STATUS PAGE

PROTOCOL **10-026**

Closed To New Accrual

Closure Effective Date: 03/01/13

No new subjects may be enrolled in the study as described above. Any questions regarding this closure should be directed to the study's Principal Investigator

DANA-FARBER CANCER INSTITUTE
DANA-FARBER / HARVARD CANCER CENTER

Office for Human Research Studies

Protocol Front Sheet

DFCI Protocol No.: 10-026

1. PROTOCOL TITLE AND VERSION

Title: Neurobehavioral Functioning and Utilization of Special Education Services in Pediatric Brain and CNS Tumor Patients after Proton Radiation Treatment: A Longitudinal Study

Protocol Version No./ Date: 4/25/11 **Sponsor Study Number:**

2. DF/HCC STUDY CONTACT INFORMATION

Study Contact for Questions: Margaret Pulsifer, Ph.D. **Email:** mpulsifer@partners.org **Phone:** 617-726-9116

OVERALL AND SITE RESPONSIBLE INVESTIGATORS (List only those under DFCI IRB, *i.e.*, from institutions listed in Section 6 below)

Overall PI:	Margaret Pulsifer, Ph.D.	**Phone:**	617-726-9116	**Institution(s):**	MGH
Site Responsible PI:	Margaret Pulsifer, Ph.D.	**Phone:**	617-726-9116	**Institution(s):**	MGH

3. DRUG / DEVICE INFORMATION N/A:

Drugs, Biologics, Devices (name & IND/IDE#): N/A
IND/IDE held by: N/A (Check if IND/IDE exempt: ☐)
Drugs, Biologics, Devices Provided by: N/A

Investigational Drug Brochure (IDB) Version No./ Date: N/A
(Check if already on file with OHRS:☐)

4. PROTOCOL COORDINATION, FUNDING, PHASE, MODE, TYPE ETC.

Protocol Coordinated By:
DF/HCC Investigator

Cancer Related: Yes If yes:
Primary Disease Program:
Pediatric Oncology
or
Primary Discipline Based Program:
Outcomes Research

Funding/Support (check all that apply)**:**
☐ Industry:
☒ Federal Organization: NCI- ended 9/2011
Grant #: 215475- ended 9/2011
☐ Internal Funding:
☐ Non-Federal:
☐ Other:

Phase: N/A

Multi-Center (i.e., non-DF/HCC site participation)**:**
No

Protocol Type: Observational: QOL
If Ancillary, provide parent protocol #:

Protocol Involves (check all that apply as listed in the protocol document, even if not part of the research but is mandated by the protocol document)**:**

☐ Chemotherapy	☐ Hormone Therapy	☐ Medical Record Review
☐ Immunotherapy	☐ Vaccine	☒ Questionnaires/Surveys/Interviews
☐ Surgery	☐ Data Repository	☐ Radiological Exams
☐ Bone Marrow/Stem Cell Transplant	☐ Exercise/Physical Therapy	☐ Required Biopsy Study
☐ Cell Based Therapy	☐ Genetic Studies	☐ Human Embryonic Stem Cell
☐ Gene Transfer (use of recombinant DNA)	☐ Human Material Banking	☐ Other:
☐ Radiation Therapy	☐ Human Material Collection	

5. SUBJECT POPULATION (also applies to medical record review and specimen collection studies)

Total Study-Wide Enrollment Goal: 225 **Greater than 25% of the overall study accrual will be at DF/HCC:** ☒ Yes ☐ No

Total DF/HCC Estimated Enrollment Goal: 225 **Adult Age Range:** 18-25 **Pediatric Age Range:** 2-17

Will all subjects be recruited from pediatric clinics? ☒ Yes ☐ No

If enrolling both adults and pediatric subjects, anticipated percent of pediatric subjects: 90

Retrospective Medical Record Reviews (Please provide date range): 2002-present

6. INSTITUTIONAL PARTICIPANTS UNDER DFCI IRB

Dana-Farber/Harvard Cancer Center: (check all that apply)
☐ Beth Israel Deaconess Medical Center
☐ Brigham and Women's Hospital
☐ Children's Hospital Boston
☐ Dana-Farber Cancer Institute
☐ Dana-Farber Cancer Institute at Faulkner Hospital
☐ Dana-Farber Cancer Institute at Londonderry Hospital
☐ Dana-Farber Cancer Institute at Milford Hospital
☐ Dana-Farber Cancer Institute at South Shore
☒ Massachusetts General Hospital
☐ Massachusetts General Hospital/North Shore Cancer Center
☐ Massachusetts General Hospital Radiation Oncology at Emerson Hospital

