Study Title:	**Phase I clinical trial of GRID therapy in pediatric osteosarcoma of the extremity**
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Study location(s):	University of Arkansas for Medical Sciences
Sponsor:	University of Arkansas for Medical Sciences
Funding Source:	TBD
Version Number:	7.0
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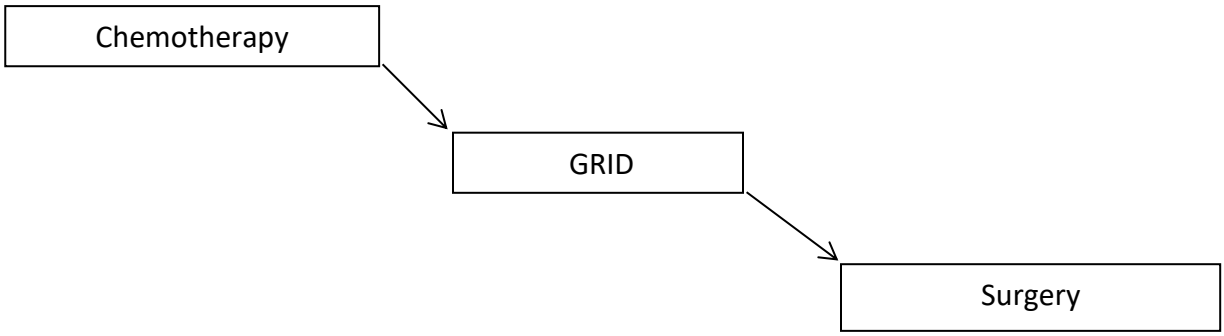
1.0 LIST OF ABBREVIATIONS

AE	Adverse Event
C3PR	Cancer Biomedical Informatics Grid
CCTO	Cancer Clinical Trials Office
Co-PI	Co-Investigator
CRA	Clinical Research Assistant
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
FDA	Federal Drug Administration
Gy	Gray
GCP	Good Clinical Practice
GRID	Spatially Fractionated Radiation Therapy
IRB	Institutional Review Board
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORRA	Office of Research Regulatory Affairs
PI	Principal Investigator
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
UAMS	University of Arkansas for Medical Sciences

2.0 STUDY SCHEMA



3.0 STUDY SUMMARY

Title	Phase I clinical trial of GRID therapy in pediatric osteosarcoma of the extremity
Protocol Number	205993
Phase	1
Methodology	Prospective, single-arm "3+3" dose-escalation design
Study Duration	12 months
Study Center(s)	Single center (UAMS)
Objectives	To evaluate the toxicity profile of GRID therapy using dose levels of 10Gy, 15Gy and 20Gy in pediatric osteosarcoma of the extremity.
Number of Subjects Treated	A minimum of 6 and maximum of 12 subjects will be treated.
Diagnosis and Main Inclusion Criteria	Subjects, 5-21 years of age, with a diagnosis of non-metastatic extremity osteosarcoma who have been prescribed GRID radiotherapy by their treating physician
Primary Outcome Measures	Dose-limiting toxicity (DLT), which is defined as a treatment-related AE of Grade 3 or higher, as assessed at either 30 days or 90 days following surgery.
Statistical Methodology	Rule-based evaluation of DLTs to determine the MTD of GRID

4.0 BACKGROUND AND RATIONALE

4.1 Disease Background

Osteosarcoma response to preoperative chemotherapy is evaluated by histological examination of the resected tumor specimen. Patients who achieve a good histological response to pre-operative chemotherapy, defined as < 10% viable tumor, experience considerably better survival than those who have a poor response (≥ 10% viable tumor). Five-year survival for good responders is in the region of 75-80%, compared to 45-55% for poor responders [1, 2]. The percentage of osteosarcoma patients who have good response to pre-operative chemotherapy has ranged in the past from 30% to 55% with recent reports clustering around 45% [1-3].

