University of Pennsylvania

PROTON RADIOTHERAPY FOR EXTREMITY SOFT TISSUE SARCOMA

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Abbreviations

EBRT:	external beam radiotherapy
Gy:	Gray
LET:	Linear Energy Transfer
RBE:	Relative Biologic Effectiveness
SOBP:	Spread Out Bragg Peak
OER:	Oxygen Enhancement Ratio
STS:	Soft Tissue Sarcoma

STUDY SUMMARY

Title	*Proton Radiotherapy for Extremity Soft Tissue Sarcoma*
Short Title	*Proton Radiotherapy for Extremity Soft Tissue Sarcoma*
Protocol Number	*UPCC# 09510 ; IRB# 811583*
Phase	*Feasibility and Phase II*
Methodology	*Open*
Study Duration	*7 years (min.)*
Study Center(s)	*University of Pennsylvania*
Objectives	1. *To determine the feasibility and toxicity of pre-operative and post-operative proton radiotherapy for soft tissue sarcomas of the extremities* 2. *To evaluate the wound complication rate of pre-operative proton radiotherapy in patients with soft tissue sarcomas of the extremity* 3. *To evaluate the functional outcome at one year after post-operative proton radiotherapy in patients with soft tissue sarcomas of the extremity* 4. *To examine the relationship between pre-treatment hypoxia as determined by F18-EF5 scanning and treatment outcome*
Number of Subjects	*Feasibility – 12 in each stratum (subtotal = 24)* *Phase II – (a) Pre-op: 50 "enrolled" to obtained 40 "eligible"* *(b) Post-op: 50 "enrolled" to obtained 40 "eligible"* *(subtotal = 80)* ***Study Total = 124 (max.) / 104 (min.)***
Diagnosis and Main Inclusion Criteria	*Soft tissue sarcoma the extremities -- resectable preoperative or postoperative patients*

INTRODUCTION

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 side of the tumor distal to the beam 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, which may result in decreased short and long-term morbidity. Theoretically, this should improve the therapeutic index, allowing for greater dose to be delivered to the tumor/target volume and decreasing dose to normal tissues.

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[1-3]. 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[4]. Therefore, one would expect that for any given dose of radiation, the biological effect of protons would be similar to photons. The clinical advantage of proton beam radiotherapy over standard photon radiation, therefore, results from the more favorable dose distributions achievable given the physical properties described above. The advantage of protons has been demonstrated for medulloblastoma, chordoma and uveal melanoma, and comparative treatment planning using protons versus photons have shown a clear advantage to protons in terms of dose distribution[5-10].

Treatment of soft sarcoma with conventional therapy

Soft tissue sarcomas (STS) are relatively rare tumors of mesenchymal origin that arise in nearly all locations of the body[11]. Although, these neoplasms represent a heterogeneous group of tumors from a histological perspective, the treatment principles are similar for STS that arise in the extremity, retroperitoneum, and trunk [12-18]. Studies have demonstrated that limb preservation using a combination of wide local excision of the primary tumor and radiotherapy has equivalent survival compared to amputation. Therefore, limb preservation has become the preferred approach for patients with extremity STS.

The mainstay of therapy, however, is surgical resection. Wide local excision is favored, if technically feasible. Radiotherapy either in the pre-operative or post-operative setting is considered standard treatment particularly for high or intermediate grade sarcomas. The combination of surgery and radiotherapy leads to local control rates of 90% or greater for these patients[12,17]

There is considerable heterogeneity in the use of post-operative vs. pre-operative radiotherapy. The advantages of pre-operative radiotherapy compared to the post-operative setting include the use of smaller radiation fields, and a lower overall total radiation dose. However, this comes with the risk of increased surgical morbidity, particularly wound healing. Post-operative radiotherapy increases the amount of normal

tissue exposed to radiation (through larger radiation fields) and requires the use of a higher total radiation dose but avoids the risk of increased surgical morbidity associated with pre-operative treatment. One Phase III randomized clinical trial has evaluated pre-operative vs. post-operative radiotherapy in patients with extremity STS[19]. The authors found no increased difference in disease free or overall survival but did observe an increase in short term wound complications in the pre-operative arm. However, preoperative radiation did lead to better long-term function[20]

Other morbidity from the combination of surgery and radiation can be substantial in patients with STS of the extremity regardless of whether it is delivered in the pre-operative or post-operative setting. Complications include acute and late damage to skin and soft tissues, lymphedema, and bone fracture. In patients with retroperitoneal sarcomas, proximity of the target volume to small bowel, kidneys, liver, and spinal cord limit lead to a risk of both acute and late toxicities and limit the doses that can safely delivered. Clearly, new radiotherapy techniques such as proton therapy are needed to improve the therapeutic index of sarcoma therapy[20,21].

Hypoxia and F18-EF5

The assessment of hypoxia in human tumors has been a subject of intense interest in recent years. The ability to identify hypoxia is considered important in radiation therapy because there is an oxygen dependence of radiation cytotoxicity (1). Knowledge of tumor hypoxia could help direct radiation dose prescription, the use of hypoxic cell modifiers (for example see (2)), hypoxic cell cytotoxins (3), oxygenation therapies such as hyperbaric oxygen (4) or blood flow/oxygen-modifying therapies (for example, see (5)). Recently, the model regarding the importance of hypoxia has been expanded because of observations that patients treated with surgery alone for uterine cervix cancers had better local control if their tumors were better oxygenated pre-operatively (6). These observations led to the suggestion that hypoxic tumors were intrinsically more biologically aggressive than well-oxygenated ones. Further support for this idea was provided by a study of high-grade extremity soft tissue sarcomas (STS) demonstrating that these cancers were more likely to metastasize if they were hypoxic at the time of initial therapy (for example see (7)). In order to treat STS more effectively, it is necessary to know which tumors contain clinically significant levels of hypoxia. This can be accomplished with non-invasive imaging techniques such as ^{18}F-EF5 PET and should allow the optimization of image-directed therapy. We have chosen to assay ^{18}F-EF5 because the non radioactive form of this drug, EF5 has proven uniform biodistribution (9) and unique predictive properties in rat models (10).

Clinical Data to Date

The safety of EF5 has previously been demonstrated in a phase I study (24). To date, colleagues in our Department including the PI of this study have given EF5 to over 132 subjects. One serious adverse event thought to be possibly or probably related to EF5. A subject with a glioblastoma was admitted to the hospital with worsening neurological symptoms. It was thought that his symptoms were related to the volume of fluid associated with the EF5 infusion. He was treated with diuretics, and his symptoms improved. One episode of Grade 1 hypotension associated with symptoms of lightheadedness was observed. [^{18}F]-EF5 has been administered to 7 subjects with brain tumors and 17 subjects with other tumor types without any adverse events related to [^{18}F]-EF5. It is important to recognize that toxicity from [^{18}F]-EF5 may potentially be due to its biochemical structure and/or the radiation from fluorine-18. Biochemically, the dose of EF5 that is administered is significantly less than that administered in studies with unlabeled EF5 which has demonstrated very minimal toxicities to date in over 132 study subjects (11, 17, 19, 25, 30). The amount of labeled drug is less than 5 mg, compared to 1500 mg (for a 70 kg subject) of unlabeled drug (factor of ≈300). Drugs similar to EF5 (i.e. misonidazole), given at much higher doses for extended periods of time as radiation sensitizers, have caused nausea, vomiting, temporary loss of sensation, numbness or tingling of the hands or feet, and temporary hearing loss. These side effects have not been observed with EF5 to date.

