Effects of Electrical Stimulation and Vitamin D supplementation on Bone Health Following Spinal Cord Injury

NCT05008484

August 17, 2021

Central Virginia Veterans Affairs Health Care System (CVHCS)
McGuire Institutional Review Board
Consent Form

Template Version Date: (3/16/2021)

Title of Research Study: Effects of Electrical Stimulation and Vitamin D Supplementation on Bone Health Following Spinal Cord Injury.

Sponsor: VA-Rehabilitation Research and Development (RR&D)

Protocol No.: N/A

Investigator Name & Address: Dora E. Ifon, Ph. D., NP
1201 Broad Rock Boulevard
Richmond, VA 23249

KEY INFORMATION:

We are asking you to consider participation in this research study being funded by VA Rehabilitation Research and Development (RR&D) about the effects of home-based neuromuscular electrical stimulation (NMES) accompanied with ankle weights plus Vitamin D or regular exercises with ankle weights plus Vitamin D on bone health in persons with spinal cord injury (SCI). NMES is electrical shock exercise for your paralyzed legs, ankle weights provide resistance training (RT) exercise to your paralyzed legs and Vitamin D may help make bones stronger.

This initial information is provided to help you decide whether or not to participate in the study. By doing this study, we hope to learn if NMES-RT for 4.5 months followed by additional 4.5 months of NMES-rowing to your paralyzed legs or passive (someone moving your paralyzed legs) exercises in combination with taking Vitamin D can improve your bone health. NMES-rowing is an electric shock exercise while on a machine that works your quads, hamstring or glutes as if you were rowing a boat)
.
Your participation in this study could last approximately 9 months and you would be required to come to the Medical Center 3 times during the study period; when you first enroll, mid-session (4.5 months) and at close-out (9 months). Each study visit at the Medical Center will last approximately I - 2 hours. The rest of the study treatment will be done at your home, with the help of your caregiver, using a smartphone, tablet or laptop two days a week.

You may want to participate in this study because NMES to your paralyzed legs may improve your bone health or you may not want to participate because of the risk of study procedures and Vitamin D.

Additional detailed information is provided for your review in the sections below. Ask the research team questions until you feel you have enough information to make your decision to participate or not. Participating in this research study is completely voluntary. Your decision to participate or not will have no effect on any of the services, benefits or rights that you are otherwise entitled.

The person in charge of this study is *Dr. Dora E. Ifon* and she can be reached at ***(804-675-5000 ext. 3413)***. Other important contact information is listed below.

1. Whom should I contact for questions?
If you have any questions, concerns or complaints regarding this study, unexpected reactions, or you are injured and become ill as a result of participation in this study please call AM or PM*:*

	Office	**Off Hours**
Dr. Dora Ifon	(804) 675-5000 ext. 3413	804-204-3349
Dr. Ashraf Gorgey	(804) 675-5000 ext. 3386	804-750-4814
Dr. Robert A. Adler	(804) 675-5425	804-659-0281
Dr. Timothy Lavis	(804) 675-5000 ext. 3391	804-659-0249
Dr. Teodoro Castillo	(804) 675-5000 ext. 4582	804-204-3712

If you are unable to reach any of the study staff listed and need immediate medical assistance, please call the McGuire VAMC operator at 800-784-8381 and ask for the Emergency Room physician to obtain advice or call the **Emergency Room directly at (804)-675-5527**. If you have any questions, concerns or complaints about your rights as a research subject you may contact the **McGuire Institutional Review Board (IRB) at (804) 675-5676.** The IRB is responsible for reviewing research in humans and making sure that their safety and rights are protected.

2. What is this research study about? (Introduction)
This study involves research with spinal cord injured people. The purpose of this research study is to determine the effect of home-based neuromuscular electrical stimulation (NMES) accompanied with ankle weights followed by NMES-rowing and Vitamin D supplementation on bone health. The expected duration of your participation is 9 months**.** The approximate number of research subjects in this study is 20 and the research is sponsored by the VA office of Rehabilitation Research and Development**.**

3. What is expected of me? (Procedures):
Day 1:
If you agree to participate, you will be asked to sign this consent form after all of your questions have been answered.

You will be asked to undergo a complete physical lasting 30-45 minutes. Your heart tracing (EKG) will be measured. Depending on the results of these tests, the study doctor will discuss with you if you are eligible to continue in this study.

If you are eligible to continue, your weight, and height measurements will be taken. Your bone measurements will be taken using DXA (measures bone strength using x-rays) and MRI (uses strong magnets and radio waves to see inside your body). You will also be asked to give blood samples (2 teaspoons) for lab tests.