The likelihood of a patient having a good response to neo-adjuvant chemotherapy is not known until after completion of pre-operative chemotherapy and surgery. The majority of patients achieving a poor response to pre-operative chemotherapy will eventually relapse even with modification in chemotherapy in the adjuvant setting. Radiation therapy is reserved for scenarios wherein complete surgical resection cannot be achieved. Radiotherapy is also recommended for inoperable sites or those with inadequate margins at the time of surgery [15]. Since there is nearly a factor-of-2 difference in survival for good versus poor responders, strategies are needed to predict poor responders to pre-operative chemotherapy so that intensification of treatment can be offered to this group of patients early in their course of treatment.

Radiation therapy can theoretically be used as intensification of therapy prior to surgery for patients with osteosarcoma. However, a 5-week course of conventional radiation therapy in the pre-operative setting may delay not only surgery but the initiation of adjuvant chemotherapy in a group of patients with potentially compromised survival.

A feasible and more tractable possibility is the use of spatially fractionated radiation therapy (GRID) because it is a single-fraction treatment (with doses of 10Gy, 15Gy or 20Gy) that has been shown to have only minor side effects.

Spatially fractionated radiotherapy (GRID) is a technique of irradiation that has been used successfully for the curative or palliative treatment of bulky tumors ≥ 6 cm [5-7]. Irradiation is delivered through a specially made grid collimator or by using a multi-leaf collimator (MLC) as a grid field shaper (5, 8-10). In GRID therapy the target volume does not receive a homogeneous dose of radiation. Only the volume under the open grid areas receives irradiation from the primary beam. Our results [11] have shown that GRID followed by definitive chemoradiation resulted in excellent control of bulky disease (79%) in patients with locally advanced squamous-cell carcinoma of the head and neck. In these patients, acute toxicity profiles were acceptable and were similar to reports of chemotherapy and radiotherapy alone. In addition, no patient has developed a local recurrence in the irradiated GRID volume, but several have developed distant metastatic disease, which is common in this population. Our series also demonstrated that GRID is a feasible and valuable therapeutic option for bulky disease presentation. The therapeutic advantage of GRID therapy has been evaluated. Zwicker [12] et al reported that, for a wide range of tumor radiosensitivities, GRID therapy may have a significant therapeutic advantage over open-field radiotherapy to achieve the same level of tumor-cell kill. Highly radioresistant,

hypoxic cells are often present in bulky untreated tumors, and it is in these cases in which GRID use appears more advantageous.

Based on the above clinical experience, we hypothesize that GRID can be used safely in pediatric patients with osteosarcoma of the extremity, and will show a favorable toxicity profile in this population. However, the toxicity profile of GRID therapy, at any dose level, in pediatric patients is unknown.

Therefore, the purpose of this phase 1 clinical trial is to investigate the toxicity profile of GRID in pediatric osteosarcoma of the extremity.

5.0 STUDY OBJECTIVES

5.1 Primary Objectives

1) **Safety** - To evaluate the toxicity profile of GRID therapy using dose levels of 10Gy, 15Gy and 20Gy in pediatric osteosarcoma of the extremity.

5.2 Secondary Objectives

1) To determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose of GRID in patients with pediatric osteosarcoma of the extremity
2) To histologically evaluate the extent of tumor necrosis after pre-operative chemotherapy combined with GRID therapy in pediatric osteosarcoma of the extremity patients.

6.0 STUDY POPULATION

Research subjects will be recruited from the Radation Oncology clinic on the UAMS campus. The potiental research subject will be identified by the physician during their routine clinic visit. Prior to any research activities, the patient will be approached for participation in the study by their physician, who will discuss the protocol along with the risks and potential benefits of participating in it. A clear statement will be made concerning the voluntary nature of participation and that the decision will have no effect on their remaining care.

We plan to consent up to 15 subjects in order to reach our maximum accrual of 12 subjects. Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be enrolled in the study. Study procedures may not begin until a subject is consented.

