University of Pennsylvania

PROTON RADIATION FOR CHORDOMAS AND CHONDROSARCOMAS

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List of Abbreviations

AE: Adverse Event
ANOVA: Analysis of Variance
BFI: Brief Fatigue Inventory
BPI: Brief Pain Inventory
CNS: Central Nervous System
CR: Complete Response
CRF: Case Report Form
CT: Computerized Axial Tomography
CTCAE: Common Terminology Criteria (CTC) for Adverse Events
CTV: Clinical Target Volume
DSMB: Data and Safety Monitoring Board
DSMC: Data and Safety Monitoring Committee
EBRT: External Beam Radiotherapy
ECG: Electrocardiogram
EORTC: European Organization for Research and Treatment of Cancer
EQ-5D: European Quality of Life Index
FACT-BR: Functional Assessment of Cancer Therapy-Brain
FACT-G: Functional Assessment of Cancer Therapy-General
FDA**:** Food and Drug Administration
FDG: Fludeoxyglucose
GTV: Gross Tumor Volume
Gy: Gray
HIPAA: Health Insurance Portability and Accountability Act
IUD: Intra-Uterine Device
LET: Linear Energy Transfer
MRI: Magnetic Resonance Imaging
NCI: National Cancer Institute
OAR: Organ at Risk Volume
OER: Oxygen Enhancement Ratio
PAR: Planning Organ at Risk Volume
PD: Progressive Disease
PBSTV: Pencil Beam Scanning Target Volume
PET: Positron Emission Tomography
PFS: Progression Free Survival
PHI: Protected Health Information
PI: Principal Investigator
PR: Partial Response
RC-REVIEW: Range Compensator Review Volume
RBE: Relative Biologic Effectiveness
RTOG: Radiation Therapy Oncology Group
SAE: Serious Adverse Event
SD: Stable Disease
SOBP: Spread Out Bragg Peak
SOP: Standard Operating Procedure
SWOG: Southwest Oncology Group
WBC: White Blood Cell Count

Study Summary

Title	Proton Beam Radiation for Chordomas and Chondrosarcomas
Short Title	
Protocol Number	UPCC#: **01310** IRB#: **811185**
Phase	Feasibility and Phase II
Methodology	Open
Study Duration	Four years (enrollment)
Study Center(s)	University of Pennsylvania
Objectives	1) To evaluate the feasibility and acute side effects of proton therapy for chordomas and chondrosarcomas 2) To evaluate clinical outcomes and long term side effects of proton beam radiation for treatment of chordomas and chondrosarcomas
Number of Subjects	50 total = (12[feasibility] + 38 [Phase II])
Diagnosis and Main Inclusion Criteria	Chordoma or Chondrosarcoma, Age18 or greater, No prior radiation

1 Introduction

1.1 Background

Chordomas are malignant tumors arising from embryonic notochord remnant. The majority of these tumors occur along the craniospinal axis: 50% grow in the sacrococcygeal regions, 35% in the base of the skull and 15% in the spine [1]; [2]. The incidence of chordoma is quite low. There is a slight male predominance in chordomas originating from the spinal cord, whereas lesions of the skull are seen more frequently in females. They have two age peaks of incidence, one in the fourth decade for skull lesions and one between the fifth and seventh decades for lesions that originate from the spinal cord and sacral region. Chondrosarcomas most commonly involve the femur with a striking predilection for the secondary ossification centers. Chondrosarcomas arising de novo present most commonly in the femur; and secondary chondrosarcomas are most prevalent in the ilium. They account for 10-20% of malignancy primary bone tumors. Age range is from 7 to 73 years with the most commons diagnosis between 30 and 60 years of age. Males predominate slightly in most series but mesenchymal chondrosarcoma occur more frequently in women. Conditions that predispose to chondrosarcoma include Ollier's disease, Paget's disease, Maffucci's syndrome, previous exposure to intravenous Thorotrast, chondromyxsoid fibroma and prior radiation therapy.

Chordomas have a slow growth and a tendency to destroy the bone locally. In their growth, they compress on adjacent tissues and structures, and this compression is responsible for most clinical symptoms. Although chordomas are essentially locally malignant tumors, they sometimes metastasize; the incidence of metastasis ranges from 10-25% [3]. They occur in the late phase of the disease or with a very large, massive primary lesion. Chondrosarcomas are locally aggressive lesion with a high propensity for local recurrence, which usually occurs within 5 years after treatment. Head and truncal chondrosarcomas have an 85% chance of recurring at the primary site. They usually follow a more indolent course. The most common site of distal metastases is the lungs, followed by bone, liver, kidney, breast and brain. Up to 10% of chondrosarcomas can dedifferentiate into aggressive fibrosarcomas or osteosarcomas.

The five year survival rate for patients with chordomas is around 80% while for chondrosarcomas is 100% [4, 5]. The standard treatment of choice remains to be treated with aggressive surgery. The standard surgical procedure is a wide total excision. The biopsy tract must be excised, and the tumor should not be exposed during the operative procedure. The recurrent rate can vary from 15% with "adequate" surgery to 87% with inadequate procedures. Close follow up is needed, as these tumors can relapse 10 years or more from surgery. Most problems in treating patients with chordomas derive from the location of the tumor. The proximity of the tumor mass remains the preferred method of treatment for spinal and sacrococcygeal chordomas. Survival after radical surgery is normally long, although most patients experience a local failure in the course of the disease. The role of radiation is these tumors are not completely defined. However, data supports the efficacy of irradiation as adjuvant treatment after incomplete surgical resection. When surgery is not possible, radiation therapy can be used as a single-modality treatment. Different techniques and different types of ionizing radiation have been used to overcome dose-limitation problems. Based on current data, a combination of surgery and postoperative irradiation can be considered standard

treatment for resectable chordomas. If surgery is not indicated because of the location of the tumor, radiation therapy as a single modality can be considered a standard procedure for definitive treatment.

Surgery is still considered the primary treatment for chordomas. However then surgical excision is incomplete or when surgery is not possible because of the tumor location, radiation can play a significant role. Particle beams and high linear energy transfer radiation represent an important alternative to the use of conventional photon beams in the treatment of lesions located in specific areas. Keisch and coworkers reported in 21 patients after incomplete resection, irradiation improved local tumor control and disease free survival especially in tumor originating in the lumbosacral regions [6]. Doses higher than 55 Gy showed a statistically significant improvement in duration of local tumor control when compared with lower doses in a report of Fuller and Bloom [7]. Chetiyawardana treated 48 patients with doses of 30-45 Gy with irradiation as adjuvant treatment after surgical resection. Stereotactic fractionated radiotherapy also has been used with promising results [8]. The study found a local relapse free survival of 82% at 2 years and 50% at 5 years with a corresponding overall survival rate of 40%. Since 1970s, particle beams have been used because they are considered more beneficial than conventional irradiation for their physical and biologic characteristics. There are two main considerations. The first is that they are located in areas in which a sharp collimation of the beam is essential to prevent the occurrence of severe side effects (e.g. base of skull). No prospective randomized trials compare the effectiveness of particle-beam versus conventional irradiation. However several retrospective studies have shown increased local tumor control when particle beams were used. The Proton Therapy Working group reviewed the matter in 2000 and reported a superior outcome for patients treated with heavy particles compared with those that received conventional therapy [9]. A radiotherapy schedule of mixed protons and photons for chordomas of the base of skull resulted in 60% local control at 5 years [4]. Suit et al treated chondrosarcomas of the cervical spine and base of skull with combined photon-proton radiation therapy [10]. Total doses ranged from 65.3 to 75 GyE with photon doses between 21.3 and 39.6 Gy and protons doses from 28.7 to 40 GyE. The proton field was used as a cone down boost field. No central nervous system toxic effects were reported; survival times without evidence of disease ranged from 4 to 74 months.

