Official Title: Zoledronic Acid to Prevent Bone Loss After Acute Spinal Cord Injury

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Thomas Jefferson University
Informed Consent Document for Human Subjects Research– OHR-8 (v.12/17/14)

Department: Rehabilitation Medicine

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Medical Study Title: Zoledronic Acid to prevent bone loss after acute spinal cord injury

Lay Study Title: A research study to determine if intravenous administration of zoledronic acid can help reduce bone loss after acute spinal cord injury

What Is Informed Consent?

You are being asked to take part in a medical research study. As required by federal regulations, this research study has been reviewed and approved by an Institutional Review Board (IRB), a University committee that reviews, approves and monitors research involving humans. Before you can make a knowledgeable decision about whether to participate, you should understand the possible risks and benefits related to this study. This process of learning and thinking about a study before you make a decision is known as *informed consent* and includes:

- Receiving detailed information about this research study;
- Being asked to read, sign and date this consent form, once you understand the study and have decided to participate. If you don't understand something about the study or if you have questions, you should ask for an explanation before signing this form;
- Being given a copy of the signed and dated consent form to keep for your own records.

You should understand that your relationship with the study doctor is different than your relationship with your treating or personal doctor. The treating doctor treats a specific health problem with the goal of improving a medical condition. A study doctor treats all subjects according to a research plan to obtain information about the experimental drug, device or procedure being studied and with the understanding that you may or may not benefit from being in the study. You should ask questions of the study doctor if you want to know more about this.

The type of study you are being asked to join is known as a "pilot study". It is studying the effectiveness of an FDA-approved drug in a population for which it has not been studied before. This study will collect information on how well the drug works in subjects with acute spinal cord injury.

What is the purpose of this study?

The purpose of this study is to find out if giving a one-time dose of a medication to prevent osteoporosis (weakening of the bone) early after a spinal cord injury can prevent the loss of bone strength in the hips and legs, for persons who have lost muscle strength from a spinal cord injury.

You are being asked to participate in this study because you have suffered an acute spinal cord injury. In this type of injury, there is the potential for extensive bone loss leading to fractures. The standard treatment currently involves testing levels of, and providing supplemental treatment with, calcium and Vitamin D medication.

This study will test the use of a single dose of Zoledronic Acid given as an intravenous infusion, or a placebo infusion of plain saline solution. Intravenous Zoledronic Acid is an FDA approved drug used to treat or prevent osteoporosis (weakening of the bones) in post-menopausal women. The use of Zoledronic Acid in this study is considered investigational as it is not approved for treatment and prevention of bone loss in patients with acute spinal cord injury.

Zoledronic Acid works by inhibiting a certain type of enzyme in bone cells (osteoclasts) that are responsible for the destruction of bone. This drug is being investigated because your spinal cord injury puts you at risk for fractures (broken bones). The drug is given only once during your inpatient hospital stay. It is an infusion delivered through an intravenous (IV) line directly to the vein. It is likely you will have an IV line during your hospitalization. If not, an IV line will be inserted to administer the medication.

How many individuals will participate in the study and how long will the study last?

We plan to enroll a total of 48 patients at Jefferson and Magee Rehabilitation Hospital. Your involvement in the study will involve a schedule of clinic visits and telephone contact for the first year. The study will then follow up with you for 4 years. We plan to contact you every 6 months to ask about your functional status, whether you experienced any bone fractures, and what medications you are taking. The entire study will take about 5 years to complete.

What will I have to do during the study?

- **Screening and Consent:** You will be screened for inclusion in the study once you are admitted to the hospital and within the first 17 days of your injury.
- **Randomization and Study Infusion:** Once the informed consent is completed, you will be randomized to receive one dose of either IV zoledronic acid or a placebo within the first 21 days of your injury.
- **Post-Infusion:** You will be asked about symptoms you might have. You will be ordered treatment with Tylenol every 4 hours for the first 24 hours and as needed after that.
- You will have contacted via telephone or seen at a clinic visit for the first year at 1 Month, 4 Months, 8 Months and 1 Year after Infusion
- You will have periodic blood tests to measure the levels of calcium, vitamin D, creatinine phosphokinase (CPK), which monitors muscle tissue and kidney function, and other markers of bone formation and breakdown. These marker blood tests include intact parathyroid hormone, N-terminal pro-peptide of Type I collagen, interleukin 1 beta, and carboxy-terminal telopeptide of type I collagen.
- You will have bone scans to determine the strength of bones in your legs at the start of treatment, 4 months after your injury, and 12 months after your injury.
- During the first year of study period you will receive supplements of vitamin D and calcium based on the results of your blood tests.