^{18}F-EF5 dosimetry

Based on our Phase I human clinical trial, unlabelled EF5 was found to be near equilibrium at the end of the intravenous infusion and its subsequent half life was 11.7+/-2.6 (SD) hr (*24*). Since the amount of EF5 in the ^{18}F-EF5 bolus injection is very small compared to the unlabelled drug (approximately 3 mg compared to 1500 mg for a 70 kg person), we expect the radioactivity to provide drug distribution information without significantly affecting the drug concentration. ^{18}F-EF5 is likely to be uniformly distributed with primarily renal and some biliary excretion. Because of the long biological half-life of EF5, we expect less than 20% of the total EF5 injected to be eliminated during the study.

In order to determine the radiation dose-limiting organ we compared the biodistribution and elimination of ^{18}F-EF5 and [F-^{18}]-F-Miso in rats. 120 minutes after injection of either radiolabeled drug, rats were sacrificed and various organs were analyzed for ^{18}F-EF5 and [F-18]-FMiso by gamma counting. In most tissues, the ratio of ^{18}F-EF5 / [F-18]-FMiso was close to one. There were some differences in biodistribution, with the level of [F-18]-FMiso 2-fold higher in the urine compared with 18F-EF5. Therefore, the dose absorbed by the bladder wall would be expected to be 2-fold higher for [F-^{18}]-FMiso than ^{18}F-EF5. The amount of radioactivity in various organs was also measured. However, the renal dose of ^{18}F-EF5 was 2-fold higher than that of [F-18]-FMiso. The organ that receives the highest dose for either drug is the urinary bladder (0.78 mGy/mCi). Based on this data, it may be reasonable to extrapolate from the results examining [F-18]-FMiso dosimetry in humans. In one study (*37*) patients were injected with 5 mCi of [F-18]-FMiso. The calculated total-body dose for a 70-kg man was 0.013 mGy/MBq (0.48mGy/mCi) and for a 57-kg woman 0.016 mGy/MBq (0.59mGy/mCi). In this study, the organ that received the maximal dose was the urinary bladder (0.021 mGy/MBq). Another [F-18] labeled agent for which there is significant experience is 2-(F-18) fluoro-2-deoxy-D-glucose (FDG). The total body dose for this agent has been calculated to be 0.39 mGy/mCi ref similar to the total body dose resulting from [F-18]-FMiso administration in humans.

^{18}F-EF5 Biodistribution and clinical data

We have recently completed a Phase I biodistribution study of ^{18}F-EF5 in cancer patients. The primary goal of this Phase I study was to determine the biodistribution and excretion of ^{18}F-EF5 and to estimate the radiation absorbed dose, metabolism, and safety of this drug. Sixteen patients (8 men, 8 women) with histologically confirmed malignancy received a mean intravenous infusion of 217 MBq (range 107-364 MBq) of ^{18}F-EF5 at the University of Pennsylvania(10) and University of Turku(6). Over a 4-6 hour period, four to five serial PET or PET/CT scans were obtained. To calculate the time-activity curves, residence times, and radiation dosimetry estimates, volumes of interest were drawn over the source organs for each PET scan or on the CT for each PET/CT scan. Serial blood samples were obtained to measure blood clearance. Bladder wall dose was calculated based on urine activity measurements. Safety was assessed by vital sign, ECG, and blood and urinalysis monitoring. The mean urinary bladder radiation absorbed dose was the largest at 0.077 ± 0.043 mSv/MBq (mean ± SD). There were no other mean organ radiation doses exceeding 0.10 mSv/MBq. The average effective dose equivalent of ^{18}F-EF5 was determined to be 0.018mSv/MBq calculated on a 4.8 hour voiding interval. ^{18}F-EF5 was well tolerated in all subjects. No serious adverse events were noted.

In conclusion, the average effective dose equivalent (EDE) and effective dose of ^{18}F-EF5 was 0.018 mSv/MBq and 0.016 mSv/MBq, respectively, which is less than that of ^{18}F-FDG (EDE = 0.030 mSv/MBq). The dose to the bladder wall was the highest.

Summary

The Roberts Proton Therapy Center within the Department of Radiation Oncology at Penn Medicine will be the largest proton therapy center in the world and will employ advanced technologies such as multileaf collimators. Although proton therapy has been used elsewhere to treat patients with soft tissue sarcoma and proton

therapy is approved by the US Food and Drug Administration, we propose this study to determine the feasibility and safety of proton therapy delivered at the Roberts Center for patients with STS of the extremity. Patients may, as part of their standard treatment regimen, also undergo other therapies as per the standard of care.

There will be 2 cohorts of patients: (1) extremity STS patients undergoing pre-operative radiotherapy and (2) extremity STS patients undergoing post-operative radiotherapy. There will be two phases of this study. In the first part of the study, the feasibility and safety (as defined below) of proton therapy will be evaluated in 12 patients within each cohort. In this feasibility study, patients with STS of either the upper or lower extremity will be evaluated. If proton radiotherapy is found to be feasible and safe, the study will proceed to Phase II. Since a majority (80%) of patients seen in the Department will have lower extremity STS and complication rates are high in this subgroup, we will restrict enrollment to STS of the lower extremity in the Phase II study. In Phase II (for the pre-operative group), we will evaluate the risk of wound complications within 4 months of surgery compared to historical data from the randomized clinical trial described above[19]. In Phase II (for the post-operative group), we will evaluate the functional outcome (e.g., fibrosis, joint stiffness, edema) of patients at two years after the completion of therapy compared to historical data from the randomized clinical trial described above [19].

1 STUDY OBJECTIVES

This study will be performed in two phases. In the first phase, feasibility will be established using the primary objectives set below. The second part will begin no earlier than 30 days after the last patient in the initial phase has completed treatment and once safety and feasibility has been verified.

Primary Objectives for feasibility phase of study

The primary objective of this study is feasibility. The study will be deemed infeasible if 10% or more 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 (95% of planning target volume covered by 95% of the dose).
b. Patient is unable to tolerate more than 25% of treatments (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) using proton radiotherapy. Note: this end-point is proton-therapy specific, and indicates feasibility of proton as opposed to photon radiotherapy. For example, if the proton-specific patient immobilization/positioning is not well tolerated or extra time in the treatment position is too long or uncomfortable, protons delivered per protocol would be deemed not feasible compared to photons. **Any treatments that cannot be delivered with protons will be delivered using photons, so that the patient receives the prescribed tumor dose.**
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 33% of patients experience a significant toxicity (defined in Section 7.1.2).