The importance of particle beams, used alone or in combination with photons, in treating lesions originating from areas that are difficult to treat safely with conventional irradiation has been largely proved with a 5 year PFS of 70% [11]. Saunders et al treated 19 patients with lesions adjacent to critical CNS structures with a high local control rate 79% and only 2 cases of major side effects [12, 13]. Data confirmed in another study of 45 patients from the same institution showed a local control 59% and nine of 45 had significant side effects. Castro treated 31 patients with lesions originating near the brainstem or spinal cord. Local control was achieved in 62% and complications occurred in 13% [14].

Saunders reported on 87.5% local control in 8 cases of chordoma of the sacrum [12, 13]. Schoenthlaer and colleagues reports on 14 cases of sacrum chordoma with local control of 55% [15]. One two major complications were seen in these patients. Technical aspects such as precise positioning of the patient and immobilization are of paramount importance when

particle beams. Further improvement especially in prevention of side effects is expected as 3D treatment planning programs become more available for daily clinical use.

Magnitude of effects is related directly to dose and field volume and is inversely related to age at the time of therapy. Endocrine dysfunction, visual changes, brainstem injury, or temporal lobe injury have been documented in around 5-10% [16]. Growth delays may results in limb joint dislocation secondary to underdeveloped joint fossa, mandibular or craniofacial abnormalities and dentition delay. Scoliosis after vertebral irradiation is possible but is usually not progressive and frequently is compensated by pelvic tilt. Inclusion of the entire width of the vertebral body in the treatment field does not appear to decrease the incidence of scoliosis. Because of radiation induced vascular changes, irradiated bone is more sensitive to infection, fracture and necrosis [17].

Rationale for Proton Therapy:
The goal of radiation therapy is to deposit most of the dose to the target while minimizing the dose to the surrounding normal tissues. Conventional photon radiotherapy deposits its dose along the entire beam path to the tumor or target volume as well as beyond the depth of the target. Techniques to minimize the dose to surrounding tissues such as using multiple beam angles, modulating the intensity of the radiation delivered through each beam have been utilized, however, these techniques still entail both entrance dose to normal tissue as it penetrates to reach a tumor at depth in tissue, and an exit dose as it exits the body in a straight path beyond the tumor. Proton radiotherapy differs from photon radiotherapy in that most of the energy is deposited at a specific depth known as the Bragg peak. The dose immediately beyond the Bragg peak is essentially zero, which allows tissues on the posterior side of the tumor to be spared. The clinical application of protons provides an improvement over photons in its ability to deliver a high-dose-volume to any configuration within an anatomical site while maintaining lower doses to surrounding normal tissues, resulting in decreased short and long-term morbidity, due to the unique Bragg Peak phenomenon of the dose distribution of protons. Theoretically, this should ease the current limitation of normal tissue tolerance as a dose-limiting factor particularly for larger tumors as well as allow greater dose to be delivered to the tumor/target volume. The current protocol proposes to allow the use of protons (which is approved by the U.S. Food and Drug Administration) for the treatment of chordomas and chondrosarcomas of the base of skull.

Protons have a similar biologic effect to photons against tumors. The biological effect of radiation is dependent on its linear energy transfer (LET). LET is defined as the rate of energy transferred by ionizing radiation per unit path length. To compare different types of radiation, we use the relative biologic effectiveness (RBE), which is defined as the ratio of the dose of particle radiation to the dose of 60Co radiation producing the same biological endpoint. Standard photon radiation therapy has a RBE of 1.0; the RBE of protons is thought to be between 1.05 to 1.25[1][18-20]. A recent review of in vivo and in vitro experiments concluded that RBE varies with dose or dose per fraction and increases with an increasing depth in the spread out Bragg Peak (SOBP) and is most significant at the distal edge of the SOBP. Overall though, based on the data to date, an average RBE of approximately 1.1 in the entrance of the SOBP is reasonable to assume[1][21]. The clinical advantage of proton beam radiotherapy over standard photon radiation results from the more favorable dose distributions achievable with its

particular physical properties as previously described. The advantage of protons has been demonstrated for medulloblastoma and, prostate cancer, and comparative treatment planning using protons versus photons have shown a clear advantage to protons in terms of dose distribution[1][22-27].

2 Study Objectives

This study will be done in two phases. In the first phase, feasibility will be established using the primary objectives set below. The second phase will begin no earlier than 90 days after the last patient in the initial phase has started treatment and once safety and feasibility has been verified. The secondary objectives will serve as the objectives for the second phase of the study.

Primary Objective

The primary objective of this study is feasibility. The study will be deemed infeasible if greater than 10% of pts experience one of the following:

a. Patient cannot be given treatment because anatomy is such that a dosimetrically satisfactory treatment plan cannot be devised as defined in Section 4.5.1.

b. For base of skull patients only. Patient receives greater than 40% of their total treatment (for any reason, i.e. unable to set patient up within acceptable limits of tolerance, patient unable to tolerate treatment position or immobilization for duration of treatment) with photon beam radiotherapy (using a backup photon plan).

For spine and all other patients. Patient receives greater than 20% of their total treatment (for any reason, i.e. unable to set patient up within acceptable limits of tolerance, patient unable to tolerate treatment position or immobilization for duration of treatment) with photon beam radiotherapy (using a backup photon plan).

c. Patient is unable to complete all of his/her treatments within 10 days of estimated date of treatment completion or requires a treatment break greater than 5 days.

d. Additionally, no greater than 20% of patients experience an unexpected acute toxicity $\geq$ Grade 3 that is probably or definitely related to radiation therapy.

Secondary Objectives

To assess acute side effects from irradiation using proton beam therapy for the treatment of chordomas or chondrosarcomas.

To assess late complications from irradiation using proton beam therapy for the treatment of chordomas or chondrosarcomas.

To compare the dose distribution to tumor and surrounding normal structures using DVH's (Dose Volume Histograms) generated from the proton plan used to treat the patient and the photon plan generated for comparison purposes.

To monitor the rates of local control as well as overall and disease specific survival using proton radiotherapy.

To evaluate the time to progression and progression free survival of chordomas or chondrosarcomas treated with protons.

To evaluate the effect of proton beam radiation on neurocognitive outcome in patients with chordomas or chondrosarcomas.