DF/PCC Network Affiliates: (check all that apply)
☐ Cape Cod Healthcare (Hyannis, MA; Mashpee, MA)
☐ Lowell General Hospital (Lowell, MA)
☐ New Hampshire Oncology-Hematology-P.A. (Concord, NH; Hooksett, NH; Laconia, NH)
☐ Newton-Wellesley Hospital (Newton, MA)

7. DF/HCC INITIATED STUDIES ONLY - INSTITUTIONAL PARTICIPANTS UNDER OTHER IRB (N/A:)

DF/HCC Multi-Center Protocols: (list institution/location)

DF/PCC Network Affiliates: (list institution/location)

Protocol Number: 10-026

Approval Date: 04/26/10 (IRB meeting date when protocol/consent approved or conditionally approved)

Activation Date: 06/01/10 (Date when protocol open to patient entry)

Approval signatures are on file in the Office for Human Research Studies, tel. 617-632-3029.

Date Posted	Revised Sections	IRB Approval Date
04/26/11	Front Sheet replaced and Study Renewal due to Continuing Review #1	04/25/11
04/24/12	Front Sheet replaced and Study Renewal due to Continuing Review #2	04/23/12
03/27/13	Permanent closure due to objectives/accrual met; Amendment #1 (Effective 03/01/13)	03/26/13
04/23/13	ON HOLD: All research must stop due to lapsed Continuing Review. Study approval expired 04/23/13.	N/A
04/29/13	ON HOLD Removed; Study renewal due to Continuing Review #3	04/07/13
04/04/14	Study Renewal due to Continuing Review #4	04/03/14
04/03/15	ON HOLD: All research must stop due to lapsed Continuing Review. Study approval expired	N/A
04/07/15	Remove Hold. Study renewal due to Continuing Review #5	04/02/15
04/04/16	ON HOLD: All research must stop due to lapsed Continuing Review. Study approval expired on 04/02/16	N/A
04/25/16	Remove Hold. Study renewal due to Continuing Review #6	04/09/16
Date Posted	**Revised Sections**	**Approved Date**
02/23/17	Study renewal due to Continuing Review #7	02/21/17
02/15/18	Study renewal due to Continuing Review #8	02/12/18
01/14/2019	Study renewal per Continuing Review #9	01/04/2019

SECTION 1: Protocol Schema

Brain tumor/ CNS tumor diagnosis →	Proton radiation treatment/ baseline neuropsychological evaluation at MGH	→	1 year or more post-treatment: ENROLLMENT IN THIS STUDY	→ Neurobehavioral outcomes via questionnaires

SECTION 2: BODY OF PROTOCOL

TABLE OF CONTENTS

1.0 INTRODUCTION

1.1 Overview

Radiation therapy is an important part of the treatment of pediatric brain tumors and Central Nervous System (CNS) tumors, but this treatment modality has long been associated with long-term neurocognitive sequelae. Proton beam radiation therapy is a relatively newer type of treatment that is expected to reduce radiation-related neurocognitive impairments.[1-2] However, there are few substantial studies of neuropsychological outcome, either at short or long term. The aim of this study is to examine neurobehavioral functioning (executive skills, emotional/behavioral functioning, and adaptive abilities) and use of special education services one year or more post-treatment in patients who received proton beam radiation therapy for the treatment of a brain tumor or CNS tumor. Participation will be maximized through the use of mail-in, standardized parental- and self-report questionnaires. Data from this study will enable a more extensive and longer-term assessment of the neurobehavioral sequelae of proton beam radiation therapy than has hitherto been published.