Primary Objectives for second phase of study:

- The primary objective of Phase II in the *pre-operative group* will be to evaluate the wound complication rate of pre-operative proton radiotherapy in patients with STS of the lower extremity.
- The primary objective of Phase II in the *post-operative group* will be to evaluate the functional outcome (e.g., fibrosis, joint stiffness, edema) at two years after post-operative proton radiotherapy in patients with STS of the lower extremity.

Secondary Objectives for both phases of study:

- To assess the local control rate, progression-free survival and overall survival of proton radiotherapy for STS of the extremity.
- To determine the acute and late toxicities of proton radiotherapy to the extremities.
- To monitor for effects of proton treatment on tumor and normal tissues using radiographic imaging (both cohorts) or *ex-vivo* analysis of tissue samples (pre-operative cohort only).
- To examine the relationship between pre-treatment hypoxia as determined by F18-EF5 scanning and treatment outcome.

2 SUBJECT SELECTION AND WITHDRAWAL

This study plans to enroll 80 evaluable subjects (40 evaluable patients in each cohort) over 7 years. For pre-operative patients, evaluablility requires a minimum of 4 months of follow-up after surgery. For post-operative patients, evaluablility requires a minimum of 2 years of follow-up from the end of radiotherapy.

Inclusion Criteria

- Patients with a histologic diagnosis of soft tissue sarcoma of the extremities are eligible for this study.
- Patient must be $\geq$ 18 years of age.
- Patients must have evidence of disease limited to the extremities.
- For the pre-operative group, patients must be considered operable/resectable and a candidate for pre-operative radiotherapy as judged by the attending surgeon and radiation oncologist. The clinical evaluation of patients will include a work up as per the standard of care. All patients in the pre-operative group will be evaluated for this protocol PRIOR to the initiation of therapy.
- For the post-operative group, patients must be considered operable/resectable (if evaluated prior to resection) and a candidate for post-operative radiotherapy by the attending surgeon and radiation oncologist. The clinical evaluation of patients will include a work up as per the standard of care. Patients in the post-operative group may be evaluated PRIOR to the initiation of any therapy or may be referred for evaluation after surgical resection.
- ECOG status of 0-2.
- Patients must sign a document that indicates that they are aware of the investigative nature of the treatment of this protocol, and the potential benefits and risks. Patients unwilling or unable to sign informed consent are excluded from the study.
- 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.
- Negative urine pregnancy test for females of childbearing potential on the day of the F18-EF5 PET scan prior to F18-EF5 injection

Exclusion Criteria

- Pregnant women, women planning to become pregnant and women that are nursing.
- Patients who experience surgical complications that prevent radiation from starting for 5 months or more, unless there is evidence of gross residual disease.

Subject Recruitment and Screening

Subjects will primarily (but not solely) be recruited from either at Penn Medical Center or the Department of Defense Oncology practices. 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. Should slots be available, a qualified member of the research team will initiate the formal consent process. This person will interview the potential subject with privacy considerations, explain the requirements of the study and provide a copy of the Informed Consent Form. The person obtaining consent will state the volunteer nature of research and advise the subject to take sufficient time to discuss the study 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 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 proton radiotherapy in Penn Medicine's Department of Radiation Oncology. Subjects will not be paid for participating in the study. All medical costs will be the responsibility of the subjects and/or their insurers. Cost of living will be the responsibility of the subjects.

At the University of Pennsylvania, we see approximately 20 cases of extremity STS per year. We anticipate that with the availability of proton radiotherapy, these numbers may increase. We estimate an annual accrual of 12 subjects per year for each cohort. We will also treat patients either preoperatively or postoperatively from Walter Reed Army Medical Center. In addition, this protocol will be listed on our web site as a formal protocol and information of its availability will be made known to treating professionals throughout our satellites as well as other referring physicians. These patients, if treated preoperatively with radiation therapy, will be required to have their surgery at the Hospital of the University of Pennsylvania.

Early Withdrawal of Subjects

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.

Subject Participation: Subjects may be withdrawn if the subject decides to refuse continuation of treatment or follow-up. Subjects may also be withdrawn for non-compliance with the protocol or withdrawal of consent. The reasons for withdrawal will be documented.

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.

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 subjects off study for toxicity and survival. Survival will be followed for a minimum of 5 years by means of scheduled appointments and available medical records. Every effort will be made to follow for overall survival.

3 RADIATION THERAPY

Treatment Planning, Imaging and Localization Requirements

Immobilization: As per standard of care, all subjects will be immobilized in a custom designed device in the appropriate position as determined by the attending radiation oncologist. Radiotherapy treatment planning CT scans and/MRI scans (with or without contrast, as per standard of care) will be required to define gross target 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 treatment planning system. All tissues to be irradiated must be included in the CT/MRI scan. The planning CT/MRI scan will be done at ≤5 mm intervals. 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 clinically indicated.

Target Contouring

Pre-operative patients:

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

Clinical Target Volume 1 (CTV1) is defined as the GTV plus areas that are considered to contain potential microscopic disease which typically would be 5 cm inferior and superior to the GTV and 2 cm either medially or laterally.

High risk CTV (CTV2) for pre-operative cases will be determined by the attending radiation oncologist in conjunction with the attending surgeon and will include areas of the GTV that are thought to be difficult to resect or at high risk for positive margins.

Planning Target Volume (PTV) will provide a margin as determined by the attending radiation oncologist around each GTV or CTV to compensate for the variability in treatment set up and internal organ motion.

Post operative patients:

GTV will represent any gross residual disease.

Clinical Target Volume 1 (CTV1) is defined as the GTV and the resection bed plus areas that are considered to contain potential microscopic disease which typically would be 7-10 cm inferior and superior and 2 cm either medially or laterally to the resection bed.

Clinical Target Volume 2 (CTV2) is defined as the GTV and the resection bed plus areas that are considered to contain potential microscopic disease which typically would be 5 cm inferior and superior and 2 cm either medially or laterally to the resection bed.

Clinical Target Volume 3 (CTV3) is defined as the GTV and the resection bed plus areas that are considered to contain potential microscopic disease which typically would be 3 cm inferior and superior and 1-2 cm either medially or laterally to the resection bed.

Clinical Target Volume 4 (CTV4) will be determined by the attending radiation oncologist in conjunction with the attending surgeon and will include areas of the resection bed that contain or are thought to be at high risk for positive margins.

Planning Target Volume (PTV) will provide a margin as determined by the attending radiation oncologist around each GTV or CTV to compensate for the variability in treatment set up and internal organ motion.

- Volumes may be modified (reduced) to reflect a compromise between the desired CTV dose to be achieved and the radiation dose limits and the cost-function parameters for the organs at risk.