To evaluate the quality of life (e.g., fatigue) in patients treated for chordomas or chondrosarcomas.

3 Subject Selection and Withdrawal

This study plans to enroll 50 subjects over a 4 year period of time. We plan to enroll male and female subjects of all races.

3.1 Inclusion Criteria

- Histologically confirmed diagnosis of chordoma or chondrosarcoma.
- Patients must have no evidence of metastatic disease based on routine imaging (Chest x-ray, CT or MRI of the chest/abdomen/pelvis, bone scan, etc).
- Patients must have an ECOG score equal to or less than 2.
- Age $\geq$ 18.
- Patients must be able to provide informed consent.
- Women of child-bearing potential as long as she agrees to use a recognized method of birth control (e.g. oral contraceptive, IUD, condoms or other barrier methods etc.). Hysterectomy or menopause must be clinically documented.
- Tumors arising in the skull and spine.

3.2 Exclusion Criteria

- Prior or simultaneous malignancies within the past two years (other than cutaneous squamous or basal cell carcinoma, melanoma in situ or thyroid carcinoma)
- Patients with the following histologies are excluded: melanoma, other soft tissue or bony sarcomas, giant cell tumor, aneurismal bone cyst or metastatic lesions from other histologies.
- Pregnant women.
- Actively being treated on any other therapeutic research study.
- Tumors arising outside of the CNS.

3.3 Subject Recruitment and Screening

Subjects will be recruited from either the Department of Defense (DOD) Oncology practices or the Department of Radiation Oncology, Neurosurgery and Otorhinolaryngology practices at The University of Pennsylvania Medical Center (Hospital of the University of Pennsylvania, Pennsylvania Hospital and Penn Presbyterian Medical Center). The treating radiation oncologist will determine if the patient is a potential research candidate and has the capacity to consent. The treating radiation oncologist will approach and inform the patient about the study, thereby initiating the informed consent process. If the patient expresses interest in the study, the treating radiation oncologist will contact a qualified member of the research team in the Radiation Oncology department at the University of Pennsylvania and request availability for

enrollment. A qualified member of the research team will interview the potential subject with privacy considerations, explain the requirements of the study and provide a copy of the Informed Consent Form (ICF). The person obtaining consent will state the volunteer nature of research and advise the subject to take sufficient time to discuss the study if necessary before making their decision to sign the informed consent document. If a decision to participate is made, the informed consent form is signed after which any screening procedures will be performed. A series of questions will be asked by the person obtaining consent to verify patient eligibility based upon the criteria outlined in Section 3.1 and Section 3.2. After the eligibility is established, a subject study number will be issued. Eligibility is confirmed with the study investigator. All members of the research team will have successfully completed patient oriented research training. **Subjects will receive all treatment in the Radiation Oncology clinic of the University of Pennsylvania.**

At the University of Pennsylvania, we see approximately 12 cases of chordoma and/or chondrosarcoma per year. We anticipate that with the availability of proton radiotherapy, these numbers may increase. We estimate an annual accrual of 12-15 subjects per year. Proton radiotherapy will be listed on our web site and in Oncolink as a formal protocol and information of its availability will be made known to treating professionals throughout our satellites and referring physicians.

3.4 Early Withdrawal of Subjects

3.4.1 When and How to Withdraw Subjects

- Recurrent or Progressive Disease: Subjects who have clinical or radiologic evidence of recurrent disease will undergo an evaluation to document the nature of the abnormality. If recurrent or progressive cancer is diagnosed, the subject will be considered off study at that time.
- PI Decision: Subjects may be withdrawn at any time during the study if the PI believes it is in the subject's best interest. In this event, the reasons for withdrawal will be documented.
- Subject Participation: Refusal to continue treatment, follow-up, comply with the protocol or withdrawal of consent. In this event, the reasons for withdrawal will be documented.
- Adverse Event (including intercurrent illness, unacceptable toxicity).

Once the subject has discontinued treatment, the primary reason for discontinuing treatment must be clearly documented in the subject's records and on the CRF. The investigator will assess each subject for response at the time of withdrawal.

Every effort will be made to follow all subjects off study for toxicity and survival unless patient withdraws consent. If subjects withdraw from the study at any time, we will ask for his/her written permission to continue to access medical records for overall survival. Acute toxicities will be assessed for 90 days from the first date of treatment. Survival will be followed for a minimum of 5 years.

4 Radiation Therapy

4.1 Treatment Planning, Imaging and Localization Requirements

4.1.1 All subjects will be immobilized in a custom designed device in the appropriate position.

4.1.2 Radiotherapy treatment planning CT scans and MRI scans will be required to define gross tumor volume (GTV) and clinical target volume (CTV). The treatment planning CT scan (or MRI scan) should be acquired with the subject in the same position and using the same immobilization device as for treatment. Treatment planning will be done using a 3D based CT or MRI treatment planning system. All tissues to be irradiated must be included in the CT/MRI scan. Planning CT/MRI scan will be done at 1.5 mm intervals depending on the site of disease (craniospinal axis). A second treatment planning CT/MRI scan may be performed during the course of radiotherapy as necessary. Imaging including FDG-PET/CT and/or MR imaging maybe fused with the planning CT images to better visualize the anatomy when indicated.

4.2 Target Contouring

4.2.1 Gross Tumor Volume (GTV) is defined as all known gross disease determined from CT, MRI, and PET imaging.

4.2.2 Clinical Target Volume (CTV) is defined as the GTV plus areas that are considered to contain potential microscopic disease (the operative site and other areas of microscopic risk).

4.3 After delineating the CTV, the margins are added to the CTV by means of enlarging the beam aperture both laterally and cephalo-caudally in the beam's eye view, and the distal and proximal margins are calculated and added. These margins cover the uncertainty due to range, set-up errors and lateral fall off of the irradiation fields. A compensator is created to control the axial dose deposition distally. Smearing and border smoothing will be routinely calculated and applied. Compensator editing may be necessary to deliver the dose as prescribed by the physician. All the above parameters are calculated and

recorded by the planner under the physicist supervision and are subject to discussion with the physician as appropriate. Review volumes called RC-review = CTV + 0.2 or 0.3 cm are created in order to facilitate the coverage evaluation process. For pencil beam scanning treatment planning, a PBSTV will be employed for treatment planning optimization purposes. All these parameters can be altered by the radiation oncology team as appropriate in order to deliver the prescribed dose and maintain sparing of the organs at risk (OAR).Normal Structures

1. Optic nerves
2. Optic chiasm
3. Eye
4. Lens
5. Brainstem
6. Cochlea
7. Spinal cord
8. Right and left hippocampus
9. Pituitary
10. Temporal lobes
11. Cerebellum
12. Hypothalamus

4.3.1 The dosimetrist will define two structures: Skin-2 (2mm thick surface) and Skin-RC-REVIEW_Review (all RC-REVIEWs subtracted from the surface contour). Skin-RC-review is the normal tissue structure is all tissue other than what is contoured as something else.

