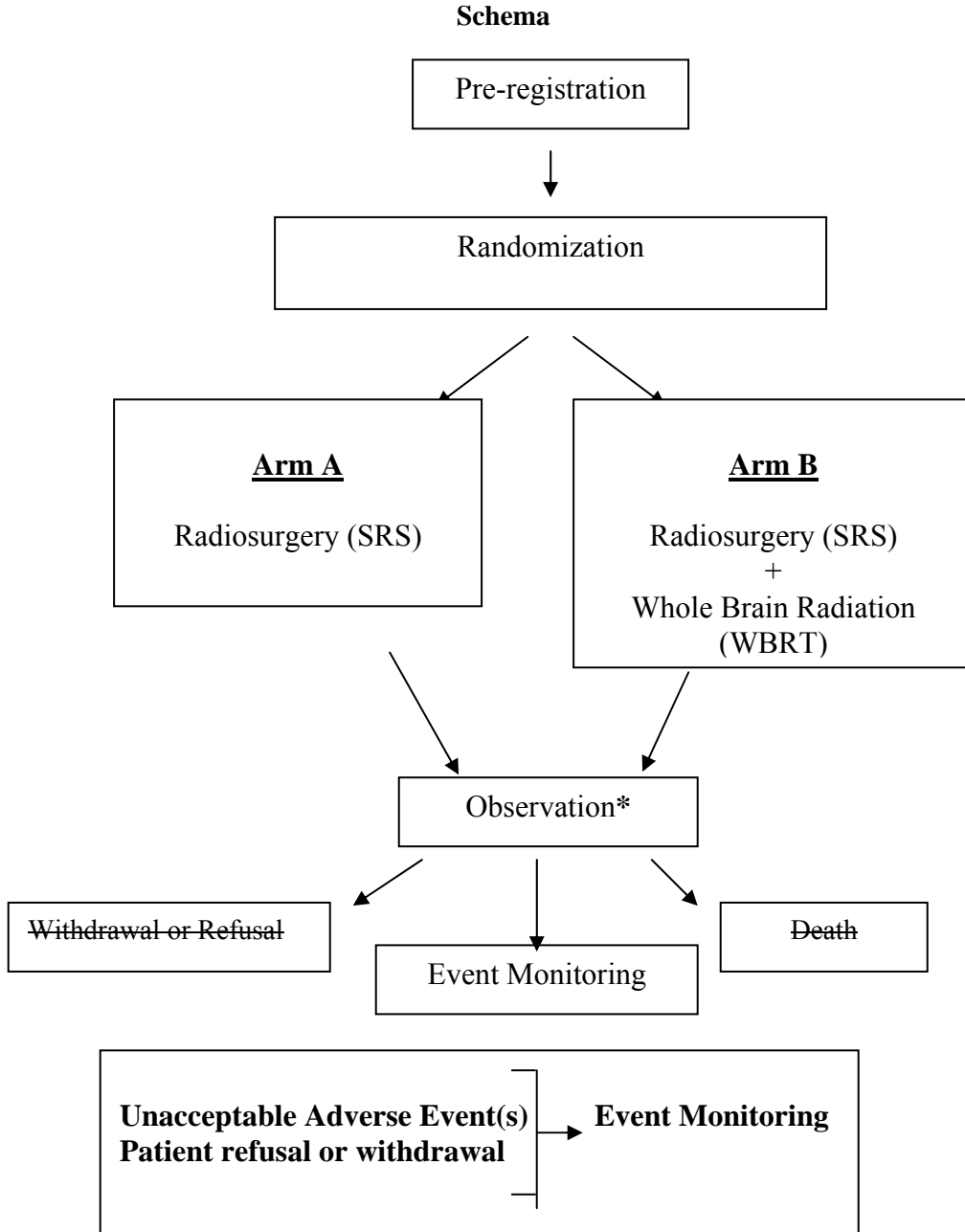
Title of Appendix IX revised as follows to clarify that the appendix contains the Neurocognitive examiners booklets and the Patient completed booklets:

Neurocognitive Practice Forms (**Neurocognitive Examiners and Patient Completed booklets**)

Schema

Page 6:

The following revisions have been made to the schema in order to comply with our current templates:



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

Section 3.0**Patient Eligibility**

Page 12:

Link corrected for Section 3.116 as follows:

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

Section 3.118 is newly added for clarification as follows:

SRS facility is RPC approved (see Section 6.1).