Normal Structures

The dosimetrist will define two structures: Skin-2 (2mm thick surface) and Skin-PTV (all PTVs will be subtracted from the surface contour). Skin-PTV is the normal tissue structure that is all tissue other than what is contoured as something else.

Organs at risk (OAR) are normal tissue structures in or near the radiation field that may put the patient at risk for toxicities. The OAR volumes are contoured as visualized on the planning scan. Planning OAR is the OAR expanded for setup uncertainty or organ motion. The PAR may be created as determined by the attending radiation oncologist.

Dose fractionation and specification

Preoperative radiotherapy: Doses for preoperative radiotherapy will be delivered 1.8-2.0 Gy (RBE)/fx/day delivered to PTV1. The total dose will be 50-50.4 Gy(RBE) to PTV1. A simultaneous in field boost of up to 4-

5.4 Gy(RBE) to PTV2 [total dose 54-55.8 Gy(RBE)] may be given as deemed appropriate by the attending radiation oncologist.
Postoperative radiotherapy: A shrinking field technique will be used. CTV1 will be treated in the initial field at 1.8 Gy(RBE)/fx/day delivering a total dose of 45 Gy(RBE) to PTV1. CTV2 will be treated with 1.8 Gy(RBE)/fx/day delivering 9 Gy(RBE) to PTV2 for a cumulative dose of 54 Gy(RBE). CTV3 will be treated with 1.8 Gy(RBE)/fx/day delivering 9 Gy(RBE) for a cumulative dose of 63 Gy(RBE). In patients with close or positive margins, CTV4 will be treated with 1.8 Gy(RBE)/fx/day delivering for a cumulative dose of between 66-72 Gy(RBE) as determined by the attending radiation oncologist. Higher doses may be delivered to localized areas of gross residual disease if clinically indicated.

For the pre-operative cohort, additional postoperative may be performed for patients with close or positive margins, patients felt to be at high risk for positive margins, or patients with gross residual disease. The dose specifications are as follows: PTV (area of concern for recurrence + margin) dose: 16-22 Gy(RBE) for close, positive, or 'at risk' margins; 22 – 32 Gy(RBE) for gross residual disease that cannot or will not be resected in a second surgical procedure.

Treatment Planning
3.1.1 Dose specification: 95% of PTV to receive ≥ 95% of the prescribed dose.

Treatment Duration
Proton radiation therapy will in most instances be completed within 6 or 8 weeks of the start of treatment for the feasibility. This may be extended if subjects require a break from treatment. Criteria for break could include any Grade 4 toxicity, depending on the clinical situation as determined by the attending radiation oncologist. Further treatment plans will be decided at the discretion of the treating physician.

External Beam Equipment and Beam Delivery
Protons: Treatments will be administered at the University of Pennsylvania Roberts Proton Facility, which houses a high energy cyclotron with fixed angle and rotating gantries that produce scattered or pencil beam scanned proton beams. All charged particle treatment will be given with the patient in the appropriate immobilization device. 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 with respiratory gating to account for respiration as appropriate.

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. All periodic and patient-based quality assurance for patient treatment will conform to established Penn Radiation Oncology Department standards and all treatment plans will be reviewed at weekly quality assurance meetings (chart rounds).

4 SURGERY , CHEMOTHERAPY AND IMAGING

Radiation therapy will be performed either preoperatively or postoperatively. This decision will be made by the attending surgeon and radiation oncologist. For patients in the preoperative cohort, surgery will be performed 4-12 weeks after completion of radiotherapy. This will consist of resection of all gross tumor with adequate margins, sampling of lymph nodes and any other areas suspicious for involvement by the sarcoma as clinically appropriate. For patients in the postoperative cohort, radiotherapy will begin 3-8 weeks following surgery.

Chemotherapy (standard of care as determined by medical oncology) may be given no sooner than day 30 after radiation therapy for the post-operative patients or day 30 after surgery if radiotherapy is pre-operative as deemed clinically appropriate by the attending surgeon and radiation oncologist.

18F-EF5 PET Scan

Up to 4 weeks prior to treatment with either surgery or proton radiation, ^{18}F-EF5 will be administered in the Department of Nuclear Medicine in the Hospital of the University of Pennsylvania (HUP) or in the Department of Radiation Oncology in the Perelman Center for Advanced Medicine. Approximately 5mCi of ^{18}F-EF5 will be administered as an IV bolus (for details of ^{18}F-EF5 synthesis, see specific methods, below). After the injection of ^{18}F-EF5, subjects will be asked to remain in the Nuclear Medicine or Radiation Oncology waiting room during the free time before their PET/CT scan, where they may relax until they are required to go to the PET/CT scan room. There is no bathroom restriction during this time. The Scan will be performed at 180 minutes (evaluation of hypoxia) following injection. Subjects will be positioned on the PET-CT imaging bed comfortably with their head secured in the head hold of the PET instrument.

TIME (APPROXIMATELY)	SCHEDULE OF EVENTS
-30 minutes	Transport to nuclear medicine facility
-10 minutes	Placement of one intravenous line
0 minutes	Injection of ^{18}F-EF5 (≈ 5 mCi)
1-179 minutes	Free time
180 minutes	PET/CT Scan
215 minutes	Study completed

Table 3: ^{18}F-EF5 PET Protocol

Expected Adverse Events Associated with radioactive ^{18}F-EF5.

The estimated radiation exposure from 5 mCi of ^{18}F-EF5 is 2.5 mGy (see section 2.4, p. 10). This is the equivalent of less than one year of exposure to natural background radiation (1 year exposure approximately 3.6 mGy assuming quality factor of 1). For comparison purposes, a bone scan is estimated to deliver an effective dose between 3.8 and 7.7 mGy ***(42)*.** A body CT scan is estimated to deliver 6-16 mGy (*42, 43*). Therefore, the amount of radiation to which patients will be exposed by ^{18}F-EF5 PET scanning is well below that delivered by other standard radiological tests and is not expected to cause problems related to radiation exposure. ^{18}F-EF5 and EF5 are identical from a chemical standpoint. The amount of labeled drug will be less that 5 mg, compared with 1500 mg (for a 70 kg patient) of unlabeled drug. Therefore no chemical toxicity can be expected for the small additional amount of labeled drug.

Radiation Exposure Based on Pharmacokinetic Studies of ^{18}F-EF5 in Human Subjects

Potential radiation toxicities are limited by the short half-life of [^{18}F] of 1.83 hours. Clinical experience with other fluorine-18 labeled agents designed to image tumor hypoxia or other metabolic events confirms that the short half-life of [^{18}F] results in no significant radiation toxicity. In order to determine more precisely the radiation exposure from [^{18}F]-EF5, pharmacokinetic studies are currently underway. The "worst case scenario" would be if the entire dose of [^{18}F]-EF5 stayed within the body. If there were uneven biodistribution, certain organs might get a relatively higher dose such as is the case with the thyroid with radioactive iodine. For EF5, the major route of excretion is through the urinary bladder with substantial excretion via the gall bladder. Based on pharmacokinetic studies to date, bladder excretion is extremely consistent for each subject, with a typical rate of approximately 5% per hour. Therefore, the radiation risk from [^{18}F]-EF5 will be predicted to be nearly identical to that for the ^{18}F-FDG dose used in a routine clinical PET scan. The estimated dose to the subject based on data from [^{18}F]-EF5 administration in human subjects is about 0.025 mSv/MBq. This results in a radiation exposure of about 4 mSv for a standard subject getting 5 mCi, and is comparable to the annual background of about 3.6 mSv. As mentioned above, organs that concentrate the radiotracer get a higher dose. Therefore, the urinary bladder wall is expected to receive about 5 times this dose (20 mSv), and the gall bladder wall receives about 2.5 times (10 mSv).