4.3.2 Organ at risk volume (OAR) is contoured as visualized on the planning CT or MR scan. Planning PAR is the OAR expanded for set-up uncertainty or organ motion. The physician will contour the OAR. The dosimetrist may create the PAR by expanding the OAR by 2-3 mm, depending on the situation.
The following structures will be contoured (depending on location of primary tumor):
***CNS (BOS)*:** spinal cord, brainstem, optic nerve (right/left), optic chiasm, eye (right/left), lens (right/left), cochlea (right/left), right and left hippocampus, pituitary, cerebellum, temporal lobes.
Head and neck (Cervical spine): salivary glands (parotid-right/left, submandibular right/left), larynx, oral cavity, upper esophagus, mandible, lungs, brachial plexus.
Spine (Thoracic/Lumbosacral): spinal cord, thecal sac.

4.4 Dose fractionation and specification

4.4.1 Dose
For chordomas, the total dose will be 72.00 to 79.2 Gy (RBE) in 40-44 fractions at 1.8 Gy (RBE) per fraction. For chondrosarcomas, the total dose will be 70.20-73.80 Gy(RBE) in 39-41 fractions at 1.80 Gy(RBE) per fraction. Proton and photon therapy will be prescribed upon consultation with Physics in order to ensure a robust plan.

Doses throughout will be prescribed as Gray (Gy) for any IMRT (if used) and in Gy Relative Biologic Effectiveness (RBE) for the proton treatment. The total dose will be the addition of the treatment received with IMRT (if used) and proton therapy. One Gy will be the equivalent of one Gy (RBE).

4.5 Treatment Planning

4.5.1 Dose specifications: 98% of CTV must be covered 95% of the dose. 100% of the GTV should be covered by at least 97% of the dose. A 1% deviation is acceptable. Larger deviations may be necessary due to target proximity to the brainstem/cord and they can be accepted after analyzing the case with the treating physician

4.5.2 Dose Constraints for organs at risk (OARs):

1. Optic nerves	62.00 Gy (RBE) (max dose, less than 0.03 cc)
2. Optic chiasm	62.00 Gy (RBE) (max dose, less than 0.03 cc)
3. Eye	10.00 Gy (RBE)
4. Lens	4.00 Gy (RBE)
5. Brainstem	67.00 Gy(RBE) to the anterior surface, 55.00 Gy (RBE) to the center and 50.00 Gy (RBE) to the posterior surface
6. Cochlea	60.00 Gy (RBE) (point dose, 30.00 Gy (RBE) to the contralateral, if well lateralized lesion
7. Spinal cord	45.00 Gy (RBE) (if base of skull primary; same constraints as brain stem if spinal cord primary)
8. Pituitary	45.00 Gy (RBE)
9. Temporal Lobes	Less than 10% to get prescription dose
10. Cerebellum	Less than 10% to get prescription dose

Note: All planning parameters can be altered by the radiation oncology team as appropriate in order to deliver the prescribed dose and maintain sparing of the organs at risk if clinically acceptable to the treating physician

4.5.2 IMRT backup plans or partial treatments may be carried out as requested by the physician. The prescription is as specified above and administered using the same scheme. The planning target volume expansion margin defined on case by case basis from the CTV volumes .The lateral margins will be defined by the multi-leaf collimator and will wary between 0.3 to 1.5 cm or as found to be appropriate in order to have adequate coverage to sparing ratio.

4.6 Treatment Duration

Proton radiation therapy will in most instances be completed within 9 weeks of the start of treatment. This may be extended if subjects require a break from treatment. Criteria for break would include any **Grade 3 or 4** toxicity, depending on the clinical situation as determined by the treating physician. All subjects experiencing Grade 4 toxicity considered probably or definitely related to radiation will be considered infeasible in the feasibility phase of the study.

Continuation of treatment and/or further treatment plans will be decided at the discretion of their treating physician.

4.7 External Beam Equipment and Beam Delivery

Protons: A high energy proton beam will be used. Treatments will be administered at the University of Pennsylvania Roberts Proton Facility and will be 72.00-79.20 Gy (RBE) for chordomas and 70.20-73.80 Gy (RBE) for chondrosarcomas. All charged particle treatment will be given with the patient in the appropriate immobilization device.

Photons: A Varian Linear Accelerator will be used. Treatments will be administered at the University of Pennsylvania and will be included in the total dose prescribed above.
Film or digital images will be taken prior to the initial treatment to verify the position of the patient and the aperture and as appropriate. A radiation oncologist will check the first film on all fields. A radiation therapist will check subsequent films taken before treatment. All set-up films will be permanently filed for all subjects. Subjects will be treated employing a respiratory motion management technique to account for respiration as appropriate.

4.8 Quality Assurance

Daily portal films, and/or daily online radiographic imaging will be performed during therapy. Fiducials will help reproduce daily set up and minimize set up variations as appropriate. Implanted hardware may be used for localization purposes as well.

5.0 Chemotherapy

None

6.0 Study Procedures

Patients will complete the Brief Fatigue Inventory and Fact Br which is specific to patients with CNS tumors. Fatigue and neurocognitive testing for these patients will continue for 3 years post radiation.

	Eligibility/ Pre-treatment	Weekly during treatment	Approx. 90 days from tx start.	Follow-Up Months (approximately from completion of treatment) 3,6,9,12,15, 18, 21, 24 (approx.)	Months 30, 36 (approximately from completion of treatment)	Year 4 and 5 (approximately from completion of treatment)
Tests and Observations						
History and PE	X			X	X	X
ECOG Score	X		X	X	X	
CT/MRI	X			X	X	X

CXR	X[3]					
Pathology	X					
Pregnancy Test	X[1]					
Toxicity Assessment	X	X	X	X	X	X
Tumor Measurement	X[2]			X[2]	X[2]	X[2]
BFI (fatigue)	X	X	X	X	X	X
Fact Br (neurocog)	X	X	X	X	X	X

(X[1] A pregnancy test will be required for females of child bearing potential within 5 days of tx)
(X[2] Applicable if there is residual tumor)
(X[3] As clinically indicated.)

6.1 Post-treatment Evaluation and Follow-up

All subjects will be evaluated weekly during the course of the proton therapy, at the inspection visit (approximately 90 days from treatment start) and approximately every three months from the last dose of treatment either by the treating radiation oncologist or a referring physician for two years, and approximately every 6 months for year 3 and then yearly for years 4 and 5. Patients will be treated and followed for 90 days from the start of radiation treatment to determine feasibility and safety (acute toxicity) for the initial phase of the study before moving to the second phase of the study.

Each follow-up examination will consist of interval history and physical examination, including a neurologic evaluation and toxicity assessment. A Brief Fatigue Inventory and FACT-Br will also be obtained. Assessment of the disease by MRI will be performed at intervals of 3 months for 2 years and then every 6 months for year 3 and annually for years 4 and 5.