6.1 Inclusion Criteria:

1. History of cytological or histological documentation of non-metastatic extremity osteosarcoma
2. 5 - 21 years of age
3. Subject is eligible for, or has already received, routine chemotherapy for osteosarcoma
4. Subject is eligible for routine surgery for the treatment of non-metastatic extremity osteosarcoma
5. Informed consent is obtained

6.2 Exclusion Criteria

1. Women with a positive urine pregnancy test are excluded from this study; women of childbearing potential (defined as those who have not undergone a hysterectomy) must agree to refrain from breast feeding and practice adequate contraception as specified in the informed consent. Adequate contraception consists of oral contraceptive, implantable contraceptives, injectable contraceptives, a double barrier method, or abstinence
2. Unable to comply with study procedures

7.0 INVESTIGATIONAL PLAN

7.1 Invesigational Plan

Upon consenting to the study, the subject will attend their scheduled routine chemotherapy as prescribed by the treating Pediatric Oncologist (unless subject has already received chemotherapy). This will be followed by radiation treatment as discussed with the Radiation Oncologist. At their radiation treatment visits, the GRID procedure will be implemented. Following the completion of the scheduled radiation treatment, the subject will proceed to routine surgery for osteosarcoma. Post-surgical chemotherapy will be prescribed as per the treating Pediatric Oncologist. Following surgery, the subject will be seen in Radiation Oncology twice for follow-up visits related to their radiation treatment.

7.2 Duration of Follow Up

Subject will not be followed once protocol procedures are completed.

7.3 Removal of Subject from Study

Subjects will be removed from the study when any of the criteria listed in Section 8.3 apply. The Principal Investigator will be notified, and treating physician will document the reason for study removal and the date the patient was removed in the subject's medical record. The study coordinator will record the reason for removal and date in the Case Report Form (CRF).

8.0 STUDY PROCEDURES

8.1 Screening/Baseline Procedures

GRID form of radiation therapy is a standard way of delivering radiation therefore no protocol-specific procedures are required.

8.2 Study Assessments:

8.2.1 Chemotherapy:

- Subject will receive routine chemotherapy for osteosarcoma (unless subject has already received chemotherapy)

8.2.2 Radiation Therapy:

- Subject will receive GRID radiation therapy. GRID radiation therapy is considered a standard radiation therapy method however is not typically used in pediatric osteosarcoma patients. This protocol will evaluate whether or not the use of this therapy will provide benefit to this patient population.

8.2.3 Surgery:

- Routine surgery for osteosarcoma

8.2.4 30 Day Post-Surgery visit (+/- 7 days):

- Physical exam
- Adverse Event (AE) assessment

8.2.5 90 day Post-Surgery visit (+/- 7 days):

- Physical exam
- Adverse Event (AE) assessment

8.3 Removal of Subjects from Study

Patients can be taken off the study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

- Patient voluntarily withdraws consent from study;
- Patient is unable to comply with protocol requirements;
- Patient experiences toxicity that makes continuation in the protocol unsafe;
- Treating physician judges continuation on the study would not be in the patient's best interest;
- Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event).

9.0 MEASUREMENT OF EFFECT

The effects of GRID radiotherapy will be determined by histological examination of the specimen(s) taken during surgery.

10.0 DEVICE INFORMATION

GRID therapy is to be delivered using a commercially available linear accelerator (Varian Truebeam STX) equipped with a commercially available GRID block (Radiation Product Design GRID block for Varian 64.5cm MLC). The GRID block discretizes the radiation beam from the linear accelerator into multiple smaller beams. The GRID block is a passive beam modifier. That is, it remains static during the delivery of the GRID therapy. The intervening areas between the smaller discretized beams receive much lower doses of radiation as compared to the dose

within the small beam volume. This creates a valley and peak type dose distribution within the GRID target.

11.0 ADVERSE EVENTS

11.1 Adverse Events Associated with GRID therapy

The potential risks of using a GRID block for radiotherapy delivery are similar to those of radiation therapy using a standard multi-leaf collimator (MLC). The risks are not due to the use of the GRID block itself, but from the actual irradiation as is the case in standard MLC radiotherapy.