1.2 Background and Rationale

Radiation therapy is an integral part of therapy for pediatric brain tumors and CNS tumors. Although clinically effective, it is associated with long-term neurocognitive sequelae. Specifically, radiation therapy treatment for brain and CNS tumors is associated with neuropsychological deficits, particularly in children.[3-8] Radiation-linked impairments are especially serious in IQ, attention, information processing speed, and executive functioning, likely reflecting damage to white matter in the brain.[9-19] These impairments often become more pronounced with time, as different skills are required at older ages, involving increased attention and executive functioning, such as planning and organizational skills. Long-term studies of children treated with craniospinal irradiation have found that declines in the rate of learning have resulted in academic problems and increased need for special education services, with children under age 7 at treatment exhibiting the greatest problems.[20-22]

Proton beam radiation therapy is a relatively new type of radiation therapy that provides better targeting of tumors with a lower dose to nearby healthy tissue than conventional photon radiation.[1] It might therefore be expected that radiation-related neurocognitive impairments would be lower after proton radiation treatment compared to traditional photon radiation treatments.[1-2] However, there are few substantial studies of neuropsychological outcome, either at short or long term.

At the Massachusetts General Hospital (MGH) Francis H. Burr Proton Center, neuropsychological testing has been routinely conducted since September 2002 with children diagnosed with brain and CNS tumors and treated with proton radiation therapy. To date, 200 patients have received baseline testing. However, only 57 patients have returned for follow-up testing. The proposed study will examine change, if any, in neurobehavioral functioning and use of special education services one year or more post-treatment in those patients who received a baseline neuropsychological evaluation. This study will maximize participation through the use of mail-in, standardized parental- and self-report questionnaires.

The proposed study can be expected to make a definitive statement on the neurobehavioral outcome of proton radiation because of its large and diverse sample. A variety of brain tumor histologies are present in this sample, and are sufficiently represented to allow study of each histology. There is also a wide variation at age of treatment, from 1 to 25 years of age. The project builds on the existing proton radiation projects examining quality of life and neurocognitive functioning being conducted with Partners' IRB approval at. It would greatly

increase the usefulness of the existing data by adding a new longitudinal component. Neuropsychological testing is the standard of care for any patient with a brain tumor and especially those that have radiation, as the tumor itself, the surgery, and the radiation can all have an effect on the functioning of the brain. We have a research database that collects the disease and clinical outcomes of the patients, including the neuropsychological assessments. The 200 neuropsychological assessments and 58 follow-up assessments were collected in the context of MGH IRB approved research protocols (Protocol # 2005P000087, MGH Pediatric Radiation Oncology Database, PI Yock; Protocol # 2009p000286: Long term Neurocognitive and Quality of Life Assessment in a Pediatric Brain Tumor Population Treated with Proton Radiation, PI Yock). The following PIs and co-investigators in the present study are also PIs and co-investigators in the aforementioned MGH research protocols: Margaret Pulsifer, Ph.D, Torunn Yock, M.D. (P.I.), Shannon MacDonald, M.D., Nancy Tarbell, M.D., and Karen Kuhlthau, Ph.D.

The study will also shed light on long-term educational support needs of the increasing number of pediatric survivors of brain tumors. Overall survival for children with brain tumors is now over 70%, thanks partly to radiation therapy. Therefore, long-term outcome is increasingly important to this population.[23] Furthermore, with more proton radiation centers opening worldwide, this population is likely to increase significantly in the future. Better understanding of survivors' ability to live independently (which is related to skills such as executive functioning and adaptive abilities) and their existing use of special education services will help in designing individual treatment plans and in setting public policy.

2.0 OBJECTIVES

The purpose of this study is to longitudinally examine neurobehavioral functioning outcomes and use of special education services in brain tumor and CNS tumor patients treated with proton radiation at MGH. Furthermore, we seek to correlate neurobehavioral data with pertinent clinical information. We anticipate better neurobehavioral functioning to be associated with use of protons (vs. photons, as reported in the literature). We also anticipate the need and utilization of special education services to be lower in brain and CNS tumor patients treated with protons (vs. photons, as reported in the literature). Lastly, we anticipate greater neurobehavioral deficits in patients whose proton radiation treatment involved the craniospinal axis compared to those who received proton radiation to the involved field.