6.1.1 Tumor Response (RECIST criteria, if measurable disease)

Target Lesions: For patients with gross or residual disease present after surgery (if surgery is feasible).
Complete Response (CR): Disappearance of all target lesions.
Partial Response (PR): At least a 30% decrease in the sum of the longest diameters of target lesion, taking as reference the baseline sum of the longest diameters.
Progressive Disease (PD): At least a 20% increase in the LD of the target lesions, taking as reference the smallest sum of the LD recorded since the treatment started or the appearance any new lesion(s).
Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

6.1.2 Confirmation of Response

To assign a PR or CR, changes in tumor measurement must be confirmed by repeat assessments no less than 4 weeks after the criteria for response are first met.

To assign SD, measurements must have met the stable disease criteria at least once after study entry at 3 month intervals.

Local failure is defined as: evidence of tumor growth in any direction beyond that present of the pre-treatment imaging studies or the appearance of tumor in tissues previously scored as sites of subclinical disease. The imaging studies are to be comparable in technical factors.
Marginal failure is defined as: appearance of tumor growth at the margin of the target volume.
Overall Survival: Duration measured from date of first treatment until death or censored at date of last follow-up for patients still alive.

7.0 Statistical Plan

7.0 Statistical Considerations

This is a study of proton therapy for patients with chordomas and chondrosarcomas. The trial will be conducted in two phases. First, a feasibility study and then, a phase II study. Since proton is a new treatment modality at PENN, the first proton trial conducted in each cancer site will be a feasibility study, in order to gain experience on both the logistics of proton planning, dosimetry, scheduling and delivery, and patient safety issues.

7.1 FEASIBILITY STUDY

7.1.1 Design and Objectives

The primary objectives are to determine feasibility and safety (acute toxicity). Secondary objectives are to determine late toxicity, long-term clinical outcomes and, fatigue and neurocognitive function.

Twelve patients will be enrolled and followed for a minimum of 90 days after start of radiotherapy to determine feasibility and acute toxicity. We expect to screen/enroll approximately 18 subjects to reach the goal of 12 evaluable subjects. A subject will be considered evaluable if they willingly remain on the study up until their first follow up visit. [note: a subject is still evaluable even if they are unable to undergo proton treatment as defined in section 2.0 or have a significant acute toxicity as these are feasibility criteria]. Ninety days of observation after start of radiotherapy will be required in all 12 patients prior to commencing the second phase of the trial. Patients enrolled in the feasibility study will continue to be followed beyond 90 days for the secondary endpoints of late toxicity, progression-free and overall survival fatigue and neurocognitive function.

7.1.2 Endpoints

7.1.2.1 Primary Endpoints

Feasibility will be based on multiple radiation planning and treatment parameters. For proton to be deemed feasible, no greater than 10% of patients should experience one of the following events: a) Patient cannot be given treatment because anatomy is such that a dosimetrically satisfactory treatment plan cannot be devised. For example, the dosimetry is unsatisfactory if

<95% of target volume is covered by 95% of the dose, b) Patient receives greater than 50% of their total treatment (for any reason-unable to set patient up within acceptable limits of tolerance, patient unable to tolerate treatment position or immobilization for duration of treatment) with photon beam radiotherapy (using a backup photon plan, c) Patient is unable to complete all of his/her treatments within 10 days of estimated date of treatment completion or requires a treatment break greater than 5 days.

Acute Toxicity is defined as any grade 3 or higher toxicity, considered probably or definitely related to radiation, observed within 90 days from start of therapy, excluding cranial nerve palsies or nerve root symptoms as these may be due to the tumor itself or prior surgery. Toxicities will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

7.1.2.2 Secondary Endpoints

Late toxicity is defined as any grade 3 or higher toxicity, considered probably or definitely related to radiation, observed later than 90 days from completion of therapy excluding cranial nerve palsies or nerve root symptoms as these may be due to the tumor itself or prior surgery. Late toxicities will be graded according to the CTCAE version 4.0. The time frame for late toxicity is open-ended and late toxicities have been known to occur a year or more after therapy. Follow-up for late toxicity will cease when a patient experiences disease progression, since 2nd line therapies may then be initiated.

Progression-free and overall survival are defined as the time from start of radiotherapy to first documented progression (local or distant event for PFS), death due to any cause or last patient contact alive. The local control rate (i.e., local progression only) may also be evaluated.

Fatigue will be scored by the Brief Fatigue Inventory (BFI), a validated instrument, which will be evaluated at the following time points: Pre-radiation, during treatment, at the inspection visit, and at approximately 3, 6, 9, 12 months post-radiation and then every 6 months for years 2 and 3, and yearly for year 4 and 5. It is expected that BFI score will increase (as fatigue worsens) in the first 6-12 months post-radiation and then the BFI score will decrease (as fatigue improves) at 12-24 months post-radiation.

Neurocognitive function will be assessed by the FACT-BR, which will be evaluated at pre-radiation, during treatment, at 3, 6, 9, 12 months post-radiation and then every 6 months.

7.1.3 Rules for Early Termination

Bayesian probability calculations will be employed to define rules of early termination for feasibility and safety. The tables below indicate termination rules after groups of 3 patients have been treated, although the Bayesian probability of an event may be calculated at any time during the trial. Hundreds of patients with certain types of cancer have undergone radiation therapy with protons. Thus, we will assume a modest amount of "prior" feasibility and safety data for proton for our Bayesian calculations. We will assume prior information equivalent to that of 6 treated patients, which is commonly required to establish safety in a standard 3+3 Phase-I trial design.

Feasibility

A feasibility rate ≥90% is considered acceptable. We will assume a beta (5,1) prior, which is information equivalent to feasibility established in 5 of 6 treated patients. If the number of patients in whom proton is deemed feasible is less than or equal to the number in the table below then termination will be considered as it is highly unlikely that the feasibility rate is >90%, as noted by the Bayesian posterior probabilities.

Bayesian Rule for Feasibility				
Patients treated in each stratum	3	6	9	12
Patients in whom proton is feasible	1	4	6	9
Posterior Prob[feasibility rate >90%]	0.04	0.09	0.04	0.08
Action	Terminate enrollment			

Acute toxicity will be divided into 2 categories to best characterize toxicities in this disease.

Non-Neurologic Acute Toxicity

Because proton therapy is expected to spare normal tissues, a non-neurologic acute toxicity rate ≤20% is considered acceptable. We will assume a beta (1,5) prior, which is information equivalent to toxicity in of treated patients. If the number of patients with non-neurologic acute toxicity equals or exceeds the number in the table, then termination will be considered as it is likely that the toxicity rate is >10%, as noted by the Bayesian posterior probabilities.

Bayesian Rule for Non-Neurologic Acute Toxicity				
Patients treated	3	6	9	12
Patients who experience acute toxicity	2	2	3	4
Posterior Prob[toxicity rate >20%]	0.80	0.62	0.70	0.76
Action	Terminate enrollment			

Neurologic Acute Toxicity

Because radiation therapy is directed to the craniospinal axis, a neurologic acute toxicity rate ≤10% is considered acceptable. We will assume a beta (1,5) prior, which is information equivalent to acute neurologic toxicity in one of 6 treated patients. If the number of patients with neurologic acute toxicity equals or exceeds the number in the table, then termination will be considered as it is likely that the toxicity rate is >10%, as noted by the Bayesian posterior probabilities.