Risks and side effects related to GRID therapy include:
Likely:

- Skin reaction (redness)
- Hair loss in the treated area

Less Likely:

- Fatigue
- Reductions in blood counts
- Treatment of large tumors with radiation, chemotherapy and surgery may results in infection or lack of healing which could result in prolonged hospitalization.

Rare:

- Fibrosis (hardening of the tissues)
- Pain in the treated limb
- Swelling
- Fracture of bone
- Bruising of skin
- Neve damage
- Amputation

There exists the potential risk for loss of confidentiality. Measures to protect the confidentiality of study particpants will be implemented as described in the Data Handling and Recordkeeping section.

There will be no direct benefits to the study participants; however, knowledge gained from the study could potentially benefits patients in the future.

11.2 Adverse Event Monitoring

Adverse event data collection and reporting, which is required as part of every clinical trial, is done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

All patients experiencing an adverse event will be monitored until the completion of the subject's post-GRID visit:

- the adverse event resolves or the symptoms or signs that constitute the adverse event

return to baseline;
- there is a satisfactory explanation other than the study agent for the changes observed; or
- death.

11.3 Definitions

11.3.1 Definition of Adverse Event

An adverse event is any untoward medical occurrence in a patient undergoing study assessments and which does not necessarily have a causal relationship with the assessments. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the study assessments, whether or not related to the assessments.

11.3.2 Severity of Adverse Events

Adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE v4 is available at http://ctep.cancer.gov/reporting/ctc.html

11.3.3 Serious Adverse Events

A "serious" adverse event is defined in regulatory terminology as any untoward medical occurrence that:

- Results in death.
  - If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
- Is life-threatening.
  - The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly/birth defect.
- Is an important medical event.

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".

For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

11.4 Reporting Requirements for Adverse Events

11.4.1 Expedited Reporting

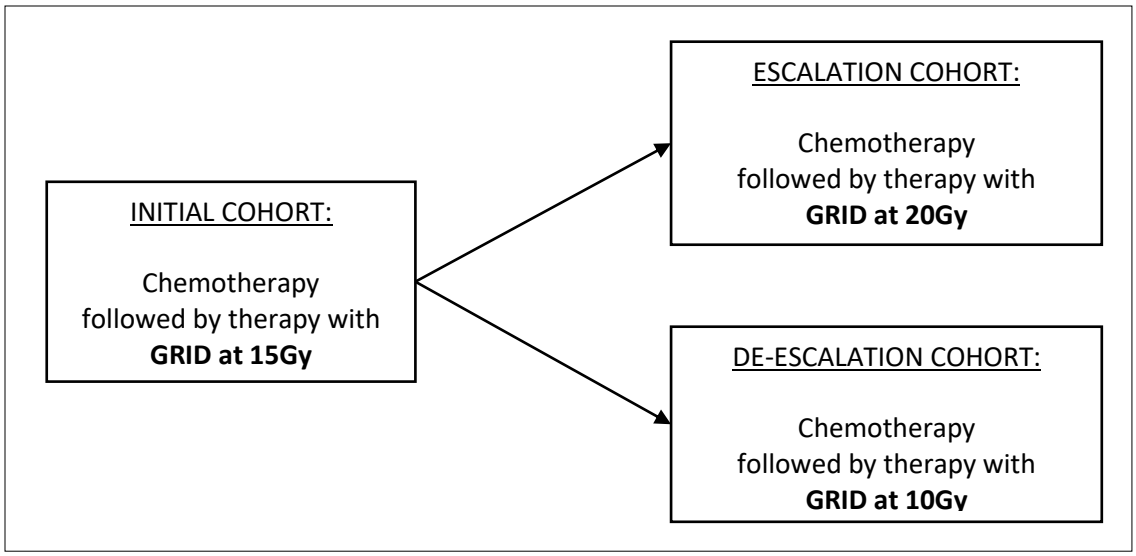
- The Principal Investigator must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study.
- The UAMS IRB must be notified within 10 business days of "any unanticipated problems involving risk to subjects or others" (UPR/UPIRTSO; See UAMS IRB Policy 10.2).

11.4.2 Routine Reporting

All other adverse events, such as those that are expected, or are unlikely or definitely not related to the study participation, are to be reported annually as part of regular IRB continuing review.