3.0 RESEARCH SUBJECT SELECTION

All children diagnosed with brain or CNS tumors and treated with proton radiation therapy at the MGH Francis H. Burr Proton Center since September 2002 who meet inclusion criteria (see below) are eligible to participate. The parents of eligible patients will be sent a packet in the mail that includes the following: a letter that communicates our research aims, the age-appropriate questionnaires, a questionnaire about the child's educational attainment and use of special education services, an addressed and stamped envelope to mail back study-related materials (e.g., questionnaires), and a form to decline participation in the event they do not wish to participate. However, if the patient is scheduled to return to MGH for yearly follow-up (≥1 year post-treatment), the questionnaires can be completed on the premises instead of via mail. In the case of a patient's death, resulting from the malignancy or another etiology, that patient will no longer be included in the study. Participation is completely voluntary, and refusal to participate or to receive further contact on this subject will in no way effect the care or treatment that patients receive here at MGH.

Inclusion Criteria

1. Children diagnosed with brain or CNS tumors and treated with proton radiation therapy at the MGH Francis H. Burr Proton Center since September 2002

2. Patients received baseline neurocognitive testing at MGH
3. Patients ≤25 years at the time of diagnosis
4. Tumor location in the brain or CNS
5. Radiation treatment consisted of only proton radiotherapy
6. No prior radiation exposure or chemotherapy

Exclusion Criteria

1. Patients receiving treatment with palliative intent
2. Patients who do not wish to participate
3. Patient is deceased at ≥1 year follow-up

4.0 RESEARCH SUBJECT ENTRY

After participants have been identified (see "RESEARCH SUBJECT SELECTION" section), they will receive a packet in the mail that includes the following: a letter that communicates our research aims, the age-appropriate questionnaires, a questionnaire about the child's educational attainment and use of special education services, an addressed and stamped envelope to mail back study-related materials (e.g., questionnaires), and a form to decline participation in the event they do not wish to participate.

The current study is requesting a waiver of consent, as it does not involve more than minimal risk, it will not adversely affect the rights and welfare of the participants, the research could not practicably be carried out without the waiver, and the participants will be provided with additional pertinent information after participation. Furthermore, this study involves no procedures or interventions for which written consent is normally required outside of the research context, as the voluntary completion of questionnaires results in the implied consent/assent to participate.

This research is centered on three relevant, validated, age-specific questionnaires of neurobehavioral functioning, which will be self-administered by the patient (≥7 years of age) and/or by a parent. In addition, parents will be asked to complete a questionnaire about the child's educational attainment and use of special education services. Participation in the study is at each participant's discretion, or in the case of a minor, at the discretion of a parent/guardian. The nature of this study therefore allows for implied consent/assent resulting from the voluntary completion of the questionnaires. Those who do not wish to participate or to receive further contact on this subject are asked to please return the enclosed form declining participation. If eligible participants do not reply, study staff may contact them to complete the questionnaire over the phone. In addition, if the patient is scheduled to return to MGH for yearly follow-up (≥1 year post-treatment), the questionnaires can be completed on the premises instead of via mail. Participation is completely voluntary, and refusal to participate will in no way effect the care or treatment that patients receive here at MGH.

The study's PI (Margaret Pulsifer, Ph.D.: 617-726-9116) will be responsible for contacting the Quality Assurance Office for Clinical Trials (QACT) to register study participants.

5.0 STUDY DESIGN AND METHODS

5.1 Design/Study Type

This study is a mixed design (i.e., cross-sectional and longitudinal) descriptive study designed to examine neurobehavioral functioning and use of special education services one year or more post-treatment in patients who received proton beam radiation therapy at MGH for the treatment of a brain tumor or CNS tumor.

5.2 Selection of Instruments

The measures that were selected for this study are three questionnaires and a survey. If the patient is under 7 years of age, only the parent will receive the questionnaires. If the patient is 7 years or older, then both the parent and the patient will be asked to complete questionnaires. The three questionnaires are: the Behavior Rating Inventory of Executive Functioning-Parent and Self-Report Forms (BRIEF),[24] the Behavior Assessment System for Children-Parent and Self-Report Forms (BASC-2),[25] and the Scales of Independent Behavior-Revised- Parent Form (SIB-R).[26] The three questionnaires are standardized and population-based norms are available for the age range of the study participants. Additionally, the Educational Services and Medical Status Profile is a peer-reviewed, brief survey designed for this study to obtain current information about the child's educational placement, use of special education services (e.g., I.E.P; 504 Accommodation Plan), and medical status.