Dose Rationale and Risk/Benefits

We have specified a dose range centered around 5 mCi (range: 2.5 – 7.5 mCi) since it is not possible to determine exactly how much [^{18}F] labeled drug will be made prior to its synthesis and purification. If an individual synthesis should produce less than 5 mCi, there is confidence that acceptable (although more noisy) data can be obtained with as little as 2.5 mCi. Yields lower than 2.5 mCi will not be used. Conversely, it would be difficult to accurately subdivide the final sterile dose if it was somewhat higher than 5 mCi. However, a dose greater than 7.5 mCi will be subdivided in order to administer a final subject dose of 5 mCi.

As described above, the estimated radiation exposure from 5 mCi of [^{18}F]-EF5 is 4 mSv based on the pre-clinical studies of [^{18}F]-EF5 dosimetry. This is the equivalent of about one year of exposure to natural background radiation. For comparison purposes, a bone scan is estimated to deliver an effective dose between 3.8 and 7.7 mSv (42). A body CT scan is estimated to deliver 6-16 mSv (42, 43). Therefore, the amount of radiation to which subjects will be exposed to by [^{18}F]-EF5 PET scanning is within the range of that delivered by other standard radiological tests and is not predicted to result in unacceptable radiation exposure. [^{18}F]-EF5 and EF5 are identical from a chemical standpoint. The amount of labeled drug will be less than 5 mg.

PHARMACEUTICAL INFORMATION - [^{18}F]-EF5
The chemical properties and synthesis of [^{18}F]-EF5 are described in detail in the INDs held by Varian Biosynergy Inc. and Stephen M. Hahn, MD.

Availability of Study Drug
[^{18}F]-EF5 will be synthesized at the cyclotron facility of the University of Pennsylvania. Dr. Richard Freifelder or his designate in the Department of Nuclear Medicine will maintain a complete log of each manufacture and disposition, including results of all SOPs.

Dispensing of Study Drug
Following the manufacture of [^{18}F]-EF5 at the PENN cyclotron facilities, it is hand-carried to the Department of Nuclear Medicine in the Hospital of the University of Pennslvania or to the Department of Radiation Oncology in the Perelman Center for Advanced Medicine where the radioactivity is assessed. It is anticipated that the activity will be in the range of 2.5-7.5 mCi. For doses greater than 7.5 mCi, the study drug will be subdivided to ensure that the dose administered will be 5 mCi. [^{18}F]-EF5 will then be drawn into a sterile syringe for intravenous subject administration.

Treatment Regimen
[^{18}F]-EF5 will be administered by a qualified user in the Department of Nuclear Medicine in the Hospital of the University of Pennsylvania or in the Department of Radiation Oncology in the Perelman Center for Advanced Medicine. It will be administered as an IV bolus injection. The dose will be approximately 5 mCi (acceptable range: 2.5-7.5 mCi).

Destruction of Study Drug
If the entire study drug dose is administered, the radioactive syringe will be disposed of into the radioactive waste in the Department of Nuclear Medicine or in the Department of Radiation Oncology in the Perelman Center for Advanced Medicine. As the radioactive half-life of ^{18}F is 1.83 hours, we anticipate that by the end of a working day, the radioactive syringe can be safely disposed of in the standard biologic waste. In the event that the study drug is not administered or only partially administered, the radioactive syringe and its contents will be disposed of in the radioactive waste in the Department of Nuclear Medicine or in the Department of Radiation Oncology in the Perelman Center for Advanced Medicine. It will be subsequently disposed of in the standard biologic waste upon sufficient decay of its radioactivity.

5 STUDY PROCEDURES

	Pre-treat	Day of F18-EF5 PET/CT Prior to injection	Weekly during RT	Visit prior to surgery	30 days post surg/RT[1]*	Q3 months for 2 years, then q6 months for years 3 - 5 after surgery/RT	Yearly (as long as the patient wishes to be followed)
Tests and Observations							
History and PE	X		X	X	X	X	X
ECOG PS	X						
Biopsy	X						
Urine Pregnancy Test		X[2]					
Toxicity Assessment	X		X			X	
Tumor Measurement	X[1]			X		X	
18F-EF5 PET Scan (optional)	X[3]						

*1- *Post radiation/surgery follow-up schedule defined for each cohort in Section 6.*

2- Urine pregnancy test is routinely performed prior to PET/CT scanning as departmental standard.

3 – Subjects may participate in study with or without perrforming 18F EF5 PET scan. This is a subject option.

Post-treatment Evaluation and follow-up

All subjects will be evaluated prior to initiation of treatment and weekly during the course of radiotherapy. For patients receiving pre-operative radiation, a visit will occur prior to surgery. This visit will involve an interval history and physical. All patients will be seen for a first post-operative/post-radiation office visit with either the attending radiation oncologist or surgeon no more than 30 days following surgery/radiotherapy or discharge from the hospital, whichever comes later. Pre-operative patients will be seen after surgery, weekly x 1 month, then every 2nd week x 1 month, then monthly for 3 months. Post-operative patients will be seen one month after surgery and then in 3 months. Follow up visits for pre-operative and post-operative patients will be with either the attending surgeon or radiation oncologist every 3 months for two years, and every 6 months thereafter for *3* years. These office follow-up visits will consist of an interval history and physical and imaging studies as clinically indicated. The wound complication endpoint will be scored at 4 months after surgery in the pre-operative group. Post-operative patients will be scored for fibrosis, edema and joint stiffness within 2 years after after radiation.

Assessment of Tumor Response

Tumor Response (RECIST criteria): RECIST criteria will only be evaluated after radiation just prior to surgery in the pre-operative patients. Post-operative patients will not be evaluated since they undergo complete resection of STS.

Target Lesions:

- **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.

Non-Target Lesions:

- **Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker levels.
- **Incomplete Response/Stable Disease (SD):** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker levels above normal limits.
- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions or any new lesion(s)

Confirmation of Response (*used only for studies with response as primary endpoint)*

- 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. (*Reflect this in your study procedures table in section 6*)
- To assign SD, measurements must have met the stable disease criteria at least once after study entry at "X" interval (*as defined by protocol*).