Bayesian Rule for Neurologic Acute Toxicity				
Patients treated	3	6	9	12

Patients who experience acute toxicity	1	1	2	2
Posterior Prob[toxicity rate >10%]	0.81	0.70	0.84	0.76
Action	Terminate enrollment			

7.1.4 Statistical Analyses

Feasibility. The initial target sample size of 12 patients will be revised to 12 additional base of skull patients to be treated with pencil beam protons and evaluated for feasibility by the new definition. It is anticipated that up to 5 additional spine patients may be enrolled. So the total enrollment after this amendment will be up to 17 patients (12 base of skull and 5 spine). The statistical analysis will calculate the posterior probability that the feasibility rate is >90%. This analysis will be conducted 2 ways: based on all 26 patients treated and on all 17 patients treated after the modification. The definition of infeasibility will be that which was current when the patient enrolled on the trial. There will be no retroactive re-grading of infeasibility in the base of skull patients.

Acute Toxicity. All toxicities observed within 90 days from start of therapy will be graded by CTC Version 4.0 and tabulated. Special attention is paid to neurologic toxicity.

Late Toxicity. All toxicities observed later than 90 days from start of therapy will be graded by the CTCAE version 4.0 and tabulated.

Progression-free and overall survival will be estimated by the survival analysis methods. It is most likely that these time-to-event outcomes will be summarized as part of the phase II study.

Fatigue is scored on a 10-point scale based on the Brief Fatigue Inventory Questionnaire. At each time point, the BFI score will be summarized by mean and standard deviation, and plotted over time. We will examine the plots for the expected worsening of function in the 6-12 months post-radiation and gradual improvement from 12-24 months. The fatigue scores will be summarized in detail in the phase II study.

Neurocognitive function (FACT-Br) will be summarized by descriptive statistics and scatter plots. It is most likely that the neurologic outcomes will be summarized as part of the phase II study.

Estimation of Event Rates. The table below displays the 90% exact binomial confidence intervals based on 12 patients treated.

No. of Events	%	90% exact CI	No. of Events	%	90% exact CI
0	0.0	17.5*	7	58.3	31.5 , 81.9
1	8.3	.43 , 33.9	8	66.7	39.1 , 87.7
2	16.7	3.0 , 43.8	9	75.0	47.2 , 92.8
3	25.0	7.2 , 52.7	10	83.3	56.1 , 97.0
4	33.3	12.3 , 60.9	11	91.7	66.1 , 99.6
5	41.7	18.1 , 68.5	12	100.0	82.5*
6	50.0	24.5 , 75.5			* 90% 1-sided CI

7.2 PHASE II STUDY

Once feasibility and safety are established in the first 12 patients, then the phase II study will commence.

7.2.1 Design and Objectives.

Proton therapy at standard doses is not expected to improve clinical outcome but will likely reduce fatigue and toxicity. **The purpose of the phase II study is to characterize toxicity rates and to summarize fatigue scores at time points during and post-radiation. Progression-free survival will also be estimated.** There will be no early stopping in this phase of the study. Outcomes from the initial 12 patients will be included in this evaluation. An additional 38 patients will be enrolled on the phase II study, for a phase II study total of 50 patients. We may have to screen/enroll up to 50 subjects to reach the goal of 38 additional patients in the phase II portion of the trial.

7.2.2 Endpoints. Same as in 7.1.2

Acute Toxicity. Late toxicity. Fatigue & Neurocognitive function. Progression-free and overall survival.

7.2.3 Rules for Early Termination; continuation of rules as in 7.1.3

Non-Neurologic Acute Toxicity

If the number of patients with non-neurologic acute toxicity equals or exceeds the number in the table, then termination will be considered as it is likely that the toxicity rate is >20%, as noted by the Bayesian posterior probabilities.

Bayesian Rule for Non-Neurologic Acute Toxicity				
Patients treated	1	2	3	4

Patients who experience acute toxicity	5 5	5 7	5 9	5 1 1
Posterior Prob[toxicity rate >20%]	0 . 8 0	0 . 7 6	0 . 7 3	0 . 7 1
Action	Terminate enrollment			

Neurologic Acute Toxicity

If the number of patients with neurologic acute toxicity equals or exceeds the number in the table, then termination will be considered as it is likely that the toxicity rate is >10%, as noted by the Bayesian posterior probabilities.

Bayesian Rule for Neurologic Acute Toxicity				
Patients treated	1 5	2 5	3 5	4 5
Patients who experience acute toxicity	3	5	6	7
Posterior Prob[toxicity rate >10%]	0 . 6 8	0 . 8 2	0 . 7 9	0 . 7 7
Action	Terminate enrollment			

7.2.4 Statistical Analyses.

Analyses of acute and late toxicity and fatigue will be completed within 1 year of completion of accrual. Time-to-event outcomes and long term longitudinal measurements of fatigue and neurocognitive function will be analyzed 2-3 years after completion of accrual. Descriptive analyses and subset analyses are likely. The purpose of these subset analyses is hypothesis generation. Subgroup analyses will likely describe time-to-event outcomes by histology (e.g., chordoma or chondrosarcoma) and extent of surgery (e.g., biopsy only, partial debulking, and maximal debulking). They will produce estimates of clinical outcomes, to aid in the design of future clinical trials.

Acute and Late Toxicity. All acute and late toxicities will be graded by CTCAE Version 4.0 and tabulated. Toxicity rates and 95% confidence intervals will be calculated. The maximum half-width of the 95% confidence interval is $\pm$14% based on 50 patients.

Time-to-Event Outcomes. Trials of chordomas and chondrosarcomas which combine proton with photon, have demonstrated 5-year progression-free survival rates (i.e., free of local failure) of 60-80%. We do not expect the 5-year PFS rate to be much different with protons. Progression-free and overall survival and time to local failure, will be estimated by the Kaplan-Meier method. Median and 5-year estimates and 95% confidence intervals will be calculated.

Fatigue (Brief Fatigue Inventory, BFI) & Neurocognitive function (FACT-Br) will be summarized by mean and standard deviation calculated and plotted over time. We will examine the plots for the expected worsening of function in the 6-12 months post-radiation and gradual improvement from 12-24 months. Pre- and post-treatment comparisons at a primary time point (e.g., at 24 months post-radiation when function should have recovered) will be evaluated by Student's paired t-test or nonparametric Wilcoxon signed ranks test. A general strategy to assess trends over time in longitudinal data is to employ linear mixed effects models, which can account for the impact of covariates such as anti-seizure medication and baseline performance status. The BFI can also be categorized as mild (1-3), moderate (4-6) and severe (7-10). The rates of patients in the severe category will be estimated at each time point. Of primary interest are the rates at 12 and 24 months post-treatment.

There are little data published on BFI and FACT-Br scores in chordoma patients treated with radiotherapy, but profound fatigue and neurocognitive impairment are known side effects of photon radiation. We anticipate that the rate of severe fatigue will be reduced with protons. We will perform one exploratory test to determine whether the 12 month rate of severe fatigue is lower than 50%.