Page 13:

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

Planned chemotherapy during the SRS and WBRT.**Section 4.0****Test Schedule**

Page 14:

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

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

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

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

Footnote #7 has been corrected as follows:

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

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

Page 15:

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

This training is found on the NCCTG website, at <https://ncctg.mayo.edu/ncctg/group/> under “Disciplines,” then under the “CRA page.”

Page 16: The following note has been added to the end of Section 6.1 to insure clarity of the certification requirements for Neurocognitive testing:

Notes:

- **An individual certification does not certify an entire institution. If more than one individual wants to administer the Neurocognitive test, each individual must be certified.**
- **The individual registering the patient does not have to complete the neurocognitive credentialing component unless they intend to be an examiner HOWEVER patients cannot be registered to the study until at minimum one person from the institution is approved for credentialing.**

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

Grooved peg board available for Neurocognitive testing.

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

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

<http://www.usmedicalsupplies.com/productSearch.do?=&grooved&n=20>

http://www3.parinc.com/products/product.aspx?Productid=GROOVE_PEGB

http://www.rehaboutlet.com/dexterity_hand_eye_coordination_tests.htm)

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

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

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

Section 7.0

Protocol Treatment

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

7.13 Chemotherapy is not allowed during the SRS and WBRT.

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

Radiosurgery for patients on this protocol can only be performed at RPC approved facilities. See protocol section 6.1 for details.

Page 18: The following new statement has been added to Section 7.221 to clarify that pinless systems may now be included in this protocol:
Modality: Gamma knife or X-rays with nominal energy of 4 megavoltage (MV) or greater for accelerator-based treatments, including mini-multi-leaf technology **or linear accelerators mounted on robotic arms utilizing skull tracking software.**

Page 20: The following opening statement has been added to Section 7.3 to clarify which facilities may be used for radiation therapy:
Radiation therapy for patients on this protocol can only be delivered at facilities which are approved by your cooperative group.

Page 20: A typographical error has been corrected in the “Note” statement in Section 7.3 as follows:
Note: For patients randomized to Arm B: SRS and WBRT, ~~the~~ initiation of WBRT is ≤ 14 days following SRS.

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

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

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

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

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

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

The first sentence of Section 8.2 has been revised for clarification as follows:
Prior to intervention and at the beginning of each scheduled study visit, the ~~study doctor~~ **treating physician** or his/her authorized designee...

Page 22: The contact information in Section 8.2 has been updated as follows:

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

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

8.3 Neurocognitive Status **Tests**

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

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

Section 10.0

Adverse Event (AE) Reporting and Monitoring

Page 25:

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

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

~~1. Hypersensitivity to the local anesthetic.~~

Section 11.0

Treatment Evaluation/Imaging Guidelines

Page 26:

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

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

Section 11.3 has been revised for clarification as follows:

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

Page 28: The contact information in Section 11.9 has been updated as follows:

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

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

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

Section 13.0

Treatment in the Event of Recurrent Cerebral Metastases

Page 28:

The last sentence in Section 13.1 has been revised for clarification as follows:

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

Section 15.0

Nursing Guidelines

Page 29:

Section 15.111 has been revised as follows as this is also stated in Section 15.211:

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

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

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

Section 16.0

Statistical Considerations

Page 31:

Typographical errors were corrected in the third sentence of Section 16.22 as follows:

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

Page 31:

Correct reference added to Section 16.23 as follows:

Three formal interim analyses will be performed at the time at which 25%, 50%, and 75% of the projected total number of events have occurred using a O'Brien-Fleming type stopping boundary (**O'Brien, 1979**~~ref~~), truncated at -3.5.

