

COVER PAGE

Clinicaltrials Title: FES Rowing for Skeletal Health After SCI

Official VA Project Title: Using Musculoskeletal Models to Assess FES Rowing for
Skeletal Health After SCI

IRB Title: Skeletal Health in the Lower Limbs Following Spinal Cord Injury

NCT #: NCT02008149

Date: 09/02/2015

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Modification
<p>1. Summarize your proposed changes.</p> <p>1) Change the status of Dr. Rebecca Lambach to take the role of the Admin Contact, with authority to edit the IRB protocol and associated documents.</p> <p>2) Modification to the inclusion criteria to allow for the recruitment of subjects over the age of 50 years, and to allow for the recruitment of subjects for the control group who have C5, C6, C7, or C8 injuries in addition to T1 to T12 injuries. The injury levels in the rowing groups remain as T1 to T12.</p>
<p>2. Indicate Level of Risk</p> <p>No Change</p>
<p>3. Update the Conflict of Interest (COI) section if any changes in COI have been made since the last protocol submission.</p> <p>N Is there a change in the conflicting interest status for any existing personnel on this protocol?</p>

Protocol Director				
Name Gary Scott Beaupre		Degree (Program/year if student) PhD		Position, e.g. Assistant Professor, Resident, etc. Professor - Consulting
Department Mechanical Engineering - Biomechanical Engineering	Mail Code 4038	Phone 650-493-5000 x64272	Fax 650-493-4919	E-mail Gary.Beaupre@va.gov
CITI Training current				Y

Admin Contact				
Name Rebecca Lambach		Degree (Program/year if student) PhD		Position, e.g. Assistant Professor, Resident, etc. Biomedical Engineer
Department Vice Provost and Dean of Research - Research Compliance	Mail Code	Phone 650-493-5000 x69411	Fax 650-493-4919	E-mail rebecca.lambach@va.gov
CITI Training current				Y

Investigator				
Name Beatrice Jenny Kiratli		Degree (Program/year if student) PhD		Position, e.g. Assistant Professor, Resident, etc. Clinical Associate Professor (Affiliated)
Department Orthopaedic Surgery	Mail Code	Phone 650-493-5000 x65095	Fax	E-mail Jenny.Kiratli@va.gov
CITI Training current				Y

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Other Contact

Name Graham Harold Creasey		Degree (Program/year if student) MD		Position, e.g. Assistant Professor, Resident, etc. Professor-Med Ctr Line
Department Neurosurgery	Mail Code 5327	Phone 650-704-2394	Fax	E-mail gcreasey@stanford.edu
CITI Training current				Y

Academic Sponsor

Name		Degree (Program/year if student)		Position, e.g. Assistant Professor, Resident, etc.
Department	Mail Code	Phone	Fax	E-mail
CITI Training current				

Other Personnel

Participant Population(s) Checklist

Yes/No

- Children (under 18) N
- Pregnant Women and Fetuses N
- Neonates (0 - 28 days) N
- Abortuses N
- Impaired Decision Making Capacity N
- Cancer Subjects N
- Laboratory Personnel N
- Healthy Volunteers N
- Students N
- Employees N
- Prisoners N
- Other (i.e., any population that is not specified above) Y

Study Location(s) Checklist

Yes/No

- Stanford University
 - Clinical & Translational Research Unit (CTRU)
 - Stanford Hospital and Clinics
 - Lucile Packard Children's Hospital (LPCH)
 - VAPAHCS (Specify PI at VA) Y
- Gary Beaupre
- Other (Click ADD to specify details)

General Checklist

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Multi-site**Yes/No**

- Is this a multi-site study? A multi-site study is generally a study that involves one or more medical or research institutions in which one site takes a lead role.(e.g., multi-site clinical trial)

N

Collaborating Institution(s)**Yes/No**

- Are there any collaborating institution(s)? A collaborating institution is generally an institution that collaborates equally on a research endeavor with one or more institutions.

N

Cancer Institute**Yes/No**

- Cancer-Related Studies (studies with cancer endpoints), Cancer Subjects (e.g., clinical trials, behavior/prevention) or Cancer Specimens (e.g., blood, tissue, cells, body fluids with a scientific hypothesis stated in the protocol).

