UNIVERSITY OF PENNSYLVANIA
COMBINED INFORMED CONSENT & HIPAA AUTHORIZATION
TO PARTICIPATE IN RESEARCH

Protocol Title:	**PROTON RADIOTHERAPY FOR EXTREMITY SOFT TISSUE SARCOMA** **UPCC # 09510** **IRB # 811583**
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Emergency Contact:	**215-662-4000; 24 hour – please ask for the Radiation Oncologist on Call**

Why am I being asked to volunteer?

You are being invited to participate in a research study conducted at the University of Pennsylvania by Curtiland Deville, MD. Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the study doctor and/or the research team about this form and anything you do not understand. If you decide to participate, you will be asked to sign this form.

About Proton Radiation Therapy

Proton therapy is a method of radiation treatment that is approved by the Food & Drug Administration (FDA). Doctors have known that protons could be used for radiation therapy for several years, but because of the advances in imaging and computers used for planning treatment, it is now possible to very accurately plan how to deliver proton radiation. Proton radiation is considered a non-experimental form of radiation treatment.

The advantage of proton radiation over standard radiation has to do with how the radiation energy is released. Both standard and proton radiation damage the cells of the body in much the same way. Both stop the cell's ability to grow. Standard radiation continuously releases energy as it travels through the body and affects everything in its path. As a result there is cell damage to normal tissue as radiation enters the body, passes through the cancer tumor and continues to damage normal tissue cells as it exits the body. Doctors often limit the radiation dose to lessen the damage to normal tissue and vital organs. Proton radiation is different because protons can be directed and shaped as the protons approach their targeted stopping point, the tumor. This is called the Bragg peak. Then there is a burst of energy that can be shaped to the shape of the tumor. The most energy is released within the targeted cancer tumor. Healthy cells near the tumor receive significantly less radiation dose than the targeted tumor cells. Since the radiation does not continue beyond the tumor, there should be no damage to the normal tissues beyond the tumor. So, it would be expected that there might be less side effects with proton therapy compared to standard radiation. It is the most precise form of radiation currently available for localized tumors.

What is the purpose of this research study?

You have been invited to participate in this research study because you have cancer known as an extremity sarcoma and your doctor believes that treatment with proton radiation therapy is a good option for you. Patients with extremity sarcoma are usually treated with a combination of surgery and radiation. Sometimes, chemotherapy is also given. Radiation therapy may be given before the surgery (pre-operative radiation) or after the surgery (post-operative radiation). Your surgeon and radiation oncologist will consult with each other and then discuss with you which treatment will be best for your individual case. This study will treat patients in two dose groups – (1) patients receiving pre-operative proton therapy and (2) patients receiving post-operative proton therapy. In each dose group, the study is divided into two phases. In the first phase of 12 patients, your study doctors will determine if treatment with proton therapy is safe and can be delivered on a regular basis to your tumor. In the second phase, your study doctors will determine if proton therapy has less long term side effects compared to standard radiation in both pre-operative patients and post-operative patients. Specifically, in the pre-operative group, your study doctors are asking whether proton therapy leads to less wound complications after surgery compared to what might be expected for standard radiation. In the post-operative group, your study doctors are asking whether proton therapy leads to less joint stiffness, long term skin changes, and better function of your arm or leg compared to what might be expected for standard radiation.

Proton radiation therapy has been given to more than 41,000 people with various cancers. Protons give a very accurate dose of radiation to the targeted tumor. This type of treatment may lessen the side effects felt with treatment, thus helping doctors to treat you more effectively. We will assess the safety of this method of treatment. We will record the side effects you experience while receiving the prescribed dose of proton radiation. Gathered information will be used to draw conclusions about possible outcomes and benefits of being treated with proton radiotherapy, as well as ways to improve it. This study may generate future research studies of how proton radiation can be used.

Proton and standard radiation both need oxygen to be present in a tumor in order to work most effectively. Previous research has shown that the level of oxygen in a tumor may affect how well a patient with sarcoma responds to standard radiation therapy. This has not been studied with proton therapy. Therefore, another purpose of the research study is to determine if the amount of oxygen in your sarcoma is related to how well you respond to proton therapy. This may be important because in the future, we may be able to use this information and change the treatment to make the radiation more effective.