The schedule for the first year of study contacts and visits is described below.

	Screening (Day 0 -17) (Inpatient)	**Baseline (Day 8-21) (Inpatient)**	**Study Drug Infusion (Inpatient - within 21 days of injury)**	**1 month + / - 4 days (Inpatient)**	**4 months + / - 7 days (Outpatient)**	**8 months + / - 14 days (Outpatient blood draw or visit)**	**1 year + / - 14 days (Outpatient)**
Medical History **Standard Care**	**X**						
Physical Exam **Standard Care**	**X**						
Basic Metabolic and Hepatic Panel) **Standard Care**	**X**						
FRAX Score **Study Specific**		**X**					
Study Drug Infusion **Study Specific**			**X**				
Acetaminophen Administration **Study Specific**			**X** [a] **X** [b]				
Serum calcium, magnesium, phos **Standard Care**	**X**	**X**		**X**	**X**	**X**	**X**
Serum 25OH-D **Standard Care**	**X**			**X**	**X**	**X**	**X**
Serum iPTH **Study Specific**	**X**			**X**	**X**		**X**
CPK Study Specific		**X**					
P1NP **Study Specific**		**X**		**X**	**X**		
IL-1 beta **Study Specific**		**X**		**X**			
Serum CTX **Study Specific**		**X**		**X**	**X**		**X**
DXA** **Study Specific**		**X** [c]			**X**		**X**

a. Administered every 4 hours for the first 24 hours following study drug infusion
b. Administered every 4 hours PRN through day 3 following study drug infusion
c. To be obtained as soon as medically stable to undergo DXA testing

After the first year, you will be contacted by telephone every 6 months with questions about functional status, fractures, medications, and treatments according to the schedule below.

	Year 1 **Every 2 Months**	**Year 2** **Month 6**	**Year 2** **Month 12**	**Year 3** **Month 6**	**Year 3** **Month 12**	**Year 4** **Month 6**	**Year 4** **Month 12**
Questions about fractures	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Questions about Vitamin D/calcium supplements	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Questions about exercise and other treatments	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Questions about functional status	**X**	**X**	**X**	**X**	**X**	**X**	**X**

Subject Initials: ___
Date: ___

What are the risks or discomforts involved?

Things you should know about side effects:

- Who will or will not have side effects is not predictable
- Some side effects are mild while others may be severe
- There may be treatments available that could reduce the severity of side effects
- The study doctor/research staff will discuss the risks listed below in greater detail with you

Possible side effects, some may be serious:

- It is likely (>10%) that you will have mild flu-like symptoms for 2-3 days after the infusion of zoledronic acid, such as a mild fever, muscle or bone aches, and fatigue. You will be given Tylenol before treatment and for 24 hours after treatment to reduce these symptoms. Other adverse reactions that have been reported are nausea, vomiting, and diarrhea.
- You may have a drop in the level of calcium in your blood after receiving the single dose of IV zoledronic acid. Low blood calcium can cause numbness and tingling around the mouth and muscle spasms. You will have your calcium levels checked before you receive the infusion and on days 1, 3, 7, 14 and 28 after the infusion.

Rare side effects:

- Rarely (<2%) you may experience a slight increase in serum creatinine, a marker of kidney function. You will be given extra fluids to help your kidneys handle the medication. Patients who have had zoledronic acid once a year for 3 years have not had a change in kidney function.
- In rare cases, you could experience severe bone, muscle or joint pain days to months after receiving zoledronic acid, or temporary noncardiac chest pain (1.3%).
- It is extremely rare (<1 in 1,000), but you may develop a serious jaw bone problem known as osteonecrosis, which means death in parts of the jaw bone after receiving zoledronic acid. This has happened most often in cancer patients who were receiving intravenous bisphosphonate drugs and who were undergoing dental procedures.
- There have also been rare reports of allergic reaction such as hives or swelling of the face, lips tongue or throat. Rare cases of anaphylactic reaction/shock and very rare cases (<0.1%) of eye inflammation have been reported in patients treated with bisphosphonates.