N

Clinical Trials**Yes/No**

- Investigational drugs, biologics, reagents, or chemicals? N
- Commercially available drugs, reagents, or other chemicals administered to subjects (even if they are not being studied)? N
- Investigational Device / Commercial Device used off-label? Y
- IDE Exempt Device (Commercial Device used according to label, Investigational In Vitro Device or Assay, or Consumer Preference/Modifications/Combinations of Approved Devices) N
- Will this study be registered on# clinicaltrials.gov? (See Stanford decision tree) N
- Is Stanford responsible for ClinicalTrials.gov registration? (See Stanford decision tree) NCT#

Tissues and Specimens**Yes/No**

- Human blood, cells, tissues, or body fluids (tissues)? N
- Tissues to be stored for future research projects? N
- Tissues to be sent out of this institution as part of a research agreement? For guidelines, please see <https://sites.stanford.edu/ico/mtas> N

Biosafety (APB)**Yes/No**

- Are you submitting a recombinant DNA vector or Human Gene Transfer investigation using biological agents? If yes, please complete and attach the Gene Transfer Protocol Application Supplemental Questions to section 16 of the eProtocol application. N

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- Are you submitting a Human study using biohazardous/infectious agents? If yes, refer to the <http://www.stanford.edu/dept/EHS/prod/researchlab/bio/index.html> Administrative Panel on BioSafety website prior to performing studies. N
- Are you submitting a Human study using samples from subjects that are known or likely to contain biohazardous/infectious agents? If yes, refer to the <http://web.stanford.edu/dept/EHS/prod/researchlab/bio/index.html> Administrative Panel on BioSafety website prior to performing studies. N

Human Embryos or Stem Cells

Yes/No

- Human Embryos or Gametes? N
- Human Stem Cells (including hESC, iPSC, cancer stem cells, progenitor cells) N

Veterans Affairs (VA)

Yes/No

- The research recruits participants at the Veterans Affairs Palo Alto Health Care System(VAPAHCS). Y
- The research involves the use of VAPAHCS non-public information to identify or contact human research participants or prospective subjects or to use such data for research purposes. Y
- The research is sponsored (i.e., funded) by VAPAHCS. Y
- The research is conducted by or under the direction of any employee or agent of VAPAHCS (full-time, part-time, intermittent, consultant, without compensation (WOC), on-station fee-basis, on-station contract, or on-station sharing agreement basis) in connection with her/his VAPAHCS responsibilities. Y
- The research is conducted using any property or facility of VAPAHCS. Y

Equipment

Yes/No

- Use of Patient related equipment? If Yes, equipment must meet the standards established by Hospital Instrumentation and Electrical Safety Committee (650-725-5000) Y
- Medical equipment used for human patients/subjects also used on animals? N
- Radioisotopes/radiation-producing machines, even if standard of care? http://www.stanford.edu/dept/EHS/prod/researchlab/radlaser/Human_use_guide.pdf More Info Y

Payment

Yes/No

- Subjects will be paid/reimbursed for participation? See payment considerations. Y

Funding

Yes/No

- Training Grant? N
- Program Project Grant? N

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- Federally Sponsored Project? Y
- Industry Sponsored Clinical Trial? N

Funding

Funding - Grants/Contracts	
Funding Administered By : VA	SPO # (if available) :
Grant # (if available) : RX001410	Funded By (include pending) : VA
Principal Investigator : Gary Beaupre	
Grant/Contract Title if different from Protocol Title :	
Using Musculoskeletal Models to Assess FES Rowing for Skeletal Health After SCI	
Y	For Federal projects, are contents of this protocol consistent with the Federal proposal?
N	Is this a Multiple Project Protocol (MPP)?
N	Is this protocol under a MPP?

Funding - Fellowships

Gift Funding

Dept. Funding

Other Funding

Resources :

a) **Qualified staff.**

Please state and justify the number and qualifications of your study staff.