Failure

- **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
- **Nodal Failure:** Failure in regional lymph nodes.
- **Distant failure** is defined as appearance of tumor at sites beyond regional nodal and marginal site.
- **Progression-Free Survival:** duration measured from first day of treatment to first documented failure, death due to any cause or last patient contact alive.
- **Overall Survival:** Duration measured from first day of treatment until death due to any cause or last patient contact alive.
- Time to local failure, time to distant failure, PFS and OS will be calculated from **first day of radiation** in the pre-operative patients and calculated from **day of surgery** in the post-operative patients.

PET scan imaging and analysis

PET studies will be performed on a PET/CT scanner in the Department of Radiology in the Hospital of the University of Pennsylvania or in the Perelman Center for Advanced Medicine. PET scans will be processed with corrections for randoms, scatter, and attenuation before reconstruction. The randoms are subtracted directly (on-line) using a delayed coincidence window. The application of an accurate scatter correction method is necessary to achieve absolute quantification, and is particularly important for 3D PET. We have developed a Single-Scatter-Simulation (SSS) algorithm for this purpose (*44*) which has been extended for TOF data**.** The basic idea is to calculate from first principles the scatter distribution associated to an activity and scatter medium distribution, under the assumption that scatter is only due to single Compton scatter events. The assumption of single-event scatter is a good approximation for a system with good energy resolution, such as LYSO, particularly with a high energy threshold as used in the Gemini TF scanner. In practice, we use an estimate of the activity distribution from the reconstructed image of total counts, and the distribution of the

scatter medium is obtained from the reconstructed transmission CT scan, which is also used for attenuation correction.

For TOF reconstruction, we use the list-mode reconstruction implemented by Philips that is based upon a TOF list-mode maximum-likelihood algorithm which was originally developed in our laboratory at the University of Pennsylvania *(45)*. This algorithm models data corrections in the algorithm and uses consecutively ordered subsets to accelerate the reconstruction. The Poisson statistics of the data are preserved by using the data in their original form (i.e., without binning) and incorporate the physical effects of PET imaging in the system model. The TOF kernel is modeled as a one-dimensional Gaussian function along the LOR and is applied in both the forward-projection and back-projection operations. We reconstruct patient studies using the protocol defined at the University of Pennsylvania that uses unrelaxed OSEM (λ=1) with 33 subsets and stops after three iterations for practical reconstruction time. A fully 3D list-mode iterative reconstruction algorithm is computationally intensive and required specialize computer equipment and software development to implement in practice. Using a 10-node (dual CPU) computer cluster, the image processing with this algorithm proceeds in parallel with data acquisition and is typically completed for clinical whole-body (multi-bed) studies 10-30 minutes after the end of the acquisition, depending on the number of counts collected.

The data corrections and 3D reconstruction that have been described help to improve the accuracy of quantification of the studies, in particular tumor contrast. Nevertheless, we do not expect that full recovery of contrast of small tumors will be achieved. Typically this is possible only if the tumor size is large compared to the spatial resolution. For example, the contrast of a 2-cm tumor is only about 50% of its true value, assuming that the region-of-interest is equal to the size of the tumor. Our image reconstruction algorithm has the capability of incorporating the measured point spread function into the system model so that we can recover the spatial resolution loss that is more significant as the distance from the center of the field-of-view increases. The resolution recovery technique will be further developed and validated for the tumor studies that will be performed for this project.

Image registration of the PET images with other modalities (CT or MRI) will be performed using a mutual information algorithm developed at PENN and similar to the approach of Mattes (*46*)**.** Our algorithm allows non-rigid, as well as rigid registration, using a set of user-defined correspondence points as constraints. For intra-patient comparisons between the PET scans and the MRI or CT, the fully automated rigid registration is expected to have sufficient accuracy.

Tumor ROIs will be drawn with the help of MRI and/or CT images. Tumor to normal tissue ratio will be determined in each voxel of the ROI.

6 STATISTICAL PLAN

This is a study of proton therapy in extremity soft tissue sarcoma (STS). Patients will be stratified into pre- and post-operative cohorts. The trial will be conducted in two phases, first, a feasibility study and then, a phase II study to detect reduced complication rates. Since proton is a new treatment modality at PENN, the first proton trial conducted in <u>each</u> 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.

6.1 FEASBILITY STUDY.

<u>Design and Objectives:</u>
This feasibility trial is designed to establish feasibility and safety of proton therapy. Patients are stratified into pre-operative and post-operative groups with 12 patients in each stratum. Patients with STS of the <u>upper or lower extremity will be treated in the feasibility study.</u> These cohorts will be accrued, evaluated and advanced to the second phase independently. Patients enrolled in the

feasibility study will continue to be followed for secondary endpoints, such as late toxicity and clinical efficacy.

Pre-operative patients will receive 5-6 weeks of radiation. Four to 12 weeks after completion of radiotherapy they will undergo surgery. In the feasibility study, pre-operative patients will be followed for a minimum of 90 days after start of radiation treatment or 30 days after surgery, whichever comes later to determine feasibility and safety (acute toxicity) before moving to the second phase of the study.

Post-operative patients will receive 8 weeks of radiation. Four weeks after completion of radiotherapy patients may receive chemotherapy, if clinically indicated. Post-operative patients will be followed for a minimum of 90 days after start of radiation treatment, to determine feasibility and safety (acute toxicity) before moving to the second phase of the study. Toxicities experienced during the post-radiation follow-up window will be carefully evaluated for relatedness to proton therapy or to surgery or chemotherapy.

Endpoints

Primary Endpoints:
(i) Feasibility will be based on multiple radiation planning and treatment parameters. Should a patient experience one of the following events, treatment will be deemed infeasible:
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.
Patient is unable to tolerate 25% of treatments using proton radiotherapy, that is, up to 25% of treatments could be delivered using photons. Reasons for missed treatments may include: unable to set patient up within acceptable limits of tolerance, patient unable to tolerate treatment position or immobilization for duration of treatment).
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.
(ii) Acute toxicity is defined as any grade 3 or higher hematologic or non-hematologic toxicity that is probably or definitely related to radiotherapy (not surgery). All toxicities observed within 90 days from start of radiotherapy, will be graded by NCI CTC Version 4.0. For pre-operative patients all toxicities observed within 90 days after start of radiation treatment or 30 days after surgery, whichever comes later, will be graded.

Secondary Endpoints:
(i) Late toxicity is defined as any grade 3 or higher hematologic or non-hematologic toxicity which occurs after 90 days from start of therapy. Late toxicities will be graded according to the RTOG/EORTC late toxicity criteria. 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.
(ii) Wound complication is defined as a secondary operation under general or regional anesthesia for wound repair or wound management without second operation. Wound management includes an invasive procedure without general or regional anesthesia, readmission for wound care such as iv antibiotics, or persistent deep packing for 120 days or longer. Patients will be assessed for wound complications which develop within 4 months after surgery.
(iii) Fibrosis and joint stiffness will be graded according to EORTC/RTOG late radiation toxicity criteria. Edema will be graded as 0= none, 1= mild, 2= moderate, 3= severe, 4= very severe, according to the criteria of Stern (Stern TN. Clinical examination: a textbook. Year Book Medical

Publishers, 1964). Patients will be assessed for fibrosis, joint stiffness and edema within 2 years of completion of radiotherapy.