Time to complete the three rating scales and the Educational Services and Medical Status Profile is approximately 30-45 minutes. Those children of age $\geq$ 7 years will be asked to complete two age-specific self-report rating scales (BASC-2 and BRIEF, self-report versions). Time to complete the two child rating scales is approximately 20-30 minutes. Completed questionnaires can be mailed to study staff in the provided addressed and stamped envelope. Participants will be contacted by telephone if the questionnaires or form declining participation are not received within two weeks of mailing.

5.3 Description of Intervention

This study is not an intervention study.

5.4 Data Collection

- Gender
- Age at initiation of proton radiation at MGH
- Current age
- Current grade in school
- Current use special education services
- Tumor histology
- Chemotherapy (yes/no)
- Resection (yes/no)
- Post-operative complications
- Post-treatment complications
- Craniospinal irradiation (yes/no)
- Total radiation dose

- BASC-2: age-based *T*-Scores
- SIB-R: age-based Standard Scores
- BRIEF: age-based *T*-scores

5.5 Description of Study Process

5.51 Instrument Administration

The parents of eligible patients will be sent a packet in the mail that includes all study materials (see "RESEARCH SUBJECT ENTRY" section). If the patient is scheduled to return to MGH for yearly follow-up (≥1 year post-treatment), the questionnaires can be completed on the premises instead of via mail. Participation in the study is at each participant's discretion, or in the case of a minor, at the discretion of a parent/guardian. The nature of this study therefore allows for implied consent/assent resulting from the voluntary completion of the questionnaires. Participation is completely voluntary, and refusal to participate or to receive further contact on this subject will in no way effect the care or treatment that patients receive here at MGH.

Those parents who choose to participate are to complete the brief survey and three questionnaires (BASC-2, BRIEF, and SIB-R, enclosed). The survey, requesting information about the child's current educational and medical status, should take about 5 minutes to complete. The three questionnaires ask questions about the child's attention, emotional/behavioral well being and daily living skills in recent months, and should take approximately 30-45 minutes to complete. They are asked to follow the directions on the individual questionnaires carefully. Those participating children who are 7 years old or older are asked to complete the self-report versions of two of the questionnaires (BASC-2 and BRIEF), which should take approximately 20-30 minutes to complete. All completed study materials should be returned in the pre-addressed, stamped envelope provided.

5.52 Special Concerns

If the completed questionnaires indicate that a child might be at psychological risk, we will contact their guardians (or the adult patient ≥18 years of age) and provide a referral to a psychologist or psychiatrist affiliated with MGH or in their local area for further evaluation.

The only risk to patients that we can anticipate is a risk to privacy and confidentiality. However, we have implemented several safety measures to ensure that personal data is protected as well as possible. Specifically, we will keep all information about patients on secure hospital networks, with access limited to those on the IRB protocol. Participants will be assigned an anonymous identification number and only that number will be associated with the patient. We will further only report data in tables that show the findings for groups of individuals.

Dr. Pulsifer will be in charge of collection, data entry, and appropriate disposal of all confidential documents. Confidentiality will be maintained according to HIPAA regulations by all investigators. All returned questionnaires will be kept in a locked container, and all data will be password protected. No copies will be made. Participants will be assigned an anonymous identification number and only that number will be associated with the patient. The patient's name and medical record number will be removed. All analysis will be performed without use of

patient identifiers. We will only report data in tables that show the findings for groups of individuals.

5.53 Compensation

A family incentive of $25 gift-certificate will be awarded to each participating family. This will be mailed to participating families upon return of completed questionnaires.

5.6 Adverse Reactions and Their Management

5.61 Reporting Adverse or Unanticipated Events

We do not anticipate safety issues because this study only involves administering questionnaires, and does not include a procedure, intervention or clinical trial. In the event that a patient is noted on the questionnaires to be at psychological risk, then the adult patient (≥18 years of age) or a child's parents/guardian will be individually contacted by telephone by Dr. Margaret Pulsifer. These patients will be offered a referral to a psychologist or psychiatrist at MGH or in their local area for further evaluation and follow-up, if needed. We plan to report to the IRB any problems or concerns reported by participants that are not immediately and easily addressed by study or clinical staff.