Gary Beaupre, PhD
 Dr. Beaupre is the Principal Investigator for this project. Dr. Beaupre is a Research Career Scientist at VA Palo Alto Health Care System (VAPAHCS) and he has overseen numerous research projects involving human subjects, including a recent one with a recruitment total of over 265 participants. Dr. Beaupre is a recognized expert in the field of skeletal biomechanics and the role of physical activity in maintaining skeletal health. He will oversee all aspects of the study, including subject recruitment, consenting, data collection, data analysis and interpretation. He will provide 20% effort on this project.

Graham Creasey, MD
 Dr. Creasey will serve as a Co-Investigator. Dr. Creasey is Professor of SCI Medicine in the Department of Neurosurgery at Stanford University and an Attending Physician in the Spinal Cord Injury Service at VAPAHCS. Dr. Creasey's subspecialty certification is in spinal injuries and his clinical focus for more than three decades has been on the care of individuals with SCI. His research focus during this time has been on the use of functional electrical stimulation (FES) to restore function and improve health after spinal cord injury and he spent 18 years in the VA Rehabilitation R&D Center on Functional Electrical Stimulation in Cleveland. He also collaborated with the VA Rehabilitation R&D Center on the Medical Consequences of Spinal Cord Injury in the Bronx on the molecular and cellular basis of the effects of electrical stimulation on

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bone density after spinal cord injury. He will assist with subject recruitment, consenting, data interpretation, and he will provide input on the use of the adapted rowing equipment for use by subjects with spinal cord injury, and on the use of the equipment for electrical stimulation of lower limb muscles. He will also contribute to manuscript preparation and dissemination of findings. He will provide 10% effort on this project.

B. Jenny Kiratli, PhD

Dr. Kiratli will serve as a Co-Investigator. Dr. Kiratli is the Director of Clinical Research in the Spinal Cord Injury Center at VAPAHCS, and has over 25 years performing research on bone loss and musculoskeletal response following spinal cord injury and paralysis. Dr. Kiratli has a long-standing interest in exercise physiology and evaluation of physical activity in individuals with SCI. She also is knowledgeable in the use of FES and has co-authored a seminal article on the effect of SCI on cardiovascular fitness and the potential benefits from FES exercise. Dr. Kiratli works closely with physicians and therapists in planning and conducting research in the clinical setting and has established protocols within the SCI Service for the efficient recruitment and screening of patients, coordination with clinical personnel related to scheduling to minimize participant burden, and maintaining communication with treating clinicians as needed in regard to potential risks and adverse events. Dr. Kiratli is a member of the VA Central IRB and well versed in human subjects protections especially as applicable within VA. Dr. Kiratli and Dr. Beaupre are long-time collaborators and co-authors. Dr. Kiratli will assist with human subjects issues including the recruitment and participation of patients with SCI, consenting, managing and promoting adherence to study protocols, and IRB submissions. She will also contribute to data interpretation, manuscript preparation and dissemination of findings. She will provide 10% effort on this project.

Rebecca Lambach, PhD

Dr. Lambach will serve as a Co-Investigator and will be directly supervised by Dr. Beaupre. Dr. Lambach has practical experience in the acquisition of kinetic and kinematic data using force plates and a multi-camera motion capture system. Dr. Lambach also has prior experience working with human subjects in research. Dr. Lambach will work closely with Dr. Creasey to learn the basic skills involved in the handling, basic health monitoring, and general interactions with individuals with spinal cord injuries, especially during year 1 of the project. Dr. Lambach has completed all required VA trainings.

Summary: The expertise and level of staffing have been carefully considered to provide appropriate skillsets and sufficient levels of effort to accomplish all of the project needs.

b) Training.

Describe the training you will provide to ensure that all persons assisting with the research are informed about the protocol and their research-related duties and functions.

The staff will read the proposal research plan and the IRB protocol and all staff will be trained regarding their specific duties and functions by Dr. Beaupre or his co-investigators. Staff will complete all trainings on proper research involving human subjects and on providing subject confidentiality.

c) Facilities.

Please describe and justify.