7.3 SAMPLE SIZE/POWER AND TRIAL DURATION.

Twelve evaluable patients will be enrolled on the feasibility portion of the trial. We estimate having to screen/enroll 18 subjects to reach the goal of 12 evaluable subjects. If feasibility and safety are acceptable, then an additional 38 patients will be enrolled for a study total of 50 patients. We may have to screen/enroll up to 50 subjects to have an additional 38 patients participate in the phase II portion of the trial. We estimate that the first 12 patients will be enrolled in 1 year. Then the study will be suspended for patient observation for 2 months for feasibility and safety evaluation. If the feasibility study is acceptable, then accrual will continue. With an accrual of 12 patients per year, the study should be actively enrolling for 4 years. To test whether the 12 month rate of severe fatigue is lower than 50%, a one sample test will be performed. With 50 patients, there is 79% power to detect a 33% rate versus a null rate of 50% by chi-square test at 1-sided 5% significance.

For the feasibility study, the initial target sample size of 12 patients will be revised to 12 additional base of skull patients to be treated with pencil beam protons and evaluated for feasibility by the new definition. There will not be a target sample size for spine patients and we will enroll those patients while filling the enrollment goal for the base of skull patients. It is anticipated that up to 5 spine patients may be enrolled. The total enrollment to the feasibility study after this amendment will be up to 17 patients (12 base of skull and 5 spine).

8 Safety and Adverse Events

The investigator or research staff will be responsible for detecting, documenting and reporting all events that meet the definition of an AE or SAE as defined in this protocol.

8.1 Definitions

Adverse Event

An ***adverse event*** (AE) is any unfavorable and unintended sign, symptom, sign (including abnormal laboratory findings), illness/disease (new or exacerbated) or experience that develops or worsens in severity temporally associated with the use of the investigational agent/device/procedure. Inter-current illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a Serious Adverse Event (SAE)
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Radiation Toxicities
Radiation side effects are typically divided into those that occur acutely and those that occur later. Common acute radiation side effects include fatigue, skin irritation or erythema, alopecia, nausea, vomiting and diarrhea. Typically, these side effects can be controlled with medication. Late side effects that are unlikely to occur would include radiation necrosis of the brain, brainstem injury, vascular effects (e.g. stroke), severe dementia, blindness, deafness, paralysis, and skin necrosis. Another rare but serious late side effect is the development of second tumors. It is hoped that proton radiation will substantially reduce both acute and late side effects by reducing the amount of normal tissue that is irradiated.

Acute radiation effects, through post treatment day 90 of treatment, and late radiation effects will be evaluated using the CTCAE 4.0..

8.2 Assessing and Recording Adverse Events

All Adverse and Serious Adverse Events will be assessed using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0).

8.3 Reporting of Serious Adverse Events

8.3.1 IRB Notification by Investigator

All events meeting the Penn IRB SOP for Unanticipated Events posing risks to subjects or others will be reported to the IRB as follows:

Unanticipated problems are:
(1) Unforeseen; and (2) indicate that participants are at increased risk of harm. The IRB requires investigators to submit reports of the following problems within 10 working days **with one exception**. The one exception for prompt reporting within 10 days applies to death of a research participant as noted below.
Adverse Event (regardless of whether the event is serious or non-serious, onsite or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is both unexpected and related to research procedures.

Note: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol,

any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts); An event is "related to the research procedures" if the event is deemed probably or definitely related.

If the adverse event involved death as unforeseen and indicates participants or others are at increased risk of harm, report in three days.

8.3.2 Data and Safety Monitoring Committee (DSMC) Notification by Investigator

All Serious Adverse Events (SAEs), regardless of grade, expectedness or attribution must be reported to the DSMC within 30 days. Deaths that are possibly, probably or definitely related to the protocol treatment/experience must be reported within 24 hours. SAEs should be reported to the DSMC for six months from the date the last subject was treated.

8.4 Stopping Rules

Refer to Section 7, Statistical Considerations for full discussion of both feasibility and Phase II rules.

8.5 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10, Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

The Medical Monitor will be Arati Desai, MD (a physician who is not directly involved in the trial and is not collaborating with the sponsor/investigator in any other trial). Because of Dr. Desai's background and experience she is an appropriate Medical Monitor (MM) for this study. In the role, she will review all AEs including grading, toxicity assignments, dose modifications, appropriateness of dose escalation and all other safety data and activity data observed in the ongoing clinical trial along with discussing relevant animal and toxicology studies and similar investigational agents. The Medical Monitor may recommend reporting of adverse events and relevant safety data not previously reported and may recommend suspension or termination of the trial. The investigator will meet with the Medical Monitor every year. Serious and unexpected issues will be handled on an ad hoc basis through calls or e-mail. Documentation of Medical Monitor activity will be maintained in the study specific Regulatory Binder. Copies of a Medical Monitor report requiring action on the part of the PI to protect subject safety or study integrity must be submitted to the DSMC within 10 business days.

Internal Safety and Compliance

The University of Pennsylvania Cancer Center (UPCC) through the Data and Safety Monitoring Committee (DSMC) will be reviewing this clinical trial. It is anticipated that with approval, the committee's role will be to ensure that the rights and well-being of all subjects are protected and that patients are treated in full compliance with the study treatment and parameters specified in the protocol. The Data and Safety Monitoring Committee (DSMC) is

responsible for overseeing the process of monitoring of studies and the conduct of audits. The investigators on this study are responsible for the continuous, close monitoring of subjects enrolled on this trial.

A DSMC audit of this trial will be performed twice a year for as long as the trial remains open for accrual. The principal investigator will be notified in advance of the selection of their protocol for review. Three randomly selected patients or 10% of the total accrual, whichever is higher will be audited. A written report is provided to the principal investigator following this audit. Any rating less than satisfactory would warrant a repeat full review at the time of the next scheduled audit or sooner, depending upon the extent of the deficiencies found. Substantial protocol deviations will be reported to the Director of the Cancer Center and the Associate Director for Clinical Research for consideration of appropriate administrative action, such as suspending accrual to the protocol.

A Medical Monitor, Arati Desai, M.D., who is not directly involved in this trial and is not collaborating with the investigator in any other trials, has been selected for this trial. The Medical Monitor will review adverse events, safety data, and activity data observed in the ongoing clinical trial. The Medical Monitor may recommend reporting of adverse events and relevant safety data not previously reported, and may recommend suspension or termination of the trial. The summary reports of all discussions of adverse events will be submitted to the Data and Safety Monitoring Committee (DSMC) on a quarterly basis or more frequently if appropriate.

The Principal Investigator or her designee of the trial will present to the Medical Monitor all adverse events observed inpatients, any activity data obtained, and whether those data invoked any stopping criteria in the clinical protocol. Adverse event reporting will follow the NCI guidelines. Results of the data from toxicology or other animal studies that are relevant will be discussed. Other information related to the safety and efficacy of the clinical study will be discussed. This includes information of similar investigational materials used in different studies.