Clinical Efficacy is defined for pre-operative patients as overall response rate (CR + PR according to RECIST criteria) which is scored after radiation and before surgery. Progression-Free Survival is defined from first day of treatment to first documented failure, death due to any cause or last patient contact alive. Overall Survival is defined from first day of treatment until death due to any cause or last patient contact alive. Time to local failure, time to distant failure, PFS and OS will be calculated from first day of radiation in the pre-operative patients and calculated from day of surgery in the post-operative patients.

Rules for Early Termination for Feasibility, Acute Toxicity and Wound Complication:
Bayesian probability calculations will be employed to define rules of early termination and end of trial evaluation for feasibility and safety. The tables below indicate termination rules after groups of 3 patients have been treated. Hundreds of patients with certain types of cancer have undergone radiation therapy with protons. Thus, we will assume some "prior" feasibility and safety data for protons delivered at the standard radiation dose for our Bayesian calculations. We will assume prior information equivalent to that of 6 treated patients, which is commonly required to establish feasibility and safety in a standard 3+3 phase I trial design.

Feasibility – conducted separately for each stratum
We will assume a beta (5,1) prior, which is information equivalent to feasibility established in 5 of 6 treated patients. A feasibility rate > 90% is considered acceptable. If the number of patients 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	**3**	**6**	**9**	**12**
Patients who are feasible	**1**	**4**	**6**	**9**
Posterior Prob[feasibility rate >90%]	**0.04**	**0.09**	**0.04**	**0.08**
Action	**Terminate enrollment**			

Acute Toxicity – conducted separately for each stratum *** excludes wound complication ***
We will assume a beta (2,4) prior, which is information equivalent to unacceptable toxicity in 2 of 6 treated patients. An acute toxicity rate < 33% is considered acceptable. If the number of patients with unacceptable toxicity is greater than or equal to the number in the table below, then termination will be considered as it is likely that the toxicity rate is > 33%, as noted by the Bayesian posterior probabilities.

Bayesian Rule for Acute Toxicity				
Patients treated	**3**	**6**	**9**	**12**
Patients who experience acute toxicity	**2**	**3**	**4**	**5**
Posterior Prob[acute toxicity rate >33%]	**0.75**	**0.72**	**0.70**	**0.68**
Action	**Terminate enrollment**			

Wound Complication – Pre-operative patients only
We will assume a beta (2,4) prior, which is information equivalent to wound complication in 2 of 6 treated patients. A wound complication rate >40% is considered unacceptable. If the number of patients with wound complications is greater than or equal to the number in the table below then termination will be considered as it is likely that the wound complication rate is >40%, as noted by the Bayesian posterior probabilities.

Bayesian Rule for Wound complication				
Patients treated & have 4 mos followup	**3**	**6**	**9**	**12**
Patients who experience wound complication	**3**	**4**	**6**	**7**
Posterior Prob[wound complication rate >40%]	**0.83**	**0.75**	**0.85**	**0.80**
Action	**Terminate enrollment**			

Statistical Analyses: (Separately by pre-operative and post-operative strata)

Feasibility. The feasibility rate and exact 90% CI will be computed. The reasons why patients were not feasible will be tabulated. At the end of the trial, a Bayesian probability will be computed, as shown in the table above.
Acute toxicity. All toxicities as defined previously, will be graded by CTC Version 4.0 and tabulated. At the end of the trial, a Bayesian probability will be computed, as shown in the table above.
Late toxicity. All toxicities as defined previously, will be graded by EORTC/RTOG late toxicity criteria and tabulated.
Wound complications, fibrosis, joint stiffness and edema will graded and tabulated. These analyses will likely be performed in the phase II stage of the trial.
Clinical Efficacy. The RECIST response rate (CR + PR based on RECIST) and 90% exact CI will be computed. Time to local recurrence, time to distant recurrence, PFS and OS will be estimated by Kaplan-Meier analysis. These analyses will likely be performed in the phase II stage of the trial.
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**

6.2 PHASE II STUDY

Design and Objectives:
This stratified phase II trial is designed to evaluate early complications (e.g., wound complication in pre-operative patients) and late complications (e.g., fibrosis, joint stiffness and edema in post-operative patients). Patients with STS of the lower extremity only will be treated in the phase II study. Justification for enrolling lower extremity STS in phase II is that 80% of STS patients treated in the Department of Radiation Oncology have lower extremity STS and they are the subgroup who may benefit most from protons. For example in the study by O'Sullivan et al (Lancet 359, 2002), in pre-operative patients, the wound complication rate from photon radiotherapy in patients with lower extremity STS was 43% (30 events in 70 patients) compared to 5.5% (1 event in 18 patients) in upper extremity STS. 40 evaluable patients (including evaluable patients from the feasibility stage) will be enrolled in each stratum.

Endpoints:
Same endpoints as in Section 6.1: Wound complication, Fibrosis and joint stiffness, Edema, Acute toxicity, Late toxicity and Clinical Efficacy.

Evaluable for analysis:
For pre-operative patients, patients must have a minimum of 4 months of follow-up post-surgery to be evaluable and included in the phase II analysis. For post-operative patients, patients must have a minimum of 2 years of follow-up from the end of radiotherapy to be evaluable and included in the phase II analysis.

Rules for Early Termination for Wound Complications:
We will assume a beta (2,4) prior, which is information equivalent to wound complication in 2 of 6 treated patients. A wound complication rate >40% is considered unacceptable. If the number of patients with wound complications is greater than or equal to the number in the table below then termination will be considered as it is likely that the wound complication rate is >40%, as noted by the Bayesian posterior probabilities.

Bayesian Rule for Wound complication						
Patients treated & followed 4 months	**15**	**20**	**25**	**30**	**35**	**40**
Patients who experience wound complication	**8**	**11**	**13**	**15**	**17**	**19**
Posterior Prob[wound complication toxicity rate >40%]	**0.76**	**0.85**	**0.82**	**0.81**	**0.79**	**0.78**
Action	**Terminate enrollment**					

6.3 STATISTICAL ANALYSES

Pre-operative patients: Toxicity data will be graded and tabulated. A one-sample one-sided chi-square test will be performed to test the null hypothesis that the wound complication rate is 45% (same as photon). Patients must have a minimum of 4 months of follow-up after surgery to be evaluable for this analysis.

Post-operative patients: Toxicity data will be graded and tabulated. In the study by Davis et al (Radiother and Oncol 75, 2005), the grade 2+ fibrosis rate was 48%, joint stiffness 23% and edema 23%. Since fibrosis is the most common post-operative toxicity, it is considered the primary endpoint and a one-sample one-sided chi-square test will be performed at the 5% significance level to test the null hypothesis of 50% (same as photon). Joint stiffness and edema are less frequent toxicities and will be treated as secondary endpoints. The null hypothesis is that the grade 2 or higher rate is 25% (same as photon) for these endpoints. Patients must have a minimum of 2 years of follow-up after surgery to be evaluable for this analysis.