We will use the study agent EF5 to measure the amount of oxygen in your sarcoma. This agent has been well studied and when given to patients with cancers like the one you have, it can bind selectively to areas in your cancer that do not have much oxygen. In the past, in order to use EF5, a biopsy of the cancer needed to be done after it was given. To avoid a biopsy, the EF5 agent has been slightly changed by adding a radioactive tag so we can identify where it goes in your body and in your cancer. A radioactive tag is a small chemical change to the agent which has been made to emit a small amount of radiation so that it can be detected by a PET scan machine. We call this radioactive form F18-EF5. We can take pictures of its location in your cancer by doing a PET scan so that we do not need to take a biopsy of your cancer. We would like to perform the PET scan with F18-EF5 before the surgery and proton radiation your doctors have recommended. Undergoing the F18-EF5 scan is an optional procedure for participation in this study of proton therapy. You may choose to not have this research imaging PET/CT scan performed and if you choose not to perform the F18-EF5 scan, your decision will not affect your care.

What am I being asked to do?

Your doctor has decided that one treatment option involves receiving proton radiotherapy. Whether you get radiation treatment before or after your surgery will depend on your individual case. The first 12 patients in each group will be given proton radiation treatment at a standard dose. If you are enrolled in this phase of the study, you are being asked to allow us to record your treatment course and use your health information for future research studies.

These standard procedures will be explained by your doctor and you will be given a treatment schedule of these procedures that explains when each treatment will take place. As with any prescribed treatment plan, you will be asked to adhere to the schedule your doctor recommends.

If you are being enrolled in the second phase of the study, we will ask that you let us record your treatment course and record any side effects.

- If you are in the *pre-operative treatment group* that is receiving proton treatment before surgery, you will receive protons every day, five days per week for 5-6 weeks.
- If you are in the *post-operative treatment group* that is receiving proton treatment after surgery you will receive protons every day, five days per week for 7-8 weeks.

For both pre-operative and post-operative patients, this is same radiation schedule that you would receive if you were being treated with standard radiation. Your doctor will let you know when to come for treatments and you will be asked to adhere to the schedule that your doctor prescribes.

You will also be asked to undergo a research F18-EF5 PET scan. If you agree to this optional procedure, a member of the research team will schedule the day you will need to come for the PET scan and will advise you of your appointment time.

The following describes what will happen when you come to the hospital for the PET scan:

1. You will report to the clinical research center/Nuclear Medicine Department at the Hospital of the University of Pennsylvania (HUP).
2. A plastic catheter (small plastic tube) will be placed in a vein in one of your arms. You will then receive the study agent, F18-EF5, quickly injected into that catheter in your arm through a

syringe. You will be asked by someone on the research team if you have any symptoms that may be due to the F18-EF5 study agent.

3. You will then have free time for about three hours (180 minutes). During this time, you may be free to walk around the department or the hospital without any restriction. However, because of the timed schedule we ask for you to please stay within the vicinity of the department. It is important to have you back to continue the study promptly after three hours, so we ask that you not leave the hospital and be aware of the time you need to return.
4. When you return, you will be asked to lie on a couch under the PET scanning machine for the procedure. A set of PET scan pictures will be taken. This will take about 30 minutes. When the PET scan is finished, you will be asked by someone on the research team if you have any symptoms that may be due to the study medicine.
5. When you leave the hospital after the scan, you are asked to drink at least 16 oz of water over the next 4 hours and to frequently urinate. This will allow you to flush the F18-EF5 study agent out of your bladder.

The following is a summary of what will occur during your visit to the nuclear medicine department:

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 Scan
215 minutes	Study completed

I understand that performing the F18-EF5 PET/CT scan is an optional procedure and my plan of care will not be affected by my decision.

I CHOOSE TO HAVE THE F-18 EF5 PET/CT RESEARCH IMAGING SCAN PERFORMED. PLEASE CIRCLE YOUR ANSWER AND INITIAL :

YES_____ NO_____

How long will I be in the study? How many other people will be in the study?

This study will be conducted at the University of Pennsylvania Health System. A minimum total of 104 people, with a maximum total of 124 people will participate in this study. If you choose to participate in this study, you will be asked to remain active in this study while you are having your prescribed proton treatment and as follow-up care continues, for a minimum of 5 years. Treatment for each patient is expected to be completed 6 to 8 weeks, unless you require a break from treatment which will be decided by your doctor. Your doctor will clinically follow your progress for as long as you choose to come for follow-up visits.

What are the possible risks or discomforts?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. The research may involve risks that are currently unknown. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects.

Risks of Radiation/ Radiotherapy:
In this study you will be receiving proton radiotherapy; we would expect that your side effects would be similar, but less severe than, if you were receiving standard radiotherapy. If on the rare occasion the proton delivery system is not operational, your radiation oncologist may decide to treat you that day with a dose of standard radiation rather than interrupt your treatment with a treatment break. Radiotherapy is a standard treatment for sarcoma and you would not be experiencing any more exposure by being in this study than you would during standard treatment. The most common side effects of radiotherapy are listed below. The side effects of radiation are either early (which occur during radiation and usually go away several weeks after the completion of radiation) or late (which occur several weeks, months or years after the completion of radiation). Late side effects are often permanent.