12.0 STATISTICAL CONSIDERATIONS

12.1 Study Design/Study Endpoints



- This is a dose-escalation study with three radiation doses: 10Gy, 15Gy, and 20Gy. It uses the traditional "3+3" design to determine whether to escalate or de-escalate doses, and thereby to determine the maximum tolerated dose (MTD) on this protocol. The initial cohort of subjects will receive a 15Gy dose of GRID therapy, as shown in the diagram. The second cohort of subjects will receive either 20Gy or 10Gy of GRID, also as shown in the diagram.
- The study endpoint is dose-limiting toxicity (DLT), which is defined as a treatment-related AE of Grade 3 or higher. Subjects will be assessed at both their 30-day post-surgery visit and their 90-day post-surgery visit for presence of a DLT.

12.2 Evaluation Plan

- **Table 1** shows how the number of DLTs in the initial cohort of will be used to determine whether to escalate or de-escalate the GRID dose in the next cohort.

Table 1: Toxicity Decision Rules for Initial Cohort (GRID at 15Gy)	
***DLTs/ Cohort*[1]**	***Action***
0/3	Begin accrual to Escalation Cohort
1/3	Expand Initial Cohort to 6 subjects
1/6	Begin accrual to Escalation Cohort
2/6, 3/6, or 4/6	Begin Accrual to De-Escalation Cohort
2/3 or 3/3	Begin Accrual to De-Escalation Cohort
[1] DLT = Dose-Limiting Toxicity	

- If the second cohort is the Escalation cohort, then **Table 2** shows how the number of DLTs will be used to determine the MTD on this protocol.

Table 2: Toxicity Decision Rules for Escalation Cohort (GRID at 20Gy)	
***DLTs/ Cohort*[1]**	***Action***
0/3 or 1/3	Expand cohort to 6 subjects
0/6 or 1/6	Stop: Declare escalation dose to be the MTD[2]
2/6, 3/6, or 4/6	Stop: Previous dose level is the MTD[2]
2/3 or 3/3	Stop: Previous dose level is the MTD[2]
[1] DLT = Dose-Limiting Toxicity [2] MTD = Maximum Tolerated Dose	

- On the other hand, if the second cohort is the De-Escalation cohort, then **Table 3** shows how the number of DLTs will be used to determine whether 10Gy is at or above the MTD on this protocol.

Table 3: Toxicity Decision Rules for De-Escalation Cohort (GRID at 10Gy)	
***DLTs/ Cohort*[1]**	***Action***
0/3 or 1/3	Expand cohort to 6 subjects.
0/6 or 1/6	Stop: De-escalation dose level is the MTD[2]
2/6, 3/6, or 4/6	Stop: De-escalation dose level is above MTD[2]
2/3 or 3/3	Stop: De-escalation dose level is above MTD[2]
[1] DLT = Dose-Limiting Toxicity [2] MTD = Maximum Tolerated Dose	

12.3 Sample Size Estimation. If the MTD on this protocol is 10Gy, 15Gy, or 20Gy, then the above 3+3 dose-escalation design will find it using a minimum of 6 and maximum of 12 subjects. On the other hand, if 10Gy is above the MTD on this protocol, then the above 3+3 dose-escalation design will uncover that fact using a minimum of 6 and maximum of 12 subjects. Therefore, the minimum number accrued to this protocol will be 6 subjects, while the maximum number accrued to this protocol will be 12 subjects.

13.0 STUDY MANAGEMENT

13.1 Registration Procedures

All patients must be registered with the Cancer Clinical Trials Office before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the Research Staff. To register a patient, call CCTO Monday through Friday, 8:00AM-4:30PM.