You should call the study doctor as soon as possible at 215-955-6579 if, during the course of this study, you develop any of these side effects or symptoms. The study doctor has told you that if your condition worsens, if side effects become very severe, or if it turns out that being in this study is not in your best interest, you will be taken out of the study.

What are the risks to fetuses, infants and pregnant women?

Pregnant women or women who are breast feeding should not be in this study because exposure to the investigational drug may be hazardous to an embryo, fetus or nursing infant. To be in this study you and your partner must practice adequate birth control measures. Birth control is very important since bisphosphonate drugs are known to cause birth defects, often severe, in animal

studies. The study doctor will discuss acceptable methods of birth control with you. If you are a woman of childbearing potential, you will have a pregnancy test before making a decision about being in this study. This requires either a urine test or that blood be drawn from a vein in your arm (1-2 tsp.) one or two days prior to the start of the study. The results of this pregnancy test will be made available to you prior to the start of the study. If you become pregnant during the course of this study, you should notify the study doctor as soon as possible.

If you are a person in a same sex relationship, it is not necessary for you to practice birth control. However, if you are female, you will still have to have pregnancy tests according to the study protocol.

Will I benefit from being in this study?

You may not benefit from being in this research, but we hope that what we learn may be helpful to future patients or society in general. There is the possibility of benefits from you being in the study. These include potentially stronger bones in your legs, a lower risk of fracture of leg bones, and information about the strength of your leg bones from the bone scans. Also, Vitamin D deficiency may be prevented.

Are there alternatives to being in the study?

You do not have to participate in this study. The bisphosphonate drug, zoledronic acid intended for osteoporosis prevention and treatment, is also available by doctor's prescription. Other alternatives that could be considered include: calcium and vitamin D supplements; other bisphosphonate drugs prescribed by your personal physician; and leg muscle exercises using electrical stimulation. The study doctor will provide information about the study and any alternative treatments available to you.

How will privacy and confidentiality (identity) be protected?

Federal regulations require that certain information about individuals be kept confidential. This information is called "protected health information" (PHI). PHI includes information that identifies you personally such as name, address and social security number, or any medical or mental health record, or test result, that may have this sort of information on it. The laws state that you may see and review your TJU, Thomas Jefferson University Hospital, or Magee Rehabilitation Hospital medical records at any time. However, in a research study, you may not see the study results or other data about the study until after the research is completed unless the study doctor decides otherwise.

If you join this study, the following individuals or entities may have access to your PHI and by law must protect it. These include investigators listed on this consent form and other personnel of Thomas Jefferson University, Thomas Jefferson University Hospitals, Magee Rehabilitation Hospital, Inc. involved in this specific study, the University's Division of Human Subjects Protection and the Institutional Review Board (IRB), and your health insurance company (if necessary for billing for standard medical care). Your PHI may also be shared with the following entities that, while not obligated by law to protect PHI, will protect it to the best of their ability:

- **The National Institute on Disability and Rehabilitation Research,** which is providing funds to Thomas Jefferson University to conduct this research

- The Food and Drug Administration (FDA)
- A Data and Safety Monitoring Committee (DSMC)
- With any person or agency required by law

Study data for analysis:
The study data elements will be collected from your medical records and from discussions with you about your symptoms and your functional status. These include: results of standard lab test and study-specific lab tests, imaging studies such as the DEXA scan, and answers to questionnaires.

Demographic data:
The demographic data collected will include your age, gender, race, and ethnicity.

If you develop an illness or injury during the course of your participation in this study, other PHI about treating and following the condition may be generated and disclosed as it relates to this study. Your PHI may be used until the end of the research study. You may quit the study and revoke permission to use and share your PHI at any time by contacting the principal investigator, in writing:

Christina V. Oleson, MD
132 South 10th Street, 375 Main Building
Philadelphia, PA 19107

If you quit the study further collection of PHI will be stopped, but PHI that has already been collected may still be used. The results of clinical tests and procedures performed as part of this research may be included in your medical records. The information from this study may be published in scientific journals or presented at scientific meetings but you will not be personally identified in these publications and presentations.

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, this Web site will include a summary of the results. You can search this Web site at any time.

