Official Study Title: HYPERTENSION INTERVENTION TO REDUCE OSTEONECROSIS IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA/ LYMPHOMA

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Informed Consent for Research

HYPERTENSION INTERVENTION TO REDUCE OSTEONECROSIS IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

Note: When we say "you" in this consent, we mean "you or your child." When we talk about research, it can be called a clinical trial, research study, or research protocol.

Key Information

We highlight here the risks and study requirements that we think you should know before deciding if you want to take part in this research study. If you're still interested, we'll then get into more detail in the paragraphs that follow.

A. Why are you being asked to volunteer in this study?

You are being asked to take part in this clinical trial, a type of research study because you are receiving chemotherapy for leukemia, which puts you at risk for osteonecrosis. Osteonecrosis results from the loss of blood supply to the bone. Without blood, the bone tissue dies and the bone collapses.

B. What is the usual approach to the condition that you have?

Some of the drugs used to treat leukemia can cause high blood pressure (hypertension). The usual approach is to treat with hypertension with medications to lower the blood pressure.

C. Why is this study being done?

Past studies have shown that hypertension (high blood pressure) can lead to a long-term complication called "osteonecrosis". Osteonecrosis is a condition in which there is a loss of blood flow to bone tissue, which causes the bone to die. It is most common in the hips, knees, shoulders, and ankles.

Researchers want to find out if treating patients with **intensive** (for example, higher doses of medication) therapy is the same, better or worse than treating patients with **standard** therapy used to control blood pressure.

D. What will happen if you decide to take part in the study?

You will start blood pressure medication on Day 4, unless you blood pressure is already in the study required range. Patients will be randomly assigned to either:

- Arm A: standard anti-hypertensive medication, or
- Arm B: intensive anti-hypertensive medication.

Key Information

E. What are the research risks and benefits of taking part in this study?

The main risk of this study is that your blood pressure could drop to low levels and your kidney function could be decreased. Your study doctor will monitor you closely for these side effects and change your therapy if needed.

F. How many people will take part in this study?

Up to 180 children and young adults will take part in this study at St. Jude and up to 4 other hospitals collaborating on this study.

G. What are your options?

You may choose to receive the usual approach, which is using standard anti-hypertensive therapy to treat high blood pressure.

If you are still interested in taking part in the HYPERION research study, more detail will be provided in the following pages.

1. Why are you being asked to volunteer for this research study?

You are being asked to take part in this clinical trial, a type of research study, because you have been enrolled on the TOT17 study to treat your leukemia or lymphoma and you are 10 years of age or older.

Please take your time in deciding and feel free to discuss it with your family, friends and St. Jude staff. Before agreeing, it is important that you read this consent form that describes the study. After you understand the study and if you agree to take part, you will be asked to sign this consent form. You will be given a copy to keep.

2. Who is sponsoring this study?

This study is being sponsored by St. Jude Children's Research Hospital.

The principal investigator (researcher) in charge of this study is Dr. Seth Karol, who can be reached by phone at 901-595-3300, if you have any questions or concerns about this research.

3. What is the purpose of this study?

Past studies have shown that high blood pressure (hypertension) can lead to a long-term complication called "osteonecrosis". Osteonecrosis is a condition in which there is a loss of blood flow to bone tissue, which causes the bone to die. It is most common in the hips, knees, shoulders, and ankles.

Researchers want to find out if treating patients with **intensive** (for example, higher doses of medication) therapy is the same, better or worse than treating patients with **standard** therapy used to control blood pressure (anti-hypertensive therapy).

Up to 180 children and young adults will take part in this study at St. Jude and up to 4 other hospitals collaborating on this study. Up to 120 will take part at St. Jude.