Likely - Early common side effects include skin changes which may include dryness, redness, burning, swelling, pain and peeling of the skin, and skin breakdown with areas that may be moist. Tiredness may also occur. Typically, these side effects can be controlled with medications.

Less common - Late side effects that could occur include permanent joint stiffness, permanent arm or leg swelling, decreased range of motion of the treated arm or leg, firmness of the tissues in the radiation field, and difficulty with wound healing after surgery which might require additional surgery. Another rare but serious late side effect is the development of second tumors.

- **Pregnancy Risks:**

There is a possibility of pregnancy risks related to Proton therapy. Since there is no direct benefit from participating in this protocol for a pregnant woman and the treatment could affect the unborn child, pregnant women are not eligible to participate in this study. If you are a woman of child-bearing potential, a negative urine pregnancy test will be required before you may participate in this study.

- **Reproductive Risks:**

You should not become pregnant while on this study because the therapy in this study can affect an unborn baby. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them.

- **Risks of F18-EF5 PET scan**

  a) **Risks from radioactivity**
  Because the EF5 has been made radioactive so that we can take PET scan pictures of it when it is in your cancer, your body will receive some radiation. Because giving the F18-EF5 agent is not normally part of your routine medical care, this radiation dose is occurring only because you are participating in this study. At the doses that you will be receiving, it is very likely that you will see no effects from this radiation. At doses much higher than you will receive, radiation is known to increase the risk of developing cancers after many years.

  b) **Risks from the EF-5 agent**
  Your physician will be checking you for side effects from EF5. Drugs similar to EF5, when given at much higher doses for longer periods of time have caused nausea, vomiting,

temporary loss of sensation, numbness or tingling of the hands or feet, and hearing loss. In these previous studies, most of the side effects disappeared after the drugs were stopped. Other side effects may be long-lasting or permanent.

c) **Pregnancy risks**
The effects of EF5 and F18-EF5 on unborn children, children who are breast-feeding and the health of the mother are unknown. For this reason, if you are pregnant, you must inform the investigator(s) and understand that you will not be included in the study. If you are a woman of childbearing age you will have a standard of care urine pregnancy test on the day of the F18-EF5 PET/CT scan prior to the administration of F18-EF5.

If you are a woman of childbearing potential, you are advised to practice a medically approved method of birth control (such as oral contraceptives, barrier, surgical sterility, or abstinence) for one month following administration of EF5. Further, for one month following the administration of EF5, you should not become pregnant; and if you do become pregnant, options regarding your pregnancy will be discussed.

If you are a man, you are advised to use a means of birth control (such as condoms, abstinence, vasectomy) while you are taking part in this study because the effect of treatment on your sperm or upon the development of an unborn child is not known. You should not father any children while on this study.

d) **Risks from placement of an IV catheter and blood drawing**
Risks include pain, swelling, bruising, bleeding and infection, and rarely, nerve damage.

- **Other Risks:**

There is a risk of breach of confidentiality (when your confidential information is used or disclosed for purposes other than you authorized). The Department of Radiation Oncology will protect your records so that your name, address, and phone number will be kept private.

For more information about risks and side effects, ask your study doctor. You should talk to your study doctor about any side effects that you have while taking part in the study.

What if new information becomes available about the study?

During the course of this study, we may find more information (good or bad) that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available. If new information is provided to you, your consent to continue participating will be re-obtained.

What are the possible benefits of the study?

You may not get any benefit from participation in this research study. 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. We do not know if using proton radiation instead of standard radiation will increase your chances of an improved outcome. Additionally, we hope the information learned from this study will benefit other patients with extremity sarcoma in the future.

What other choices do I have if I do not participate?

You have the right to decide not to participate in this study. Standard radiation is an option for you and you should discuss this with your doctor. If you choose not to participate, you will not have any negative effects on the regular cancer care that you would normally receive. You can talk to your doctor(s) about your choices before you decide if you will take part in this study.

Will I be paid for being in this study?

You will not receive payment for your participation in this study

Will I have to pay for anything?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The F18-EF5 PET scan is being performed for the purpose of research. You will not have to pay anything for receiving the F18-EF5 PET scan. This means that you will not be billed for the scan or for receiving the EF5 agent. Also, your insurance company will also not be billed for the scan or for the costs of the agent. There will be no charge for blood tests drawn for the research tests that are done on your tumor. The cost of the PET scan will be paid for by funds supporting the research.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage . You can print a copy of the "Clinical Trials and Insurance Coverage" information from the above Website.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured or hurt during the study?