Measurements:
DXA: While lying on a table, we will measure bone strength for your total body, spine, hips and knees. A DXA takes about 30 minutes**. The DXA will be done three times – at the beginning, 4.5 months and at the end of the study.**

MRI: We will obtain measurements of your thigh bone (femur) and shinbone (tibia), lower leg muscles size and bone strength in your legs. This procedure involves lying still on a table during the scan period. The MRI takes about 20 minutes. **The MRI will be done three times – at the beginning, 4.5 months and at the end of the study.**

Blood sample: You will be asked to provide a fasting blood sample (no food or drink for 8 hours) 3 times during the study to measure your vitamin D and calcium levels. This will be done in SCI clinic. It involves tying a rubber band around your arm to make your vein pop out, then a needle will be inserted into your arm vein to collect the blood samples into a couple of blood tubes. The needle will then be removed and a Band-Aid applied over the site to stop you from bleeding from the needle site. Blood sample will be collected at the beginning of the study, 4.5 months later and at the end of the study (9 months).

Diet: We will ask you about your diet to help us measure the amount of protein, sodium, calcium, and phosphorous in your diet. These are some of the key nutrients in bone health. A diet recall form will be given to you to record everything you eat and drink (including snacks) for 3 days each week you are in the study. The study staff will collect this form from you. You will also receive a telephone or video call once a month from the dietitian with diet advice. The time commitment is about 5 -15 minutes a week for diet recall and 10-15 minutes a month with the dietitian for diet advice.

Randomization:
You will be assigned to one of two groups by chance (like tossing a coin). Participants will be grouped as follows: Group 1 – NMES-RT/Rowing and Cholecalciferol (Vit. D supplement) OR Group 2 – Passive exercise and Cholecalciferol.

After Day 1
Intervention for 9 months:

Vit D: You will receive 30-day supply of 2000 IU vitamin D to take by mouth once a day at about the same time every day. If your baseline Vitamin D is low, we will give you a

higher dose (depending on how low your level is) for the first two weeks. The Vitamin D will be refilled every 25 days to make sure that you do not run out. We will also call you every 30 days for a pill count to make sure that you are taking the vitamin D.

Resistance training (RT) and Rowing Exercise: If you are assigned to the NMES-RT/Rowing with Vitamin D group, you will receive 4.5 months of electrical leg shocks with ankle weights (no ankle weights in the first week), twice a week, that will be done while sitting in your wheelchair. Two adhesive patches (electrodes) will be placed on the skin over the knee muscles. Electrical current from the stimulator will be slowly increased in 5-second intervals to cause full leg extension (leg straightens out). Once full extension is achieved in a sitting position, an extra 2 lbs. of weight will be added on a weekly basis. Each session will be consisted of 4 sets of 10 knee extensions and it will last for 30-40 minutes. Training will be alternated between right and left legs. You and a caregiver will be trained on how to set up the device so you can use it at home.

After 4.5 months, you will be provided a rowing machine (Murtisol Magnetic Rowing machine) to use twice weekly. You will be asked to transfer to the rowing machine with assistance by your caregiver, using a sliding board or a portable lift. Patches for NMES will be placed on both knee extensors (muscles that straighten out your legs) and flexors (muscles that bend your leg at the knee) and the electrical current will be alternated 5 seconds on, then 10 seconds off on both muscle groups. You will be using your arms to start off the extension and flexion of both legs. If you do not have full trunk control, you will be provided with an adhesive belt to secure your trunk during exercise as well as special hand mittens to secure your hands to the rowing machine, if needed. Each session will be consisted of 4 sets of 10 knee extension and flexion, and it will last for 30 - 40 minutes. Training will be alternated between right and left legs each day of exercise.

Passive range of motion or passive stretching : If you are assigned to the passive exercise and Vitamin D group, your caregiver will be asked to sit on a stool and cup your leg above your ankle joint and move it from 90-degrees of knee flexion to full knee extension. The leg will be maintained in extension for 5 seconds and returned to flexion for 5 seconds. The passive actions is repeated in the manner described in the RT protocol; 10 reps on the right leg followed by 10 reps on left leg for a total of 4 sets x 10 reps. This training will be conducted twice weekly. This exercise will last 30 – 40 minutes.

Blood Pressure (BP) monitoring during exercise: Since this is a 30 – 40 minutes exercise, your caregiver will check your blood pressure at the beginning, 15 minutes into the exercise and at the end. This is to detect if you develop Autonomic Dysreflexia (AD) during or after the exercise. If you do not currently have a BP machine, the study team will help you get one.