4. What will be done in this study?

Screening (before you begin the study treatment)

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- A medical history and physical exam
- Blood tests for routine safety labs
- Pregnancy test (if you are a female who could have children)
- Test to measure your heart function (echocardiogram or ECHO)

Treatment Phase

You will be randomly assigned to one of two treatment arms:

- Group A: Standard anti-hypertensive therapy
- Group B: Intensive anti-hypertensive therapy

Randomly assigned means that the treatment is assigned based on chance. It is a lot like flipping a coin, except that it is done by computer. You and your doctor will not pick which treatment you get. You will have a 1 out of 2 chance of assignment to Group A, and the same chance of assignment to Group B. Using chance to assign people to groups means that the treatments can be compared more fairly.

You will begin anti-hypertensive therapy on Day 4 of treatment on the TOT17 study.

If you are assigned to Group A, the dose of your anti-hypertensive medications will be adjusted to keep your blood pressure within the 90-95th percentile of people who are your age, gender and height.

If you are assigned to Group B the dose of your anti-hypertensive medications will be adjusted to keep your blood pressure within the 50-75th percentile of people who are your age, gender and height.

You will be monitored closely for side effects and your medication will be changed if your blood pressure falls or rises to unsafe levels, or you have other side effects like headache, vision changes, or you feel faint or light-headed.

You will continue anti-hypertensive therapy during the parts of TOT17 therapy that includes steroids, which are known to cause high blood pressure.

Research tests and procedures during the study

You will have the following tests during this study. These tests would not be done if you do not enroll on this study.

- You will wear a blood pressure monitor around your arm for about 1 day (12-30 hours), once during Days 4-7 and once during Days 23-28 of TOT17 Remission Induction Therapy.

- You will have an MRI scan of your hip and knees once during Days 23-28 of Remission Induction, and once during Reinduction II. The MRI during Reinduction II is part of the TOT17 study. If you need to be sedated to have an MRI, it will not be done.

- Vasomotor testing (a hand-held scan that measures the opening and narrowing of blood vessels) will be done once during Days 23-28 of TOT17 Remission Induction therapy, once between Early Intensification day 57 and Consolidation day 28 , and once at the end of all treatment on TOT17 therapy.

- Blood (15 ml or 1 tablespoon) will be collected twice for blood vessel research:

    - Once on Day 22 of TOT17 Remission Induction Therapy and
    - Once before you start Week 17 of TOT17 Reinduction II therapy.

  A total of 30 ml (2 tablespoons) will be collected for this research.

- You will have an echocardiogram (ECHO) to measure your heart function once during Week 17-19 of TOT17 Reinduction II therapy.

- You will be asked to complete surveys that ask you to describe your symptoms such as pain, physical activity and mobility (your ability to move freely and easily) on Week 17 and Week 49 of TOT17 Continuation Therapy. It will take about 20-30 minutes to complete the forms.

- You will be interviewed by a trained examiner about your treatment, your leukemia or lymphoma, and your symptoms on Week 49 of TOT17 Continuation Therapy. This interview will be recorded and will take about 30-45 minutes.

5. What are the risks and benefits of taking part in this study?

Risks of the study

The main risk of blood pressure medications are feeling tired, weak, drowsy or having a lack of energy. Other side effects can include decreased kidney function, cough, diarrhea or constipation, dizziness or lightheadedness, problems getting an erection (for males), anxiety, headache, nausea or vomiting.

There is also a risk that your blood pressure will drop too low, especially if you are on the intensive anti-hypertensive therapy group.

Some side effects are rare and life-threatening, your study doctor will be closely watching your medical status for any side effects and will provide treatment as necessary.

Unknown risks

In addition to the risks described above, there may be unknown risks, or risks that we did not anticipate, associated with being in this study.

You will be given any new information that becomes available during the study that might affect your decision to continue taking part in the study. Be sure to tell your study doctor about any illness or discomfort you experience while you are in the study.

Loss of privacy: Very rarely, personal information from your records could be given out by accident. This might make you upset, embarrass you, or affect your ability to get insurance. To stop this from happening, we:

- Store records apart from names or other personal information,
- Allow only members of the study team to see the records,
- Store electronic data only on computers protected with a password and encryption software,
- Report study results on the whole group and never identify one single person in any reports.