13.2 Data Management

13.3 Data must be submitted according to protocol requirements for ALL subjects registered, whether or not study procedures are performed. For screen failures, only the eligibility criteria case report form will be completed. Data obtained during the study will be collected at each subject visit and entered into the protocol database. Subjects will be registered in RPRS, a cancer Biomedical Informatics Grid (*caBIG®,* NCI) application. Data will be entered into OpenClinica through electronic web-based case report forms (CRFs). OpenClinica is a secure open source system for electronic data capture and clinical data management. All information in OpenClinica will be coded with a unique identifier and will be stored in the database indefinitely. In the event that a subject fails screening, only the eligibility criteria case report form will be completed. The Principal Investigator will carefully monitor study procedures to protect the safety of research subjects, the quality of the data and integrity of the study. Monitoring and Auditing

13.3.1 Medical Monitor:

The Medical Monitor, Principal Investigators and study staff will meet to review safety data after each of the Data Monitor periodic visit.

13.3.2 Data Monitor:

UAMS is the Sponsor. One (or more) Data Monitor(s) will be appointed by the monitoring division of the UAMS Office of Research regulatory Affairs (ORRA) to assure that the rights and well-being of human subjects are protected, that the data are accurate, complete and verifiable from source documents and that the trial is conducted in compliance with currently approved protocol/amendments, with GCP, and with the applicable regulatory requirements set forth in *21 CFR 312*.

The Data Monitor(s) will be familiar with the protocol, the informed consent form, any other information provided to the subjects, SOPs, GCP and applicable regulatory requirements.

Data Monitor(s) will have access to research subjects' medical records and other study-related records. The investigator agrees to cooperate with the study coordinator and Medical Monitor to ensure that any problems detected in the course of these monitoring visits are resolved. Personal contact between the Data Monitor, Medical Monitor, study staff and the investigator will be maintained throughout the clinical trial to assure that the investigator is fulfilling his/her obligations and that the facilities used in the clinical trial remain acceptable.

13.3.3 Research Subject Safety and Stopping Rules:

If 2 SAEs occur with attribution to the study, the trial will be suspended until further review is completed by the Medical Monitor, PI, sponsor and FDA. This will be accomplished by the

study team, the PI, Co-PI, biostatistician, Medical Monitor and CRA, either at the regular meeting or a special meeting called by the Medical Monitor or the PI because of the SAEs.

13.4 Ethical Considerations

This study will be conducted in accordance with all applicable government regulations and University of Arkansas for Medical Sciences research policies and procedures. This protocol and any amendments will be submitted and approved by the UAMS Institutional Review Board (IRB) to conduct the study.

The formal consent of each subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. All subjects for this study will be provided a consent form describing this study and providing sufficient information in language suitable for subjects to make an informed decision about their participation in this study. The person obtaining consent will thoroughly explain each element of the document and outline the risks and benefits, alternate treatment(s), and requirements of the study. The consent process will take place in a quiet and private room, and subjects may take as much time as needed to make a decision about their participation. Participation privacy will be maintained and questions regarding participation will be answered. No coercion or undue influence will be used in the consent process. This consent form must be signed by the subject or legally authorized representative (only if applicable), and the individual obtaining the consent. A copy of the signed consent will be given to the participant, and the informed consent process will be documented in each subject's research record. If assent is required, include a statement that assent will be obtained and that assenting minors will be consented if they reach the age of majority during the study (if applicable).

13.5 Dissemination of Data

Results of this study may be used for presentations, posters, or publications. The publications will not contain any identifiable information that could be linked to a participant.

14.0 REFERENCES

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CONSENT FORM
AND
INFORMATION ABOUT

Phase I clinical trial of GRID therapy in pediatric osteosarcoma of the extremity

TO BE CONDUCTED AT
UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES

(Principal Investigator: Leslie Harrell, DO)

SUBJECT NAME _____ HOSPITAL I.D. NUMBER _____

INTRODUCTION

This is a clinical trial, a type of research study being conducted at the University of Arkansas for Medical Sciences (UAMS). This research is being sponsored by UAMS. Your doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your research doctor for more information.

You are being asked to take part in this research study because you have osteosarcoma.

WHY IS THIS RESEARCH BEING DONE?