You and/or your caregiver will train on the use of neuromuscular electrical stimulation and passive range of motion (ROM). After the training, you or your caregiver will be responsible for placing and removing skin electrodes (patches) and checking the skin

afterward for skin breakdown. You or your caregiver will also be responsible for adjusting the stimulator current. For those undergoing passive ROM, the caregiver will be responsible for moving the paralyzed legs (one at a time) while holding it above the ankle, from 90 degree of knee flexion (bent knee) to full knee extension (straighten out). Your caregiver will also be responsible for adding ankle weights during the exercise every week . Your caregiver will also assist you to transfer (if you are unable to do so). The study team will review transfer with sliding board or portable lift with your caregiver.

Quality of Life (QoL) Survey:

You will be given a questionnaire regarding your health, wellness, and quality of life to complete. This questionnaire will be given two times during the study (at the beginning and the end of the study). The questionnaire will take about 15 minutes to complete.

Home Video Telehealth Service:

Telehealth is a service offered by the VA for use to provide virtual care. Telehealth will be done by video conference call. If you are not enrolled to participate in VA Telehealth activities then a form will be completed to register and provide us permission to use VA Telehealth with you before you may participate. You will need to have a smart phone, a tablet or computer with a web cam and internet access in order to be able to participate. However, if do not have one of these, you will be provided a tablet with web camera and internet access and we will help you create an e-mail account if you do not already have one.

You will need a quiet space in your home for the training. The study team will make sure that your address is accessible to EMS (Emergency Medical Services), in the event of an emergency. If it is not accessible to EMS, you will not be able to participate in this study. At the start of each session, the PI will verify your address and telephone number and an alternate contact person and a phone number for use in emergency situations or communication failure. Should the need arise, the study team will contact EMS or the National VA Teleheath Crisis Line for additional help.

Before starting the exercise training session, the microphone, speakers and web camera will be tested to make sure things are working fine from both ends. We will request that you be ready 20-30 min prior to the video call by asking your caregiver to place the electrodes on your legs, make sure the batteries of the stimulator is fully charged, electrodes are connected to the stimulator and the ankle weights are positioned. Once the setup is completed and Telehealth connection is established, the training will begin.

Training sessions will be conducted twice weekly. At the end of each session, the PI will confirm your next appointment, and request that you confirm your next appointment online 24 hours before the next session. If you are unable to keep your appointment for any reason, we can reschedule your appointment for another day and time so long as you have 2 sessions in a week.

4. Will my data and/or samples be kept for use in the future? (Future use of data/samples)
Your information and/or biospecimens collected as part of this research, even if identifiers are removed, will not be used or distributed for future research studies.

5. Will the research benefit me? (Benefits)
No benefit is guaranteed**.** However, the information we get from this study might help others with your condition.

6. What are my alternatives to being a research subject? (Alternative Therapy)
You do not have to participate in this study to receive treatment for your condition. Your alternative is to decline participation in this study.

7. What are my risks? (Risks, Inconveniences, Discomforts).
Participation in this study may involve risks that are unknown at this time. Your condition may stay the same, may improve or may worsen from study participation.

All drugs and supplements have the potential to cause allergic reactions including the vitamin D used in this study. Allergic reactions may be mild to severe, and include the following symptoms: chills, fever, skin rash, hives, itching, watery eyes, swelling, headache, difficulty breathing, difficulty swallowing, severely low blood pressure, organ failure, and death. Serious allergic reactions require immediate medical attention.

Potential risks and sources:

Potential source of risk	Potential Risk	Possibility of occurring
Pressure to skin from weights or skin irritation from weights or during exercise	Break in your skin creating a wound requiring daily wound care.	Occasionally but no more than usual from daily activities
DXA	This research study will involve MRI and exposure to radiation from 3 DXA scans. This research study may require imaging which involves exposure to radiation in the form of X-rays. This radiation exposure is not necessary for your medical care and is for research purposes only. All radiation increases the risk of developing cancer in the future. The total amount of radiation that you will receive in this study is equal to about 3 - 4	Unlikely