Benefits

We believe that this study can help you personally, but we do not know if it will. A potential benefit to you is that keeping your blood pressure under better control may result in a decreased risk of osteonecrosis.

We expect that the information learned from this study will benefit other patients in the future.

6. What are the risks to pregnancy, to an unborn child, and to the ability to have children when taking part in this study?

The risks of this treatment to an unborn or nursing child are unknown. Females in the study must not be pregnant or nursing when they start the study and must not get pregnant during the study. If you think you may have become pregnant during the study, you must tell the researcher right away. If you become pregnant, you will be taken out of the study.

Males in the study must not father a child during the study. Males should talk to the researcher about the option of freezing sperm before taking part in this study.

Participants in this study must use effective forms of birth control. The researcher can tell you about the best birth control methods to use during this study. Effective forms of birth control may include birth control pills taken by mouth, condoms, and not having sex. Birth control methods should be continued for 6 months after treatment to avoid pregnancy. We also do not know if there may be unknown long-term effects to your future children.

7. Can you stop taking part in this study?

a. Can you change your mind about taking part in this research study?

You may change your mind about taking part in this research study or stop at any time. The decision will not affect your care or your relationship with your doctor or St. Jude. If available, you may receive routine medical care at St. Jude Children's Research Hospital.

b. **Can you be taken out of this study without your consent?**

Your St. Jude doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest,
- If new information becomes available,
- If you do not follow the study rules,
- If the study is stopped by the sponsor, St. Jude.

8. What are your other options?

If you choose not to take part in this study, you will still be able to receive standard anti-hypertension care. You can speak with your primary doctor or other healthcare professionals regarding options and alternatives for treatment.

9. How much will it cost you?

If you have health care coverage, we will bill your health care insurer for all standard of care services, tests, and procedures. Billing your health care insurer impacts your annual deductible and life-time maximum, if any. This may affect your health care coverage to some extent if you go to another health care provider or institution in the future.

At St. Jude, you will not be responsible for or receive bills for co-pays, co-insurance, deductibles, or similar patient-liability amounts, or for the cost of medical care not covered by your health insurer. This includes research-only costs. Research-only tests and procedures will not be billed to you or your health care insurer.

10. Will you be paid for your time or expenses?

You will not be paid for your time or expenses. Also, your samples and/or information may be used to develop a new product or medical test, which may be sold. If this happens, you will not receive any payments for these new products.

11. What if there is a problem?

If you have any questions about this study or if you are injured because of this study, contact Dr. Karol, at 901-595-3300 immediately. If you are injured from being in this research study, St. Jude will offer you reasonable and necessary medical treatment for that injury. If you need more care than St. Jude can provide or if you prefer to seek treatment elsewhere, we will help you find medical care somewhere else. St. Jude may bill your insurance company or other third parties, if appropriate. It is not the hospital's policy to provide payment for other types of costs, such as lost wages, disability, or discomfort if you are injured from being in this study. You are not giving up any of your rights by signing this consent form.

12. How will new finding related to your participation in this study be shared with you?

The researcher will tell you of any new information learned during your study participation which might cause you to change your mind about continuing the study.

13. How will you find out the results of the study?

The researcher will give you information about the overall results of this study. Whether you will know your personal test results will be discussed in another part of this document. St. Jude researchers share information with people in studies in many ways including:

- Articles on www.stjude.org,
- In newsletters,
- In medical or scientific journals,
- In the media,
- A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by the U.S. Law. This website will not include information that can identify you. At most the website will include a summary of the results. You can search this website at any time.

14. What about privacy and confidentiality?

Privacy

Information from research testing, imaging, and other procedures or studies, including genomic and genetic and other sensitive information, is relevant to your health and is placed in your medical record unless it is from a research-only laboratory. When you first registered at St. Jude, you received a copy of the St. Jude Notice of Privacy Practices. It tells how your PHI (protected health information), including research information placed in your medical record, may be used or given to someone outside of the hospital. You have the right to read the Notice of Privacy Practices before you sign this form. It may have changed since you first registered at St. Jude. You can find it at the bottom of every page on the St. Jude internet website: www.stjude.org.