- Page 32: The first and second sentences in the first paragraph of Section 16.4 have been revised as follows:
- The primary QOL objective is to ascertain at 3 months (**12 weeks**) post-treatment whether patients assigned to Arm 1 (SRS) have better QOL than patients on Arm 2 (SRS + WBRT).
- The potential side effects of the additional WBRT treatment (e.g., fatigue, alopecia, cognitive decline, and diminished hearing) suggest the combination Arm 2 ~~has worse~~ **will have reduced** QOL.
- Page 32: Editorial changes to Section 16.4, second, fourth, fifth and sixth paragraphs as follows:
- The QOL will be assessed at baseline (prior to randomization), at weeks 6, ~~week~~ and 12, **and at** months 6, ~~month-9, month-12, month-16, month-24, month-36, month-48~~ -and ~~at month~~ 60 -(essentially QOL will be obtained out to 5 years after the completion of the SRS treatment).
- Exploratory Generalized Estimating Equations (GEE) analysis [Horton 1999] will be used to investigate the effect of treatment over time, incorporating baseline and follow-up visits to 12 months, as well as the correlations \leq within a patient's data over time.
- The **Quality-Adjusted Survival (QAS)** analysis will adjust each patient's time on study, by weighting neurological signs and symptoms (a variety of weighting schemes will be explored); the resultant weighted sum is defined as the patient's QTIME. Subtracting the impact of AEs and re-treatment gives the QAS ~~subtracting QAS value~~ for each patient [Murray 1995]. The QAS values will be compared between treatment arms by the two-sample t-test.
- Functional Independence: The duration of functional independence, where Barthel ADL Index score is maintained **at or** above baseline level, will be compared between treatment **arms** by the logrank test.
- Page 33: Section 16.5. Editorial revision for clarification as follows:
- Physician-assessed ratings of neurological signs and symptoms and treatment adverse events will be tabulated, descriptively, by treatment **arm**.
- A new Section 16.7 has been added in accordance with the requirements of the Data Monitoring Committee (DMC) as follows:
- In accordance with NCI's current DMC policy, the NCCTG External Data Monitoring Committee will meet every 6 months in conjunction with the NCCTG semi-annual group meetings to review the progress of this protocol.**
- A new section heading has been added before the ethnic table as follows:
- 16.8 Inclusion of Women and Minorities**

Section 18.0**Records and Data Collection Procedures**

Page 34:

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

Section 18.1, title of form revised as follows:

Neurocognitive ~~Evaluation~~ **Booklet** Submission Fax Form

Page 35:

Section 18.1, the contact information in Footnote #1 and 1g have been updated as follows:

For patients who receive partial or complete radiation therapy, submit the following materials ≤14 days after the last day of radiation to **the NCCTG Operations Office**, Radiation Coordinator, ~~Cancer Center Statistics~~ **RO_FF_03_24-CC/NW** Clinic, 200 First Street SW, Rochester, MN 55905.

g. Copies of pre-registration and planning contrasted MRI brain scans

Note: When films are submitted on CD(s), they must include a viewing tool.

Section 18.1, the second sentence in Footnote #3 has been revised for clarification as follows:

Images on CDs are preferred to film but must be DICOM compatible **with a viewing tool.**

Appendix I**Consent Form**

Page 2:

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

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

Under the “Whole Brain Radiation Therapy” section, the following revision has been made to the first paragraph, last sentence as requested by the Adult CIRB:

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

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

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

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

Localized hair loss

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

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

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

Dry mouth

Taste changes

Temporary ear and ear canal redness

Page 4 Under the “Reproductive risks” section, revised as follows for clarification:
Therefore, pregnant women may not participate in the study. If you are a woman who can become pregnant, a urine or blood pregnancy test will be done within 7 days prior to radiosurgery. ~~(using~~ **If the pregnancy test is done using blood, approximately 1 teaspoon of blood will be drawn from a vein by needle-stick).**

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

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

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

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

This is to ensure that no one will be able to tell that you took part **in this study**.

Page 6: The bullet items under the “WHAT ABOUT CONFIDENTIALITY” section have been revised for better readability as follows:

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

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

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

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

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

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

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Appendix II CANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES

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

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

~~These peg boards can be purchased for approximately \$105.00 at the following web address:~~
<http://www.ausmed.com/medecat/rs/ecatalog/details.asp?productid=10225A>

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

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

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

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

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

Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 ~~between the hours of 9:00 a.m. and 7:00 p.m., Mon-Fri, Eastern Time (excluding holidays).~~

Under **CTSU Procedures for Patient Randomization (Step 2)**, the following note was revised as requested by CTSU

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

Appendix V Administration of Neurocognitive Evaluations Instructions

Page 1:

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

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

Page 2:

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

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

It is very important that the person administering the neurocognitive tests fax ~~in~~ a completed Neurocognitive ~~checklist~~ Booklet **Submission Fax Form (Appendix VI)** indicating who administered the tests with the appropriate contact information.

Appendix VI Neurocognitive Booklet Submission Form

Page 1:

Title revised and moved to top of page as follows:

Neurocognitive Booklet Evaluation Submission Form

Additional editorial/administrative changes:

- Added: **Fax completed form to:**
- Changed: ~~To:~~ Elana Farace, Ph.D.
- Changed: ~~(Fax) #~~ 717-531-0748
- Changed: Re: Neurocognitive Booklet Submission Form
- Changed: Attention: ~~The~~ 2 Neurocognitive booklets (**Examiners and Patient completed**) have been sent to you via **surface** mail, as of _____ (date).
- Added: **Patient's study ID #:**

Appendix VII Neurocognitive Booklet Order Form

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