	weeks of exposure from natural background radiation. The McGuire VA Medical Center Radiation Safety Committee has reviewed the use of radiation in this research study and has approved this use as involving acceptable risk and necessary to obtain the research information desired. Please tell your doctor if you have taken part in other research studies or received any other medical care recently involving radiation.	
Electrical stimulator/weights (Risk of fracture, skin breakdown)	1. SCI is commonly associated with bone weakness and exercising on the rowing machine may increase risk of fracture to already weakened bones. 2. Light-headedness, shortness of breath and altered heart rate & blood pressure leading to autonomic dysreflexia. 3. Muscle soreness at your neck, upper back, shoulders, arms & hands. 4. Pressure ulcer 5. Autonomic dysreflexia (slow heart rate, high blood pressure, headache flushing &sweating) which may be life threatening. 6. Fainting, heart attacks or death 7.	Rare Unlikely Unlikely Unlikely Unlikely
Autonomic Dysreflexia (AD)	Symptoms of autonomic dysreflexia (AD) include sudden high blood pressure and possibly headache, sweats, blurred vision, stuffy nose, and nervousness. There is a small risk that blood pressure could become very high and cause a stroke. If AD occurs, the study is stopped, and the bladder emptied, which usually causes the AD to resolve on its own. A medication	Rare

	called nitroglycerin paste is kept in the laboratory (or your home, among you prescribed medications) in case it is needed to apply to the chest for AD. This medication can cause low blood pressure, dizziness and headache, which is treated by removing the paste and leaning your head down.	
Falls	Falls could occur during training or transfer unto testing equipment (MRI/DXA table) or in the home during transfer to/from wheelchair unto rowing machine. This could result in injury, including broken bones.	Rare
Supplement (Vitamin D3)	Vitamin D toxicity can lead to high calcium levels and kidney stones, which can cause you to have severe back pain, blood in your urine, urinary tract infection, nausea, vomiting, fever and chills. To reduce this risk you vitamin D level will be checked at the 4.5 month and 9 month visits.	Rare
Rowing equipment	It is possible that the rowing machine may breakdown. To avoid this we will inspect the machine for any problems before using it in the study.	Rare
Risks of MRI	Anxiety, dizziness, claustrophobia (fear of being in a confined space), If you have fear of being in a confined space, the MRI tech will give you an eye mask to wear and talk with you every 3-5 minutes. You may be offered mild sedation if you prefer. The study doctor will discuss the risk of sedation medicine with you. You will also need someone to drive you the day you have the MRI. You may experience changes in your blood pressure and heart rate. Your breathing may slow down a little bit, and you may have a headache, feel nauseated or vomit. Implanted metallic devices may pose risk for using MRI, for example, an implanted	Rare

	stimulator or intrathecal pump device may not work following MRI exposure.	

8. Will I get paid? (Compensation)
You will receive a total of $300 for your participation, $150 after you complete the first 4.5 months of the testing and $150 at the end of the testing in the 9th month. If you receive payments from the Department of Veterans Affairs, they will be reported to the IRS along with your social security number.

The information that you are providing for this research study may lead to new clinical or educational knowledge, tests, treatments or products. These products could have some financial value. There are no plans to provide financial payment to you or your relatives if this occurs.

9. Will I have to pay? (Cost of Participation)
You will not have to pay, and your insurance will not be billed for treatments or procedures that are part of this study regardless of whether you are a Veteran or a non-Veteran. If you get a bill for research services, contact your study doctor or research nurse. Some Veterans are required to pay co-payments for medical care and services provided by the CVHCS. These co-payment requirements will continue to apply to medical care and services provided by the VA that are not part of the study. There is no cost to participate in this study.

There is no guarantee that the vitamin D you will receive during this study will be continued after the study is completed. If you are a Veteran and are eligible for care you may continue to receive the same supplement after the study only if the supplement is routinely available at CVHCS pharmacy and your physician decides that it is the most appropriate treatment.

10. Does pregnancy prevent me from participating? (Pregnancy)
Every effort will be made to have females enter this study. Medically accepted birth control is required to enter this study. If on birth control, maintain the same and do not switch birth control. This may include, but is not limited to, birth control pills, IUD's, condoms, diaphragms, implants, being surgically sterile, or being in a post-menopausal state. However, no birth control method eliminates the risk of pregnancy. If you are a female and if pregnancy occurs there may be a risk of miscarriage, birth defects, other medical complications or unforeseen risks to yourself or to the unborn baby (i.e. embryo or fetus). If you are a female of childbearing age, you must have a negative pregnancy test before entering the study. This test will be repeated monthly during the course of the study. If the test is positive, you will not be able to continue in the study.