VA Palo Alto Biomotion Laboratory

The Biomotion Laboratory is a 600 square foot motion capture studio that is dedicated to the analysis of human movement for biomedical applications. The lab includes a ten-camera analysis 240 Hz Qualiys motion capture system along with two Bertec force plates mounted on a raised floor.

VA Palo Alto Bone Densitometry Facilities

Bone density measurements will be made using a Hologic QDR-1000W pencil beam DXA scanner located in the Spinal Cord Injury Unit (Bldg 7) and a Stratec XCT3000 pQCT scanner located in the

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Musculoskeletal Research Laboratory (Bldg. 51).

Additional laboratory space exists in Bldg. 51 to accommodate the rowing machine used for the rowing exercise sessions.

Additional office space exists in Bldg. 7 and Bldg 51 for the investigators and associated staff.

d) Sufficient time.

Explain whether you will have sufficient time to conduct and complete the research. Include how much time is required.

We believe staffing levels are sufficient given the total recruitment target of 10 individuals with SCI and the tasks to be accomplished during the two-year study.

e) Access to target population.

Explain and justify whether you will have access to a population that will allow recruitment of the required number of participants.

We expect to enroll a total of 10 participants with SCI; five individuals in a standard-of-care control group and five individuals in an FES-rowing group. Approximately 35 new patients with SCI are seen per year at the VA Palo Alto Spinal Cord Injury Center. If recruitment from VA Palo Alto proves to be insufficient, we will contact Dr. James Crew who is the Chief of Spinal Cord Injury, Department of Physical Medicine & Rehabilitation, at the Santa Clara Valley (SCV) Medical Center In San Jose. Dr. Crew has agreed to provide consulting assistance as needed on the recruitment of potential participants with spinal cord injuries receiving their medical care at the SCV Medical Center. Approximately 125 new patients with SCI are seen per year at the SCI Rehabilitation Center at SCV Medical Center. Between VAPAHCS and SCV Medical Center, we do not anticipate difficulty in achieving our recruitment target.

f) Access to resources if needed as a consequence of the research.

State whether you have medical or psychological resources available that participants might require as a consequence of the research when applicable. Please describe these resources.

The VA SCI Center provides comprehensive care to patient with SCI on an in- and out-patient basis. There are dedicated physicians, nurses, therapists, and psychologists on staff with extensive experience addressing the medical and mental needs of this patient population. While it is unlikely that there will be research-related events that will require significant medical follow-up, these services are readily available within the facility.

g) Lead Investigator or Coordinating Institution in Multi-site Study.

Please explain (i) your role in coordinating the studies, (ii) procedures for routine communication with other sites, (iii) documentation of routine communications with other sites, (iv) planned management of communication of adverse outcomes, unexpected problems involving risk to participants or others, protocol modifications or interim findings.

1. Purpose

a) In layperson's language state the purpose of the study in 3-5 sentences.

Following a complete spinal cord injury (SCI), individuals experience progressive bone loss, especially in the legs, with up to 70% of persons with SCI sustaining a fracture at some point during their lifetime. Fractures following SCI are costly to treat and more than half of patients experience a medical complication, requiring extended hospitalization, resulting

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in a substantial impact on their quality of life. To reduce the incidence of fractures, more effective rehabilitation strategies to prevent bone loss are needed. The goal of this research is to determine if bone health can be preserved using an indoor rowing exercise program in which the leg muscles are electrically stimulated using several, small surface electrode pads that are placed on the skin on the front and back thigh muscles. An encouraging case study has recently shown remarkable bone preservation in one individual with SCI who participated in an electrical stimulation rowing program, however, whether other individuals with SCI can achieve the same benefit is currently unknown.

b) State what the Investigator(s) hope to learn from the study. Include an assessment of the importance of this new knowledge.