Protocol Deviations/Exceptions

Occasionally, the investigator may need to deviate from the approved protocol. Deviations are categorized as reportable and non-reportable. Reportable deviations may be urgent or not. Urgent deviations may occur on the spot as necessary to protect the safety of a study subject and do not allow enough time for reporting in advance. However, they must be reported as soon as possible.

All deviations/exceptions will be reviewed and approved by the study Medical Monitor before being sent to the IRB and Data and Safety Monitoring Committee (DSMC). All deviations from the study protocol will be handled as follows:

Eligibility- Deviations from established eligibility criteria will not be allowed. If the investigator believes that a subject would truly benefit from the protocol therapy and there are no other viable options, then the protocol should be amended to reflect the change in restrictions. There may be situations where the deviation from eligibility may not warrant a

study amendment (e.g. a necessary test/procedure being a few days outside of the eligibility window, subject taking a concomitant medication within recent timeframe etc.). These deviations must still be reviewed and approved in advance of enrolling the subject.

The IRB must be notified of the planned deviation and a copy of all applicable amended study documents must be sent to the IRB. The planned deviation must also be submitted to the DSMC for evaluation. The DSMC does not approve deviations but rather provides and unbiased assessment of the appropriateness of the request. Both committees must be given sufficient time to review the request, gather additional information as necessary and make a decision. The Medical Monitor should be consulted first for all such deviations. Documentation of the Medical Monitor's assessment and opinion should be included with your initial report to both committees.

Other Reportable - Deviations that affect the protocol treatment administration (i.e. dose administered, route/method of administration, etc.), dose adjustment schema, stopping rules, modification to follow-up, removal of safety assessments/follow-up visits, accrual goal or any deviation that may affect the study outcome analysis or study integrity must be approved by the IRB and reviewed by the DSMC.

Non-Reportable - During the course of a study, there may be times when deviations are outside of the control of the investigator (i.e. subject not showing up for a study visit, lab errors, subject confusion, etc.). These type of deviations are not reportable (unless they occur at a level that impacts any of the reportable categories) but must be documented in a timely manner to show the impact of the deviation and corrective/follow-up actions that were taken. Documentation can be in the clinic/progress notes or note/memo to file. Notes/memos should be signed and dated.

Reporting Deviations/Exceptions
Reports to the IRB and DSMC will be done via the DSMC website www.ctsrmc.org. Reportable deviations must also be sent to the study Medical Monitor (if applicable).

9.0 Data Handling and Record Keeping

All patients must have a signed Informed Consent Form and an On-study (confirmation of eligibility) form filled out and signed by a participating investigator prior to entering the study.

Confidential research charts will be kept in locked cabinets at each participating institution. Subjects will be assigned a study number at the time of study enrollment. This study number and not the subject's name will be used on all case report forms.

HIPAA Compliance:
Patients will be asked to read and sign a separate consent form acknowledging the uses and disclosures of protected health information (PHI) in this study as required by The Health Insurance Portability and Accountability Act (HIPAA). PHI will not be shared with any outside institution except as required by law. Any reporting of the results of this study will be done only with de-identified patient data. Confidentiality will be protected as outlined below.

- Each subject will sign a study informed consent and a study-specific HIPAA authorization form prior to surgery.

- Each subject will be assigned a study number. All research-related material (to include specimens for research) will be labeled with the subject study number and the subject's initials.
- A list of the subject names with the associated subject numbers will be maintained in a locked cabinet and computer by the principal investigator and study coordinator.
- All research subject records will be kept in a study chart.
- An electronic database will be maintained. No subject names will be used in this database. Study numbers will be used. Only data which constitutes a limited data set (as defined by the University of Pennsylvania Health System in the HIPAA Privacy Education website) will be used.

9.1 Data Entry

All patients must have a signed Informed Consent Form and an On-study confirmation of eligibility form filled out and signed by a participating investigator prior to entering the study.

9.2 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subject(s) in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2.1 Unintentional Disclosure:

Upon discovering that PHI may have been or has been disclosed to anyone not specified in the HIPAA disclosure consent, the investigator will report the disclosure to the Institutional Officer in the Office of Research Compliance and Integrity. The report should contain details about the type of data disclosed and the extent of the disclosure (number of subjects, who received it etc.).

9.3 Records Retention

HIPAA Retention Period (45 CFR164.530(j):

Protected Health Information (PHI) Research Requests (HIPAA1-008): Records documenting research requests, privacy board review or privacy officer expedited review, background material, and acceptance or denial of request. Retain 6 years after research completed.

Protected Health Information Disclosure Records (HIPAA1-009): Documenting the release of PHI, including **both authorized and unauthorized** releases. Should include the date of

release, to whom the information was released, and the circumstances of the release. Retain 6 years after research completed.

Maintenance of HIPAA records is independent of the regulations for clinical study records. All records of PHI research requests and any type of release will maintained for 6 years after the research is fully terminated.

10.0 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The study PI is responsible for ensuring the ongoing quality and integrity of the research study. In addition, this study will be monitored or audited in accordance with Abramson Cancer Center's NCI approved Institutional Data and Safety Monitoring Plan.

The University of Pennsylvania Cancer Center (UPCC) has a formal plan for Data Safety and Monitoring of Clinical Trials. The clinical trial, "Proton Beam Radiation for Chordomas and Chondrosarcomas" is a trial that is subject to oversight of the UPCC through the Clinical Trials Scientific Review and Monitoring Committee (CTSRMC). The CTSRMC role is to ensure that the rights and well-being of all subjects are protected and that patients are treated in full compliance with the study treatment and parameters specified in the protocol. The Data Safety Monitoring Committee (DSMC) is responsible for overseeing the process of monitoring of studies and the conduct of audits. The investigators on this study are responsible for the continuous, close monitoring of subjects enrolled on this trial.

Auditing and Inspecting
The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

A DSMC audit of this trial will be performed once a year for as long as the trial remains open for accrual. The principal investigator will be notified in advance of the selection of their protocol for review. Three randomly selected patients or 10% of the total accrual, whichever is higher will be audited. A written report is provided to the principal investigator following this audit. Any rating less than satisfactory would warrant a repeat full review at the time of the next scheduled audit or sooner, depending upon the extent of the deficiencies found. Substantial protocol deviations will be reported to the DSMC through the Director of Compliance for consideration of appropriate administrative action, such as suspending accrual to the protocol.

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11.0 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be maintained in the study specific Regulatory Binder which contains "Essential Study Documents". In addition, NCI requires all cancer based studies to have an independent scientific review. This protocol must be reviewed and fully approved by the Clinical Trials Scientific Review and Monitoring Committee (CTSRMC) prior to enrolling any subjects. Documentation of CTSRMC approval must also be maintained in the study specific Regulatory Binder.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB and CTSRMC for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed and dated by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12.0 Study Finances

12.1 Funding Source

Funding will be provided by the Department of Radiation Oncology of the University of Pennsylvania.

13.0 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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