Imaging of Osteonecrosis With Ferumoxytol-Enhanced MRI

Informed Consent Form

NCT02893293

June 20, 2023

Office Use Only

PLACE PATIENT STICKER HERE

Please check one of the following:

_____ You are an adult participant in this study.

_____ You are the parent or guardian granting permission for a child in this study.

Print child's name here: _____

The following information applies to the adult participant or to the child or ward. If the participant is a child or ward, the use of "you" refers to "your child" or "your ward."

Are you participating in any other research studies? _____ Yes _____No

SUMMARY

Your consent is being sought for participation in a research study. Your participation is voluntary. The purpose of the research study is to evaluate the ability of an iron supplement (Ferumoxytol) to improve the diagnosis and treatment monitoring of bone lesions with magnetic resonance imaging (MRI). The study involves an intravenous injection of the iron supplement ferumoxytol, followed by an MRI imaging test. Since the MRI machine is composed of a strong magnet, patients with ferromagnetic / metallic implants in their body will need to be tested for MRI compatibility. Patients with pacemakers or MRI incompatible implants cannot be enrolled in this study. In addition, the administration of the iron supplement can rarely cause allergic reactions. Eligible patients will be carefully evaluated for any history of allergic reactions. Potential benefits of the study include an improved delineation and improved therapy response assessment of lesions in the bones. Alternate procedures include a conventional MRI, with or without administration of gadolinium chelates, a computed tomography exam, a bone scan or a positron emission tomography (PET) scan. Thus far, more than 100 patients have received a ferumoxytol-MRI at our institution and our team has not encountered major side effects of the administered iron supplement.

INTRODUCTION TO RESEARCH STUDIES

A research study is designed to answer specific questions, sometimes about a drug's or device's safety and effectiveness. Being in a research study is different from being a

patient. When you are a patient, you and your doctor have a great deal of freedom in making decisions about your health care. When you are a research participant, the Protocol Director and the research staff will follow the rules of the research study (protocol) as closely as possible, without compromising your health.

PURPOSE OF RESEARCH

You are invited to participate in a research study on evaluation of bone abnormalities such as distinguishing between cancer and infection or inflammation, or evaluation of areas of dead bone using MRI and a new contrast agent (ferumoxytol). You will be asked to have at least two MRIs. If you are being evaluated to distinguish between cancer and infection or inflammation, you will have one MRI with a contrast injection, and one a day later to see if we can still see the contrast agent in your bones. If you are being evaluated for areas of dead bone, you will have one MRI with contrast injection before having surgery to treat the area of dead bone, and then have another MRI within 1 to 2 weeks after the surgery and 6 months after the surgery to evaluate the same area. We hope to learn how to tell the difference between different conditions or evaluate the effectiveness of the surgery with a simple MRI scan. You were selected as a possible participant in this study because you were seen in the clinic for one of these conditions. Currently, ferumoxytol is only approved for use in adults to treat anemia (low iron levels in the blood). Use of ferumoxytol as a contrast agent, and use of ferumoxytol in children, is not approved by the FDA, and is experimental.

Your participation in this study is entirely voluntary.

If you have/will have a biopsy and/or resection as part of your routine clinical care, we hope to have our pathologist examine the samples with special stains to look for cells called macrophages within the samples that can be present both in infection and cancer. We just ask for your permission to look at these tissues only in case you have a procedure as part of your clinical care.

Your decision whether or not to participate will not prejudice you or your medical care. If you decide to participate, you are free to withdraw your consent, and to discontinue participation at any time without prejudice to you or effect on your medical care. If you decide to terminate your participation in this study, you should notify Heike Daldrup-Link M.D. at [redacted].

This research study is looking for 30 patients with cancer and 10 patients with infection or inflammation and 20 patients with osteonecrosis (dead bone) able to receive a ferumoxytol injection and 10 patients with osteonecrosis who will not receive ferumoxytol as a control. Enrollment will only occur at Stanford University. Stanford University expects to enroll 70 research study participants.

DURATION OF STUDY INVOLVEMENT

Your participation in this research study is expected to take 2 days.

PROCEDURES

If you choose to participate, the Protocol Director and her research study staff will schedule you for if possible at least two MRIs. If you are being evaluated for bone cancer or infection/inflammation, you will have one MRI of about an hour's duration, with a contrast injection before that, and one MRI a day later of 45-60 minutes duration. We understand that sometimes due to irreconcilable circumstances only one scan can be done, in this case one scan will be done about 24 hours or so after the contrast injection.