5.62 Anticipated Reactions

Because this research only involves the administration of questionnaires, it is unlikely that individuals will feel any significant physical or psychological discomfort due to study participation. While there is the chance that participants will be upset by a study questionnaire, we do not expect participants to experience any other type of emotional distress while participating in this research.

5.63 Reaction Management

If any type of emotional discomfort does occur in response to the research study questionnaires, participants can call Margaret Pulsifer, Ph.D. at 617-726-9116, or the Office for Human Research Studies at 617-632-3029. They can feel free to skip any question, including those that they found to be particularly upsetting. We will offer our psychological counseling services to any participants who experience questionnaire-related distress. We plan to report to the IRB any problems or concerns reported by participants that are not immediately and easily addressed by study or clinical staff.

The only risk to patients that we can anticipate is a risk to privacy and confidentiality. However, we have implemented several safety measures to ensure that personal data is protected as well as possible. Specifically, we will keep all information about patients on secure hospital networks, with access limited to those on the IRB protocol. Participants will be assigned an anonymous identification number and only that number will be associated with the patient. We will further only report data in tables that show the findings for groups of individuals.

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we do not expect participants to experience any other type of emotional distress while participating in this research. If any type of emotional discomfort does occur, we will offer our psychological counseling services to address it or provide a referral to a psychologist or psychiatrist at MGH or in their local area, if needed.

6.0 STATISTICAL ANALYSIS

6.1 Primary and secondary endpoints.

This study design has only one endpoint- that is to assess neurobehavioral functioning via questionnaires at ≥ 1 year following completion of proton radiation treatment.

6.2 Sample size and statistical power or precision associated with the sample size. The length of time required to accrue an adequate number of subjects to the study should be indicated.

The expected sample size is 200 participants. However, with an approximate 60% participation rate, 120 participants are anticipated to have complete data by the end of the funding period (one year). For analyses involving comparisons of pre- and post- proton radiation treatment data, this sample will be large enough to detect group differences of .5 s.d. or greater with a power of 90% and alpha of .05 (using two-tailed tests).

6.3 Stratification factors and intervention allocation plan for randomized studies.

N/A; This is not a randomized design and does not have an intervention or procedure.

6.5 Stratification factors and their impact on design.

N/A; There is no stratification in this study.

6.6 Early stopping rules, if appropriate.

N/A

6.7 Definition of and allowance in design for unevaluable/ineligible participants.

In this study, an unevaluable participant is one who does not complete the questionnaires or provide implied consent. Unevaluable participants will not be included in analyses that examine neurobehavioral functioning at ≥ 1 year following completion of proton radiation treatment.

6.8 Analysis plan.

Data analysis will include 1) analyzing the group data at follow-up (i.e., ≥1 year after completion of proton radiation treatment) for those participants with completed questionnaires, and 2) comparing pre- and post- proton radiation treatment data both in aggregate and in various groups. Subject groups will be based on several patient and treatment variables, including: 1) age at initiation of proton radiation; 2) gender; 3) histology of brain tumor; 4) proton radiation dose; 5) treatment consisted of craniospinal

irradiation or only involved field radiation; 6) post-operative and post-treatment complications, 7) treatment with chemotherapy; and 8) age at follow-up. Descriptive statistics will be obtained for the total group and standardized test scores (standard scores; T-scores) will be compared within and between groups using paired t-tests and analysis of variance (ANOVA).

6.9 Handling of missing data in the analysis.

The expected sample size is 200 participants. However, an approximate 60% participation rate is expected, resulting in a conservative estimate of 120 participants. It is possible that those participants who remain in the study are systematically different from those who do not complete the study. For example, it may be the case that those who do not complete the study may have lower neurocognitive functioning at baseline. Investigators have access to baseline data on individuals who decide not to participate because they were previously consented within the context of a prior study by the same investigators. Therefore, in order to identify a missing data pattern, investigators will compare the baseline neurocognitive data of those who complete the follow-up study to those who do not. If a pattern is identified, the conclusions of the study need to be adapted accordingly (i.e., results can only generalize to the specific population on which complete data were collected).

7.0 REFERENCES

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