A decision to take part in this research means that you agree to let the research team use and share your PHI with other researchers for purposes of the study explained above. This information will be kept indefinitely. You have the right to see, copy, and ask for changes to your protected health information that will be used or given out. However, research information may not be seen until the end of the study.

These groups, agencies or people may view your information from your research and medical records:

- Food and Drug Administration (FDA)
- Office of Human Research Protections (OHRP)
- National Institutes of Health (NIH)
- Other government agencies
- Your insurance company and other health benefits plan
- St. Jude Children's Research Hospital Institutional Review Board (IRB)
- Other committees or people involved in overseeing research studies

Confidentiality

If you consent to take part in this study, information obtained from this study, as well as information about disease signs and symptoms, will be entered into one or more scientific databases maintained by St. Jude Children's Research Hospital and the Federal Government. The information will be held securely electronically at St. Jude Children's Research Hospital. Your name will not be passed on to anyone else outside the research team who is not involved in the study. You will be allocated a study number, which will be used as a code to identify you on all study forms. Any research-related information about you that leaves the hospital will have your name and address removed so that you cannot be recognized.

Your records will be available to people authorized to work on the study. The study is being carried out at St. Jude Children's Research Hospital and other hospitals collaborating with St. Jude. The data collected about you during the study may be sent to study investigators outside the USA. The data will be sent with your unique study number and all personal identifiers will be removed so you cannot be identified. By signing this consent form, you agree to this access for

the current study and any further research that may be conducted in relation to it, even if you withdraw from the current study. The information collected about you may also be shown to authorized people from the US Regulatory Authority (FDA) to ensure that the study is carried out to the highest possible scientific standards.

The study is covered by a Certificate of Confidentiality from the federal government. With this Certificate, the researchers cannot be forced to give out your personal information, document or specimen, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other process. The Certificate of Confidentiality does not protect release of information in certain circumstances. These include clinical or research data that are placed in the medical record for the purposes of clinical research and clinical care. The researchers will use the Certificate to block any demands for information or specimens that would identify you, except in the cases listed below:

- United States Government for audit or to check federally funded projects
- To meet the needs of the FDA

This Certificate will not keep researchers or hospital staff from making reports required of them. These include the following:

- Suspected child abuse
- Disease that spread from person to person
- Threat of harm to self or others

15. Permission to use your data/information: permission/HIPAA

If you sign this document, you give permission to all researchers and their staff at St. Jude Children's Research Hospital to use or disclose (release) your health information that identifies you for the research study described in this document.

The health information that we may use or release for this research includes information from your medical record, results of physical examinations, medical history, lab tests, and medical tests and procedures.

St. Jude Children's Research Hospital is required by law to protect your health information. By signing this document, you give St. Jude Children's Research Hospital permission to use and/or disclose (release) your health information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

If you sign this document, you give St. Jude permission to share your information for future research studies and for the placement of information on databases as described in #15 of this consent form. By signing, you will also give St. Jude permission to put your research information, including testing, imaging, genomic and genetic information, other information and studies, and other sensitive information in your medical record (unless the research information is from a research-only laboratory). Any information placed in the medical record becomes a permanent part of your medical record and is not protected by the Certificate of Confidentiality discussed in #14 of this consent form, but is protected like any other part of your medical record as described in the Notice of Privacy Practices. The following entities will disclose information:

- the Food and Drug Administration (FDA)
- the Office for Human Research Protections (OHRP)
- the National Institutes of Health (NIH)
- St. Jude Children's Research Hospital Institutional Review Board (IRB)

You do not have to sign this document and give your permission, but if you do not, you may not receive research-related treatment.

Please note that you may change your mind and revoke (take back) this permission at any time. Even if you revoke your permission, St. Jude Children's Research Hospital may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. To revoke this permission, you must write to:

HIPAA Privacy Officer
St. Jude Children's Research Hospital
262 Danny Thomas Place, Mail Stop 280
Memphis, TN 38105

This permission does not have an expiration date.