Acute toxicity (Late toxicity): Toxicities will graded and tabulated by stratum.

Clinical Efficacy: For pre-operative patients, the RECIST response rate (CR + PR based on RECIST) and 90% exact CI will be computed. For each stratum, time to local recurrence, time to distant recurrence, PFS and OS will be estimated by Kaplan-Meier analysis.

Exploratory Analyses of [^{18}F]-EF5:
The relationship between pre-treatment hypoxia as determined by F18-EF5 scanning and treatment outcome will be examined, stratified by pre- and post-operative cohorts. The clinical outcomes are: RECIST response rate (pre-operative patients only), time to local recurrence, time to distant recurrence, PFS and OS. We hypothesize that high ^{18}F-EF5 signal of the primary tumor (e.g. high levels of hypoxia) will relate to poorer clinical outcome (lower response rate, shorter time to local recurrence, shorter time to distant recurrence, shorter PFS, and shorter OS) in this group of patients. We will examine the prognostic values of hypoxia, as measured by ^{18}F-EF5, summarized from regions of the primary tumors. These analyses will be stratified by pre- or post-operative cohorts. Each subject will have summary statistics for hypoxia using ^{18}F-EF5 PET available from the primary tumor for this analysis. The Kaplan-Meier method will be applied to estimate the distribution of time-to-event outcome variables for patients with ^{18}F-EF signal above or below median of the summarized values. The association between RECIST response and hypoxia (binary coding) will be assessed by chi-square test. The association between time-to-event outcomes and hypoxia will be established by the Cox proportional hazards models. Both binary and continuous summary measures of ^{18}F-EF5 signal will be evaluated. A binary indicator for a hypoxic tumor can be defined as ^{18}F-EF5 signal above versus below median signal or based on other previously defined cut points. The direction and magnitude of the association will be assessed by hazard ratio and its 95% confidence interval.

6.4 SAMPLE SIZE/POWER AND TRIAL DURATION.

With 12 patients per year enrolled to each stratum and accounting for required follow-up time for feasibility and toxicities, this study should be active for 7 years. Twelve pre-operative and 12 post-operative patients will be enrolled on the feasibility portion of the trial. If feasibility and safety are acceptable then 40 evaluable pre-operative patients and 40 evaluable post-operative patients with STS of the lower extremity (each group includes evaluable patients from the feasibility stage) will be enrolled in the phase II portion of the trial. Up to 50 pre-operative patients may need to be enrolled to yield 40 evaluable patients with lower extremity STS who undergo surgery and have 4 months of follow-up post-surgery. With 40 evaluable patients, there will be 84% power for a chi-square test at one-sided 5% type I error to test a grade 2 or higher wound complication rate of 45% versus an alternative rate of 25%.

Similarly, up to 50 post-operative patients may need to be enrolled to yield 40 evaluable patients with lower extremity STS who receive post-operative radiotherapy and remain on-study for 2 years from the end of radiotherapy. With 40 evaluable patients, there will be 83% power for a chi-square test at one-sided 5% type I error to test a grade 2 or higher fibrosis rate of 50% versus an alternative rate of 30%. In addition, there will be 80% power for chi-square tests at one-sided 2.5% type I error to test grade 2 or higher joint stiffness and

edema, each with rates of 25% versus alternative rates of 9%. These secondary analyses will be tested at a 2.5% significance level, to control the overall type I error.

All correlative analyses of hypoxia and clinical outcome are exploratory. Results from this unique study will be used to estimate the magnitude of the associations for both RECIST response and time-to-event outcomes and will provide important guidance for future studies of the prognostic importance of hypoxia in STS patients.

7 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.

Definition

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. Intercurrent 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 Effect

Radiation side effects are typically divided into those that occur acutely (during radiation and up to 3 months after radiation) and those that occur later (>3 months post-radiation). Common acute radiation side effects include fatigue, skin irritation or erythema. Typically, these side effects can be controlled with medication. Late side effects that are unlikely to occur are paralysis or cardiac complications. 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.

For acute radiation effect, through post treatment day 90 of treatment, CTCAE 4.0 will be employed. Late radiation effects will be evaluated using the RTOG/EORTC Late Radiation Morbidity Scoring System.

Assessing and Recording Adverse Events

All Adverse and Serious Adverse Events will be assessed using NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0) with the exception of late radiation effects as noted above.

Reporting of Serious Adverse Events

(a) 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**.

(b) 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**.

(c) FDA Notification by Sponsor

The study investigator shall notify the FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the protocol agent/treatment/device as soon as possible but no later than 7 calendar days of knowledge of the event. If all details of the event are not immediately know, a partial report should be sent to ensure compliance with reporting timeframes. A follow-up report shall be submitted as soon as the relevant information is available.

If a previous event that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor will submit the event in a written report to the FDA as soon as possible, but no later than 15 calendar days from the day the determination is made.

(d) Varian Biosynergy, Inc.

All Unanticipated problems including Serious Adverse Events related to the study drug should be reported promptly to the Sponsor within 24 hours of discovery of the event. All other adverse events will be reported to Varian in an Annual Report at the Company's Request.

Stopping Rules

(Please see Section 6 for "Stopping Rules")

8 MEDICAL MONITOR

Data Safety and Monitoring Committee

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 every six months 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, Stephen Keefe, 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 bi-yearly basis or more frequently if appropriate.

The Principal Investigator or his/her designee of the trial will present to the Medical Monitor all adverse events observed in-patients, 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.

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 11.2). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

The Medical Monitor will be Stephen Keefe, M.D. (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. Keefe's background and experience in medical oncology, he is an appropriate Medical Monitor (MM) for this study. In the role, he 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 MM 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 MM every three months. Serious and unexpected issues will be handled on an ad hoc basis through calls or e-mail. Documentation of MM activity will be maintained in the study specific Regulatory Binder. Copies of an MM 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.

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 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.

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
All deviations/exceptions will be reviewed and approved by the study Medical Monitor before being sent to the IRB and DSMC. 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.

9 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. Subjects will be assigned a patient ID at the time of study enrollment. This 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 combined informed consent form and HIPAA authorization 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 combined informed consent and HIPAA authorization form prior to study enrollment.
- Each subject will be assigned a patient ID. All research-related material (to include specimens for research) will be labeled with patient IDs only.
- A list of the subject names with the associated patient IDs 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.

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. Case report forms will be used to standardize data-keeping.

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.).

10 Records Retention

10.1 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.

11 STUDY MONITORING, AUDITING, AND INSPECTING

11.1 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 RADIOTHERAPY FOR EXTREMITY SOFT TISSUE SARCOMA" 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.

11.2 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 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 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.

12 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.

13 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

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