What happens in case of injury as a result of being in this study?
In the event that you experience a research-related injury, necessary and available medical care (including hospitalization) will be provided. A research-related injury is a physical injury or illness resulting to you that is directly caused by any procedure or treatment used in this study that is different from the treatment you would receive if you were not participating in a research study. If you are physically injured due to any drug/substance or procedure properly given under the plan for this study, medical expenses for treating the injury will be billed to your insurance carrier. You should be aware that some costs may not be covered by insurance and may become your responsibility. There is no plan to provide compensation for loss of wages, lost time from work, personal discomfort, or for injuries or problems related to your underlying medical condition(s). If you receive a bill related to a research-related injury that seems wrong, please discuss it with the study doctor or research coordinator.

Will I be paid for being in this study?

You will not receive payment for your participation in this study. However, reimbursement for transportation costs will be provided for any special study visits taking place outside of your regularly scheduled clinic visits.

Are there costs related to being in this study?

There are no financial costs to you related to being in this study. The National Institute on Disability and Rehabilitation Research is providing funds to conduct this research.

Research Procedures

The investigational agent (a single dose of IV Zoledronic Acid) and the cost of the bone scans and research-specific blood tests will be paid for with funding from the sponsoring agency.

Standard Testing Procedures

Procedures, tests and doctor's charges resulting from being in the study that are considered standard of care will be billed to your health insurance carrier. These are charges that you would have whether or not you were participating in a research study. It is possible that your insurance company may deny payment. If that happens you may be responsible for some or all of these charges. The study doctor will explain to you which procedures, tests and doctor visits are considered standard of care. If you receive a bill that you think is wrong, please discuss it with the study doctor or research coordinator.

Will I be told about any new findings?

Anything learned during the study, beneficial or not, that may affect your health or your willingness to continue in the study, will be told to you and explained.

Can I be removed from the study or quit the study?

Your decision to participate in this research study is entirely voluntary. You have been told what being in this study will involve, including the possible risks and benefits. Your participation in this research project may be terminated by the study doctor without your consent for any reason that he/she feels is appropriate. You may refuse to participate in this investigation or withdraw consent and quit this study without penalty and without affecting your ability to receive medical care at Thomas Jefferson University.

If you withdraw from this study, you may continue treatment with your Jefferson doctor, or you may seek treatment from another doctor of your choice. Should you decide to withdraw from the study, please be sure to inform the study doctor. Additional tests or procedures may be needed to ensure your safety. The study doctor will explain why these tests or procedures are necessary.

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CONTACT INFORMATION

Telephone number for questions about your rights as a research participant	Jefferson Institutional Review Board	215-503-8966
For questions, concerns or complaints about the research, or if you suspect a research-related injury	Principal Investigator: Dr. Christina Oleson, or any co-investigator listed at the beginning of this form	215-955-6579
If you have difficulty contacting the study staff call the Jefferson OHR	Jefferson Office of Human Research	215-503-0203

For more information about the Jefferson Institutional Review Board or Jefferson's Human Research Protection Program, please visit our website http://www.jefferson.edu/human_research/irb/index.cfm.

Subject Communications

Do you wish to communicate with the study staff by e-mail? YES _____ NO _____

If you checked yes, please print your e-mail address on the line below.

_____

RISKS: E-mail correspondence is not always secure and there is a risk of loss of confidentiality. To help protect against loss of confidentiality, all e-mail that originates from Jefferson University or Jefferson Hospital employees using Jefferson University or Jefferson Hospital e-mail addresses is encrypted. That means, unless you have allowed others to have access to your e-mail, only you will see the e-mail.

YOU SHOULD **NEVER** USE E-MAIL TO REPORT A SUSPECTED ADVERSE EVENT OR ANY OTHER MEDICAL PROBLEM. THESE SHOULD BE REPORTED BY TELEPHONE.

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Non-Waiver of Legal Rights Statement

- ✓ **By your agreement to participate in this study, and by signing this consent form, you are not waiving any of your legal rights.**
- ✓ **In order to be in this research study, you must sign this consent form.**
- ✓ **You affirm that you have read this consent form. You have been told that you will receive a copy.**

SIGNATURES

_____
Your Name

_____
Your Signature Date

_____
Name of Person Conducting Consent Interview

_____
Signature of Person Conducting Consent Interview Date

_____
Witness Signature *(only required if subject understands and speaks English but cannot read English or if subject is blind or cannot physically sign the consent form)* Date

***The subject is physically unable to sign the consent form. All pages of the consent form were reviewed with the subject, who voluntarily consented to participate in this study.**
Witness Initials:_____

_____
Signature of Principal Investigator or Co-Investigator Date

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_____
Copy of Signed and Dated Consent given to Subject by (*Signature above)* Date