If you have a medical emergency during the study you should go to the nearest emergency room. You may contact the Principal Investigator or Emergency contact listed on page one of this form. You may also contact your own doctor, or seek treatment outside of the University of Pennsylvania. Be sure to tell the doctor or his/her staff that you are in a research study being conducted at the University of Pennsylvania. Ask them to call the telephone numbers on the first page of this consent form for further instructions or information about your care.

In the event that you are hurt or injured as a result of participation in this research study, please contact the principal investigator listed on page one of this form.

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for the University of Pennsylvania to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, tell the person in charge of the research study as soon as possible. The researcher's name and phone number are listed in the consent form.

When is the Study over? Can I leave the Study before it ends?

This study is expected to end after all participants have completed all visits, and all information has been collected. This study may also be stopped at any time by your physician or the Food and Drug Administration (FDA) without your consent because:

- The Primary Investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- The Food and Drug Administration (FDA) has decided to stop the study.

Your participation in this research is voluntary. If you decide not to participate, you are free to leave the study at anytime. Withdrawal will not interfere with your future care, or other services to which you are otherwise entitled.

Please be sure to talk to your study doctor if you are thinking about stopping or have decided to stop. It is important to tell the study doctor if you are thinking about stopping so any risks from the study can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

Who can see or use my information? How will my personal information be protected?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law or court order. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. Authorized representatives of the FDA and other University of Pennsylvania entities may need to review records of individual subjects. As a result they may see your name, but they are bound by rules of confidentiality not to reveal your identity.

What information about me may be collected, used or shared with others?
The following personal health information will be collected, used for research and may be disclosed or released during your involvement with this research study:

- Name, address, and telephone number
- Demographics (date of birth, age, race, ethnicity)
- Family medical history
- Allergies
- Current and past medications or therapies
- Information from a physical examination that generally also includes blood pressure reading, heart rate, breathing rate and temperature
- Blood test results including blood cell counts, blood chemistry measurements, blood tests that measure your liver and kidney function, blood or urine pregnancy test if you are a female of childbearing potential
- X-rays including Chest x-rays,CT scans, MRI exams, PET scan
- Information obtained from the chart maintained during hospitalization which includes the results of blood tests, surgery, physical examinations as well as other tests performed while you were in the hospital
- After your discharge, the results of physical examinations, blood tests, and CT scans will be obtained whether these are performed here by one of the study doctors or at outside facilities.

Why is my information being used?
Your information is used by the research team to contact you during the study. Your information and results of tests and procedures are being collected to:

- do the research
- oversee the research
- to see if the research was done right
- aid in finding advancements in clinical care

Your doctor may also use the results of these tests and procedures to treat you.

Who may use and share information about me?
The following individuals may use or share your information for this research study:

- The Principal Investigator and the Investigator's study team (other University staff associated with the study)
- The University of Pennsylvania Institutional Review Boards (the committees charged with overseeing research on human subjects) and University of Pennsylvania Office of Regulatory Affairs
- The University of Pennsylvania Office of Human Research (the office which monitors research studies)
- Authorized members of the University of Pennsylvania and University of Pennsylvania Health System and School of Medicine workforce who may need to access your information in the performance of their duties (for example: to provide treatment, to ensure integrity of the research, accounting or billing matters, etc.)

Who, outside of the School of Medicine, might receive my information?
As part of the study, the Principal Investigator, study team and others listed above, may disclose your personal health information, including the results of the research study tests and procedures to the following:

- Government Agency and/or their representative such as the Food and Drug Administration
- All research centers participating in the study, even if they are not part of the School of Medicine
- Varian Biosynergy, Inc., the company owns the manufacturing rights to EF5 and F18 EF5.

Once your personal health information is disclosed to others outside the School of Medicine, it may no longer be covered by federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may the School of Medicine use or disclose my personal health information?
Your authorization for use of your personal health information for this specific study does not expire.

Your information will be held in a research database. However, the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The University of Pennsylvania's Institutional Review Board grants permission
- As permitted by law

Can I change my mind about giving permission for use of my information?
Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending **written** notice to the principal investigator for the study at the address listed on page one of this form. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

What are my rights if I take part in this study? Who can I call about my rights?
Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.
We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study. In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

If you have questions regarding your participation in this research study or if you have any questions about your rights as a research subject don't hesitate to speak with the Principal Investigator or any other investigator listed on page one of this form. Concerning your rights as a research subject, you may also contact the Office of Regulatory Affairs at the University of Pennsylvania by calling (215) 898-2614.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania Health System and the School of Medicine to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania Health System and the School of Medicine to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this Consent/HIPAA authorization form will be given to you.

_____	_____	_____
Name of Subject (Please Print)	Signature of Subject	Date
_____	_____	_____
Name of Person Obtaining Consent (Please Print)	Signature	Date