If you are being evaluated for dead bone, you will have one MRI of about an hour's duration with a contrast injection before your surgery and another MRI without contrast injection within 1 to 2 weeks of your surgery and if possible, one MRI after 6 months of your surgery.

If you have iron overload or any other contraindications for receiving ferumoxytol, we would preform MRI without contrast agent.

The experimental part of this study is the contrast injection and how it appears on the MR images.

MRI (Magnetic Resonance Imaging)
MRI machines use a strong magnet and radiofrequency magnetic fields to make images of the body interior. The scanning procedure is very much like an X-ray or CT scan. You will be asked to lie on a long narrow couch for up to an hour while the machine gathers data. During this time you will not be exposed to x-rays, but rather a strong magnetic field and radiofrequency magnetic fields, which you will not feel. You will, however, hear repetitive tapping noises that arise from the Magnetic Resonance scanner. We will provide earplugs or headphones that you will be required to wear. The space within the large magnet in which you lie is somewhat confined, although we have taken many steps to relieve the "claustrophobic" feeling.

Risks:
Magnetic fields do not cause harmful effects at the levels used in the MRI machine. However, the MR scanner uses a very strong magnet that will attract some metals and affect some electronic devices. If you have a cardiac pacemaker or any other biomedical device in or on your body, it is very important that you tell the operator/investigator immediately. As metallic objects may experience a strong attraction to the magnet, it is

also very important that you notify the operator of any metal objects (especially surgical clips), devices, or implants that are in or on your body before entering the magnet room. All such objects must be removed (if possible) before entering the magnet room. In some cases, having those devices means you should not have an MRI scan performed. In addition, watches and credit cards should also be removed as these could be damaged. You will be provided a way to secure these items. If you have any history of head or eye injury involving metal fragments, if you have ever worked in a metal shop, or if you could be pregnant, you should notify the operator/investigator. You should also notify the operator/investigator if you have any tattoos on your body, including eyeliner and other permanent makeup. Tattoos could become warm and irritated during the scan and remain so for several days. If you would prefer not to participate in the MR scan due to the presence of tattoos on your body, please inform a research team member.

If you have kidney problems, please tell the operator.

There is a possibility that you will experience a localized twitching sensation due to the magnetic field changes during the scan. This is expected and should not be painful.

If you have had a previous reaction to contrast agents or a history of severe allergies, please notify the operator or investigator.

Some of the radio frequency imaging coils, imaging software and devices being used in your scan are not approved by the FDA but are similar to counterparts that have been approved by the FDA. There is a small risk of heating from the cables associated with these devices. Please report any heating sensation immediately.

Dizziness or nausea may occur if you move your head rapidly within the magnet.
Blood tests for iron levels.

We would like to measure your blood iron levels, cell composition and protein content immediately before and up to 6 months (3-4 times in total) after the contrast injection because the contrast we use is an FDA approved iron supplement which can affect these blood components. To avoid additional visits and needle sticks, we will obtain small blood samples when you receive the contrast agent intravenously or when you visit Stanford for routine blood tests ordered by your doctors. Therefore, you are unlikely to have additional visits and needle sticks. This study provides us important data regarding the metabolism and clearance of the contrast agent, but it is optional.

IF YOU FEEL DISCOMFORT AT ANY TIME, NOTIFY THE OPERATOR AND YOU CAN DISCONTINUE THE EXAM AT ANY TIME.

The scans performed in this study are for specific research purposes and are not optimized to find medical abnormalities. The investigators for this project may not be trained to perform medical diagnosis. The investigators and Stanford are not responsible for failure to find existing abnormalities with these MRI scans. However, on occasion the investigator may notice a finding on an MRI scan that seems abnormal. When this occurs, a physician will be consulted as to whether the findings merit further investigation, in which case the investigator will contact you and your primary care physician and inform you of the finding. The decision as to whether to proceed with further examination or treatment lies solely with you and your physician. The investigators, the consulting physician, and Stanford are not responsible for any examination or treatment that you undertake based on these findings. Because the images collected in this study may not comprise a proper clinical MRI scan, these images will not be made available for diagnostic purposes.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions of the Protocol Director and study staff.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the Protocol Director or research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the Protocol Director or research study staff about any side effects, doctor visits, or hospitalizations that you may have.
- Ask questions as you think of them.
- Tell the Protocol Director or research staff if you change your mind about staying in the study.

While participating in this research study, you should not take part in any other research project without approval from the Protocol Directors of each study. This is to protect you from possible injury arising from such things the possible interaction(s) of research drugs, or other similar hazards.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

The Protocol Director may also withdraw you from the study without your consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and study staff.