The main purpose of this research study is to evaluate the safety of three dose levels of GRID radiotherapy in pediatric osteosarcoma. The safety of GRID radiotherapy is well understood in adult patients but not in pediatric patients. GRID radiotherapy is a descriptive term for Spatially Fractionated Radiotherapy. This pattern is similar to a checkerboard where every other space is exposed to radiation. This type of radiation is common in other types of diseases but has never been tested in osteosarcoma pediatric patients. This device is experimental and is not approved by the FDA for use in this disease.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

We will enroll up to 12 patients, ages 5 -21 years of age.

WHAT WILL HAPPEN DURING THIS STUDY?

The required portion of the study is split into four parts. These are only required for participation in this study and will not affect your care at UAMS. Delivery of GRID radiotherapy requires only one dose of radiation. The time to deliver this one dose of radiation is approximately 25 minutes. After this one dose of radiation you will continue with standard osteosarcoma therapy under the care of your pediatric oncologist and surgeon. Return visits to the Radiation Oncology Center will be needed to assess the safety of GRID therapy.

At the beginning of the research, 3 research participants will be treated with a dose of GRID radiotherapy. If this does not cause any side effects, the dose will be made higher as new research participants take part in the study. If there are too many side effects, the next group of participants will receive a lower dose.

- Chemotherapy
    - You will receive routine chemotherapy for osteosarcoma unless you have already finished chemotherapy (You will receive the same chemotherapy you would get even if you don't join the study. Your chemotherapy regimen and scheduling will be determined by your doctor)
- Radiation therapy
    - You will receive radiation therapy through the experimental GRID technique (research procedures)
- Surgery
    - You will receive routine surgery for osteosarcoma (You will receive the same surgery you would get even if you don't join the study. Your surgery will be determined by your doctor)
- Follow-up (research procedures)
    - 30 Day Post-Surgery visit
        - Physical examination
        - Adverse Event (side effects) assessment
    - 90 Day Post-Surgery visit
        - Physical examination
        - Adverse Event (side effects) assessment

HOW LONG WILL I BE IN THE RESEARCH?

The approximate length of complete study participation will be around 12 months. This timeframe begins at the time of consent and ends upon completion of the 90 day post-surgery visit. Participation in this study will require two extra visits than routine care would require (30 day and 90 day post-surgery).

WHAT OTHER CHOICES DO YOU HAVE IF YOU DECIDE NOT TO TAKE PART?

Being part of this study is voluntary. This means you can decide to say yes or no to being part of this study. Neither decision will affect your present or future medical care. This informed consent may contain words you do not understand. You are free to ask as many questions as you like before you decide whether you want to participate

in this research study. You are free to ask questions at any time before, during, or after your participation in this research. You will not incur a penalty or loss of benefits if you refuse to participate or withdraw early from the study. If you choose not join the study, you can seek other kinds of treatment for your disease. Your doctor can explain your treatment choices to you.

If you agree to take part in this study, you must sign this consent form. A signed copy of the consent form will be given to you. You are not waiving any legal right by signing this consent form.

CAN I STOP BEING IN THE RESEARCH?

Yes. You can decide to stop at any time. Contact the research staff and/or Principal Investigator if you decide to stop your participation. If you decide to end your participation early, the information already collected before your withdrawal will continue to be used and will not be removed from the study database.

In addition, your physician may stop you from taking part in the study at any time if he/she believes that is it in your best interest; if you do not follow the study rules; or if the study is stopped. This may happen without your consent.

WILL I BE COMPENSATED FOR TAKING PART IN THIS STUDY?

You will not receive any form of compensation or payment for your participation in this research.

WHAT WILL IT COST YOU TO TAKE PART IN THIS STUDY?

The radiation therapy provided in this study will be paid for by the research study and will not be billed to your insurance company. Some of the tests or treatments (i.e. chemotherapy and surgery) used in this study may be part of standard care used to maintain your health even if you did not take part in this study. You or your insurance company may be responsible for the cost of this standard care. It is possible that your insurance company may deny paying for any tests and procedures related to a research study, making you responsible for any charges. You will be responsible for normal co-pays, deductibles and non-covered services that are not the responsibility of the study. There is never any guarantee with any hospital service that you will not incur some financial responsibility. Staff is available to assist with talking to your insurance company to review your specific benefits and coverage before deciding to participate. All trial-related costs that are done solely for research purposes will be provided at no cost to you.