16. Further Information and Contact Details for Questions About This Research Study

You are encouraged to ask any questions you wish, before, during or after your treatment. If you have any questions about the study, please speak to your study nurse or doctor, who will be able to provide you with up to date information about the drug(s)/procedure(s) involved. If you wish to read the research on which this study is based, please ask your study nurse or doctor.

If there is anything you do not understand, or have any other questions, please contact the researcher listed below.

IF AT ANY TIME DURING THE STUDY YOU EXPERIENCE ANY DISCOMFORT OR UNUSUAL SYMPTOMS, OR SIDE EFFECTS, PLEASE CONTACT THE DOCTOR LISTED BELOW:

Principal Investigator, Researcher:
Dr. Seth Karol
St. Jude Children's Research Hospital
262 Danny Thomas Place
Memphis, TN
Telephone: (901) 595-3300

If you require any medical or surgical treatments outside of St. Jude such as with your local doctor or another hospital during this study, your researcher and their team must be informed.

You can get more details about your rights as a research participant by calling the St. Jude Institutional Review Board at 901-595-4357 or the Research Participant Advocate at 901-595-4644 or 901-595-1139.

The Research Participant Advocate is an individual who is not part of the research study team and is available to you to discuss problems, concerns, and questions. The Advocate can help you obtain information and can relay any input you may have concerning the research to the research study team. If you are outside of the Memphis area, please call toll-free 1-866-583-3472 (1-866-JUDE-IRB).

If you decide you would like to take part, then please read and sign this consent form. You will be given a copy of this information and the consent form to keep. A copy of the consent form will be filed in your patient notes, one will be filed with the study records and one will be retained by St. Jude Children's Research Hospital (the study sponsor).

You can have more time to think this over if you are at all unsure.

Thank you for taking the time to read this information sheet and to consider this study.

PARENT/GUARDIAN STATEMENT (Required for participants younger than 18 years): I have read this document or it was read to me. I have been encouraged to ask questions and all my questions have been answered. I give permission for my child to be in this research study.

_____	_____	_____ AM/PM
Parent/Legal Guardian Signature	Date	Time (circle one)

ASSENT DISCUSSION (Required for participants 7–13 years old):

☐ The research was explained to the minor participant in age-appropriate terms and the minor verbally agreed to take part in the study.

☐ Minor declined to take part in the study. The minor declined for the following reason(s):

_____

☐ An assent discussion was not initiated with the minor for the following reason(s):

- ☐ Minor is under 7 years of age.
- ☐ Minor is incapacitated.
- ☐ Minor refused to take part in the discussion.
- ☐ Other_____

RESEARCH PARTICIPANT STATEMENT (14–17 years old and Adult Participants 18 years and older): I have read this document or it was read to me. I have been encouraged to ask questions and all my questions were answered. I agree to take part in this research study.

_____	_____	_____ AM/PM
Research Participant Signature	Date	Time (circle one)

RESEARCHER/DESIGNEE STATEMENT: I have explained the research to the participant and his/her parent(s) or legal guardian(s). The research participant and parent(s)/guardian(s) were encouraged to ask questions and all questions were answered to their satisfaction. A copy of this form has been given to the participant or his/her representative.

_____	_____	_____ AM/PM
Researcher/Designee Signature	Date	Time (circle one)

_____
Print Name

_____	_____	_____ AM/PM
Interpreter (if needed)	Date	Time

RESEARCH PARTICIPANT ADVOCATE STATEMENT: I observed the informed consent process. The research study, intervention/observation, risks, benefits, and alternatives were presented to the research participant and/or legal guardian(s). They were encouraged to ask questions, and research team members answered all their questions. The participant /parent(s) indicated that they: 1) understood the information presented; and 2) voluntarily consented /agreed to take part in the research.

_____	_____	_____
Research Participant Advocate	Date	Time AM/PM (circle one)

PLEASE FAX CONSENT FORM TO PROTOCOL OFFICE #6265