We hope to learn if participation in a 36-week exercise program consisting of Functional Electrical Stimulation (FES) leg muscle conditioning followed by FES-rowing can significantly attenuate bone loss in the lower limbs in individuals with acute and sub-acute SCI. Reports in the literature of attempts to prevent bone loss following SCI, via the use of anti-osteoporosis drugs, or with static loading in a standing frame, or with dynamic loading from FES-cycling have produced disappointing clinical results. If we are able to show better bone preservation than has been reported previously in a pilot group of five individuals participating in an FES-rowing program, our study will be considered a seminal and clinically important achievement.

c) Explain why human subjects must be used for this project. (i.e. purpose of study is to test efficacy of investigational device in individuals with specific condition; purpose of study is to examine specific behavioral traits in humans in classroom or other environment)

The objective of this study is to determine if participation in an FES-rowing exercise program can better preserve bone density in the lower limbs of individuals with spinal cord injury than have others types of activities or rehabilitation strategies. Previous literature studies using animals and computer models suggest that the repetitive mechanical stimulation derived from regular participation in a FES-rowing program may be sufficient to attenuate bone loss following SCI. No further animal studies or computer models can confirm the actual benefit in humans, therefore there is no other way to obtain this information without using human subjects.

2. Study Procedures

a) Please SUMMARIZE the research procedures, screening through closeout, which the human subject will undergo. Refer to sections in the protocol attached in section 16, BUT do not copy the clinical protocol. Be clear on what is to be done for research and what is part of standard of care.

In this study we expect to enroll a total of 10 participants with SCI. Five participants will be assigned to a Standard-of-Care (control) group and five participants will be assigned to an FES-rowing intervention group. Group assignment will be partly based on the preference of each potential participant and their willingness to make the necessary time commitment required for participation in a given group, with the added goal, to the extent possible, of matching the two groups for age, gender and time since injury. Only those individuals who have a strong desire to participate in a regular exercise program and who express a willingness to travel to VA Palo Alto the necessary number of times per week to perform FES-rowing will be potential candidates for inclusion in the rowing group.

Bone density measurements for both the Standard-of-Care group and the FES-rowing group will be performed using Dual energy X-ray Absorptiometry (DXA) and peripheral Quantitative Computed Tomography (pQCT). The Standard-of-Care group will undergo no other research procedures.

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The subjects in the FES-rowing group will undergo a muscle conditioning and rowing program developed and refined over the past decade by two of our consultants in England, Dr. Brian Andrews and Mr. Robin Gibbons. These consultants have pioneered the use of FES-rowing, and they have directly facilitated the establishment of ongoing FES-rowing programs in multiple locations in England, the US (Harvard/Spaulding Rehab, Boston), and Canada (University of Alberta).

The muscle conditioning program is accomplished through electrical stimulation of the quadriceps and hamstring muscles using a 4-channel electrical stimulator that applies stimulation using surface electrodes adhered using gel to the skin overlying the quadriceps and hamstrings muscles. The muscle strengthening initially takes place three times per week, sixty minutes per session, progressing up to five sessions per week, for approximately 8 weeks. The muscle strengthening program ensures that subjects have sufficient muscle strength and endurance before they embark on the rowing program. Following the 8-week muscle strengthening program, subjects will begin FES-rowing, with three sessions per week, thirty minutes per session for the following 28 weeks. In the FES-rowing group, we will measure isometric knee extension strength at the start of week 0, and at the end of weeks 8, 22 and 36.

For the rowing group, we will capture 3D kinetics and kinematics in our motion capture laboratory during FES-rowing at the end of weeks 8, 22 and 36. Kinematics during rowing will be collected from fifty passive retroreflective markers that will be placed on each participant to capture the position and orientation of the 12 interconnected body segments used to represent each subject.

A participant will be recruited to do a subset of the measurement procedures, as that individual will be an experienced rower, and thus does not need to undergo a muscle conditioning/strengthening program. The target individual is someone who is a consultant on the study and who has 13 years of FES-rowing experience. The procedures for this individual are described in a new consent in section 13.

b) Explain how the above research procedures are the least risky that can be performed consistent with sound research design.

The procedures we will use in this FES muscle strengthening and rowing program are modeled exactly after established FES-rowing research procedures in current use at Spaulding Rehab in Boston and at several research FES-rowing facilities in England. We know of no other way approaches to ask and answer the main research questions in this study.

c) State if deception will be used. If so, provide the rationale and describe debriefing procedures. Since you will not be fully informing the participant in your consent process and form, complete an alteration of consent (in section 13). Submit a debriefing script (in section 16).