- The Protocol Director decides that continuing your participation could be harmful to you.
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director if you have any questions.

MRI: Magnetic fields do not cause harmful effects at the levels used in the MRI machine. However, the MRI scanner uses a very strong magnet that will attract some metals and affect some electronic devices. If you have a cardiac pacemaker or any other biomedical device in or on your body, it is very important that you tell the operator/investigator immediately. As metallic objects may experience strong attraction to the magnet, it is also very important that you notify the operator of any metal objects (especially surgical clips), devices, or implants that are in or on your body before entering the magnet room. All such objects must be removed (if possible) before entering the magnet room. In some cases, having those devices means you should not have an MRI scan performed. In addition, watches and credit cards should also be removed as these could be damaged. You will be provided a way to secure these items. If you have any history of ear or eye injury involving metal fragments, or if you have ever worked in a metal shop, you should notify the operator/investigator.

If you feel discomfort at any time, you can notify the operator to discontinue the exam at any time.

IV: With any intravenous injection, there are risks of bruising, bleeding, or infection from the venipuncture; and allergic reaction to the injected contrast. Allergic reactions to the injection of ferumoxytol can include low blood pressure, infusion site swelling, chest pain, diarrhea, dizziness, skin rash, itching, chronic renal failure, and hives. Serious allergic reactions like anaphylaxis can very rarely occur with ferumoxytol (reported incidence 0.2%). You will be closely monitored for an allergic reaction. Your IV injection site will be examined at the second MRI scan to assess for bruising and infection. In the extremely rare situation of a serious allergic reaction, a state licensed MD will be present to provide emergency treatment. If you have soreness or redness after the IV injection, notify Dr. Daldrup-Link immediately by calling her at [redacted] or [redacted].

Women of Childbearing Potential

If you are pregnant or currently breast feeding, you may not participate in this study. You understand that if you are pregnant, if you become pregnant, or if you are breast-feeding during this study, you or your child may be exposed to an unknown risk. To confirm to the extent medically possible that you are not pregnant, you agree to have a pregnancy test done before beginning this research study.

As part of this study, pregnancy testing will be performed. The results of pregnancy tests for those under 18 are confidential according to California Minor Consent Laws. If you are a parent whose child is participating in this study, results will be given to your child by one of the study nurses or doctors in private. Every effort will be made to maintain confidentiality regarding positive pregnancy test results. Although we will not typically tell parent(s) or guardian(s) without your child's permission, under certain circumstances, we might be compelled to reveal this information. For example, if your child's life or someone else's life is at risk or if abuse is suspected, it may be necessary to inform you as parent(s) or guardian(s) of a positive pregnancy test. If we believe it's necessary to tell a parent or guardian of a positive pregnancy test without your child's permission, we will meet with your child first in private to discuss our concerns before divulging any information regarding pregnancy. During research, if your child has a positive pregnancy test, we may withdraw your child from the study. This means that even if we do not reveal the results, you may suspect that your child is pregnant despite our best efforts to maintain confidentiality. If your child becomes pregnant or if there is any chance that your child is pregnant (late menstrual period), please contact the study personnel immediately so that we may provide medical assistance and counseling.

POTENTIAL BENEFITS

We expect to be able to clearly see whether you have a cancer or an infection.

WE CANNOT AND DO NOT GUARANTEE OR PROMISE THAT YOU WILL RECEIVE ANY BENEFITS FROM THIS STUDY.

ALTERNATIVES

You may choose not to participate in this research study, in which case your doctor will choose some other diagnostic study, as appropriate, which may include:

- Invasive bone biopsy
- Diagnostic imaging such as PET, x-rays or CT scans, which include exposure to ionizing radiation
- An MRI with gadolinium-based contrast, which is not very good at distinguishing between tumors and infections/inflammations.

- Surgery for dead bone (decompression surgery) with routine evaluation which may not give you early information on how your healing is progressing.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction.

If you decide not to participate, tell the Protocol Director. You will still receive care for your disease and will not lose any benefits to which you would otherwise be entitled.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

ClinicalTrials.gov

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.

CONFIDENTIALITY

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by NIH which is funding this project or for information that must be disclosed in order to meet the requirements

of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document. We will include results of your research imaging scan in your medical record.

Your identity will be kept as confidential as possible as required by law. Except as required by law, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier. Your research records may be disclosed outside of Stanford, but in this case, you will be identified only by a unique code number. Information about the code will be kept in a secure location and access limited to research study personnel.

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. However, your identity will not be disclosed.

Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

Authorization to Use Your Health Information for Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?
You are invited to participate in a research study of the use of a new contrast agent for MRI. We hope to improve differential diagnosis of cancer vs. infection/inflammation. For patients undergoing surgery for treatment of dead bone, we hope to improve how we evaluate the progress and healing after the surgery. The results of this research study may be presented at scientific or medical meetings or published in scientific journals. However, your identity will not be disclosed.

Do I have to sign this authorization form?
You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study. Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?
If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research).

If you wish to revoke your authorization for the research use or disclosure of your health information in this study, you must write to: Heike Daldrup-Link,

M.D.; Pediatric Radiology, Lucile Packard Children's Hospital, 725 Welch Road, Stanford, CA 94305.

What Personal Information Will Be Used or Disclosed?
Your health information related to this study may be used or disclosed in connection with this research study, including but not limited to, your Stanford-assigned medical record number, your name, your age or date of birth, gender, raw data and information about your MR imaging sessions, and some MR images (de-identified and exported from the PACs for publication). Additionally, for patients being evaluated for dead bone, we will be collecting questionnaire related to the degree of pain you feel and your functional level.

Research using private information is an important way to try to understand human disease. You are being given this information because the investigators want to save private information for future research. Identifiers will be removed from identifiable private information and, after such removal, the information could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you.

Who May Use or Disclose the Information?
The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director, Heike Daldrup-Link, M.D.
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Research Staff

Who May Receive or Use the Information?
The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- National Institutes of Health (NIH)

- The Food and Drug Administration

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?
Your authorization for the use and/or disclosure of your health information will end on 12/31/2050, or when the research project ends, whichever is earlier.

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

If the participant is a child:

_____ _____
Signature of Legally Authorized Representative Date

_____
Print Name of LAR

_____
Description of Representative's Authority to Act for Subject
(Describe relationship – parent, guardian, etc.)

FINANCIAL CONSIDERATIONS

Payment
You will not be paid to participate in this research study.

Costs
If you participate in this study, there may be additional costs to you. These include the personal time it will take to come to all of the study visits.

The study will pay for those services, supplies, procedures, and care associated with this study that are not a part of your routine medical care. If you would like to review the list of such covered services, supplies, procedures and care, please tell us now or at any time during the study.

Participation in this study is not a substitute for health insurance. You and/or your health insurance must pay for those services, supplies, procedures, and care that you require during this study for routine medical care. **You will be responsible for any co-payments and/or deductibles as required by your insurance.**

Sponsor
The Sarcoma Foundation of America and the National Institutes of Health (grant number 5R01AR054458) are providing financial support and/or material for this study.

COMPENSATION for Research-Related Injury

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.**

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital. You do not waive any liability rights for personal injury by signing this form.

CONTACT INFORMATION

If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the Protocol Director, Heike Daldrup-Link M.D., at [redacted]. You should also contact her at any time if you feel you have been hurt by being a part of this study.

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650) 723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 1705 El Camino Real, Palo Alto, CA 94306.

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

May we contact you about future studies that may be of interest to you?
____ Yes ____ No

Signing your name means you agree to be in this study and that you will receive a copy of this signed and dated consent form.

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

_____ _____
Signature of LAR (Parent, Guardian or Conservator) Date

_____
Print Name of LAR

_____
Authority to act for participant (describe relationship)

_____ _____
(If available) Signature of Other Parent or Guardian Date

_____
Print Name of Other Parent/Guardian

_____
Authority to act for participant (describe relationship)

The IRB determined that the permission of one parent is sufficient for research to be conducted under 21 CFR 50.52 and 21 CFR 46.405 in accordance with 21 CFR 50.55 and 45 CFR 46.408(b).

_____ _____

Signature of Person Obtaining Consent Date

_____

Print Name of Person Obtaining Consent

The following witness line is to be signed only if the consent is provided as a summary form and accompanied by a short form foreign language consent.

_____ _____

Signature of Witness Date

_____

Print Name of Witness

(e.g., staff, translator/interpreter, family member)

- *Translated short form must be signed and dated by both the participant (or their LAR) AND the witness.*
- *The English consent form (referred to as the "Summary Form" in the regulations):*
  - *Must be signed by the witness AND the Person Obtaining Consent (POC).*
  - *The non-English speaking participant/LAR does not sign the English consent.*
  - *The non-English speaking participant/LAR should not sign the HIPAA participant line*
  - *If the participant or the LAR is non-English speaking, the Person Obtaining Consent (POC) must ensure that 1) the LAR's Description of Authority is completed and 2) that any questions or options presented by the consent form are documented and initialed by the POC on the Summary Form, per the participant's wishes, as they are understood during the consent process.*