WHAT ARE THE POTENTIAL BENEFITS TO ME IF I TAKE PART IN THIS STUDY?

There are no direct benefits for the participants volunteering to take part in the study. Knowledge gained from this study could potentially benefit patients in the future.

WHAT ARE THE RISKS IF I TAKE PART IN THIS STUDY?

Radiation Therapy is part of the standard care that has been recommended by your physician. In this study we are evaluating a new technique to deliver the radiation. This technique is called a GRID procedure. Utilizing this technique is common in other types of cancer but has not been tested in pediatric osteosarcoma patients. Your

physician will discuss the risk associated with GRID procedure with you before the procedure. The potential risks of using a GRID block for radiation therapy are similar to those of regular radiation therapy. This study may involve risks that are currently unknown. The risks described below are not due to the use of the GRID block itself, but from the actual irradiation as is the case in standard therapy.

Likely

- Skin reaction (redness)
- Hair loss in the treated area

Less Likely

- Fatigue
- Reductions in blood counts
- Treatment of large tumors with combined radiation, chemotherapy and surgery may result in infection or lack of healing which could result in prolonged hospitalization

Rare

- Fibrosis (hardening of the tissues)
- Pain in the treated limb
- Swelling
- Fracture of bone
- Bruising of skin
- Nerve damage
- Amputation

Another potential risk to study participants is the potential for loss of confidentiality. The Principal Investigator will carefully monitor study procedures to protect the safety of research subjects, the quality of the data and the integrity of the study. Research records will be stored in a locked area with access to study personnel only.

WHAT IF I AM INJURED WHILE PARTICIPATING IN THIS RESEARCH?

In the event you are hurt by being in this research, treatment will be available. This treatment may include: first aid, emergency treatment, and/or follow-up care. This treatment may be billed to you or your insurance company in the normal manner. Normally, no other form of compensation is available. If you think you have been hurt by this research, let the Principal Investigator know right away by calling Leslie Harrell, DO at (501) 526-6591. After hours you may reach the oncology physician on call at (501) 686-8530.

WILL MY MEDICAL INFORMATION REMAIN CONFIDENTIAL?

We will do our best to make sure 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. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. Participants may be identified by study numbers only on all research documents. The connection with the participants name will be kept by research personnel in a locked facility. Records for this research study will be retained indefinitely.

A record of your participation in this research will be maintained, but this record will be kept confidential to the extent allowed by law. The results of this study may be published in a medical journal, but you will not be identified by name. Representatives of the UAMS Institutional Review Board (IRB), other institutional oversight offices, the Food and Drug Administration and the Office for Human Research Protections (OHRP) may be given access to research study records and pertinent medical records that may contain your name or other identifying information.

By law, the study team must release certain information to the appropriate authorities if at any time during the study there is concern that child abuse or elder abuse has possible occurred or you disclose a desire to harm yourself or others.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS RESEARCH?

Taking part in this research is your choice. You may choose either to take part or not to take part in the research. 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. Your relationship with your doctor or with UAMS will not be affected by not participating or leaving the research. Leaving the research 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. You can refuse to sign this form. If you do not sign this form you will not be able to take part in this research study. However, your health care and benefits outside of this study will not change.

WHO CAN ANSWER MY QUESTIONS ABOUT THE RESEARCH?

If you have any questions, concerns or complaints about this study, call Leslie Harrell, DO at (501) 526-6591.

If you have questions about your rights, general questions, complaints, or issues as a person taking part in this study, call the UAMS IRB at (501) 686-5667. You are also encouraged to call this number if you wish to speak with someone not directly related to this study.

STATEMENT OF PARTICIPANT

I have been told that I will be given a copy of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I understand my participation in this study is voluntary. I agree to take part in this study.

Participant Signature	Date & Time
Person Obtaining Consent Signature	Date & Time