11. What if I get injured? (Research Related Injury)
In the event of a research injury from your participation in this study, necessary medical treatment will be provided to assist your recovery from the injury. If you are a CVHCS

study participant (Veteran or Non-Veteran), the CVHCS (not you or your insurance) will provide necessary medical treatment should you be injured by being in this study. You will be treated for the injury at no cost to you. This care may be provided by the CVHCS or arrangements may be made for care at another facility. You have not released this institution from liability for negligence. In the event of injury resulting from your participation in this research study, you should contact your study team. If you want to speak to someone who is not a member of the study team to discuss problems, ask questions or voice concerns, you can call the McGuire IRB at (804) 675-5676.

This agreement does not include treatment for injury/illness that is not a result of the study. To help avoid injury, it is very important to follow all study directions. You are not giving up any of your legal rights by signing this form.

12. Who Will See My Information? (Confidentiality)

The study team *will* put information about your participation in this study in your medical record for your safety. It is important for other health care providers taking care of you to know any study drugs or study treatments you are receiving.

The confidentiality of your research records will be maintained according to professional standards of confidentiality and Veterans Health Administration (VHA) regulations. Records identifying you may be reviewed by the members of the research team, the representatives of VA Rehabilitation Research and Development and their agents of this study, the Research and Development Committee and its sub-committees, accrediting agencies, officials from the VHA, the Office of Research Oversight, the VA Office of the Inspector General, CVHCS, and other federal oversight agencies such as the Food and Drug Administration, Office for Human Research Protections, or as required by law.

The records and data pertaining to participants in this study will be protected by keeping them in locked file cabinets, on a computer protected with passwords, and only the PI, Dora E. Ifon, will have access to the data.

Clinically relevant research results will be disclosed to you if, for example, you have an abnormal blood work result(s), so that you can seek further treatment.

You will have access to your research related health records while participating in this study.

The ways your study doctor will use your study-related health information and the people who may receive it are identified in a separate form entitled, Authorization for Use & Release of Individual Identifiable Health Information for Veterans Health Administration Research. You will be asked to sign that form to show that you give permission for these uses and sharing of your information. You do not have to sign the authorization form. However, if you do not sign, you will not be able to participate in the study.

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.

Information published or presented about the results of this study will not identify you. If you are a non-Veteran receiving care as part of this study, you will have an electronic CVHCS medical record created for you. You will also be given a VA Notice of Privacy Practices.

13. Do I have to participate in this study, or can I withdraw from the study? (Voluntary Participation and Withdrawal)

Participation in this study is voluntary and you may refuse to participate without penalty or loss of benefits to which you are otherwise entitled. The study staff will answer any questions you may have about the study. You are free to withdraw your consent and stop participation at any time. If you decide to withdraw from this study, you should contact *Dr. Ifon* to discuss termination of your participation. It is important that you do this so that Dr. Ifon can withdraw you safely. Stopping will in no way change the quality of care you receive now or in the future at this institution or your right to participate in other studies.

Any data collected prior to withdrawal will continue to be used for the study by the investigator and samples collected cannot be withdrawn.

Any significant new findings that develop during the research study that may affect your decision to continue participating will be provided to you as soon as possible.

Your participation in this research study may be ended without your consent for the following reasons:

- If the study doctor believes, for any reason, that it is within your best interest.
- If you develop side effects that are considered dangerous.
- If you refuse to take the Vitamin D as prescribed or fail to follow the study doctor's instructions.
- If you refuse to have tests that are needed to determine whether the vitamin D and NMES is safe and effective.
- If you require treatment with drugs that are not allowed in this study.
- If you become pregnant.
- If other causes prevent continuation of the clinical research study.
- VA RR&D, FDA, McGuire IRB may also end the study at any time.

14. Date of Consent Form Revision: 8-11-2021

Subject Name:_____ **Date:**_____

Title of Research Study: Effects of Electrical Stimulation and Vitamin D Supplementation on Bone Health Following Spinal Cord Injury.

Principal Investigator*:* Dora E. Ifon, Ph.D., NP **CVHCS:** Richmond

RESEARCH SUBJECTS' RIGHTS: I have read or have had read to me all of the above.

Dr. Ifon (or an associate) has explained the study to me and answered all my questions. I have been told of the risks or discomforts and possible benefits of the study. I have been told of other choices of treatment available to me. I have been given the chance to ask questions and obtain answers.

I understand that I do not have to take part in this study, and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw from this study at any time without penalty or loss of VA or other benefits to which I am entitled. The results of this study may be published, but my records will not be revealed unless required by law. By signing below, I am agreeing to participate in this research study. I will receive a signed copy of this consent form.

_____ _____

Subject's Signature **Date**

As a caregiver, I agree to participate in the project as described above.

_____ _____

Caregiver's Signature **Date**

_____ _____

Signature of Person Obtaining Informed Consent **Print name/Date**