Deception will not be used.

d) State if audio or video recording will occur. Describe what will become of the recording after use, e.g., shown at scientific meetings, erased. Describe the final disposition of the recordings.

Video recordings may be made while subjects perform research-related tasks, with possible use at scientific meetings. Should any videos be used during a scientific presentation the subject's face will be photographically or electronically masked to conceal their identity.

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All videos will be erased or destroyed after they are no longer required for use at scientific meetings. When not in use, all videos will be stored in a locked filing cabinet, in lockable office, in VA Bldg 51, which a secured building at VA Palo Alto HCS.

- e) **Describe alternative procedures or courses of treatment, if any, that might be advantageous to the participant. Describe potential risks and benefits associated with these. Any standard treatment that is being withheld must be disclosed in the consent process and form. (i.e. standard-of-care drug, different interventional procedure, no procedure or treatment, palliative care, other research studies).**

N/A

- f) **Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?**

It would only be possible to continue FES-rowing using research equipment at VA Palo Alto if a follow-on research study is conducted and if a given subject continues to qualify for participation at the time of a subsequently approved study.

- g) **Study Endpoint. What are the guidelines or end points by which you can evaluate the different treatments (i.e. study drug, device, procedure) during the study? If one proves to be clearly more effective than another (or others) during the course of a study, will the study be terminated before the projected total participant population has been enrolled? When will the study end if no important differences are detected?**

The goal of this pilot study is to obtain preliminary data for five subjects participating in a 36-week FES-rowing group. Because of the small number of subjects, it is important to acquire data for all subjects and for all time points in order to determine the best estimates for key descriptive statistics including the mean, standard deviation and range of bone density changes. The study will not end until five subjects have completed the 36-week FES-rowing program.

3. Background

- a) **Describe past experimental and/or clinical findings leading to the formulation of the study.**

In 1993, Wheeler and colleagues at the University of Alberta, Canada, introduced the first functional electrical stimulation-assisted rowing system. In 1997 and in 2002, Garry Wheeler, Brian Andrews, and colleagues reported refinements to the FES-rowing system and demonstrated clinically important health benefits, such as improvements in cardiovascular function. Throughout the past decade, Brian Andrews and Robin Gibbons in the United Kingdom have continued to make design improvements to the rower and optimize training protocols for FES-rowing. In addition, they have been steadfast advocates for the establishment of FES-rowing programs targeting community participation and they have promoted FES-rowing competitions at international venues. Due to their efforts, FES-rowing programs now exist at four locations in the greater London area (Brunel and Coventry Universities, Aspire National Training Centre, and the London Regatta Centre). The Aspire group recently announced plans for creating additional FES-rowing facilities around the UK. Between 2007 and 2009, Andrews and Gibbons facilitated the creation of two FES-rowing stations for installation at Spaulding Rehabilitation Hospital in Boston, MA. This effort was accomplished in collaboration with Dr. Andrew Taylor, Director of the Cardiovascular Research Laboratory at Harvard Medical School and Spaulding Rehab. Taylor and his team have since established the Exercise for Persons with Disabilities (ExPD) program at Spaulding and

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ExPD has in turn recently partnered with Community Rowing Inc. to offer FES-assisted rowing systems at several locations in the Boston metropolitan area. Community Rowing also offers free rowing programs (including adapted rowing and FES-assisted rowing) to any US military service member or veteran. A similar FES-rowing program exists at the Steadward Centre for Personal & Physical Achievement at the University of Alberta. The Alberta group reports that interest in their FES-rowing program far exceeds capacity, with wait-list times of 1.5 to 3 years. These rowing programs in the UK, Alberta, and Boston have attracted many individuals with SCI who are interested in promoting health benefits via exercise and recreation, and for competition in events such as the British Indoor Rowing Championship (FES-rowing first included in 2004) and the World Indoor Rowing Championship (FES-rowing first included in 2006).

As might be expected with any sufficiently strenuous whole-body exercise regimen, FES-rowing has been reported to result in improvements in cardiovascular fitness, glucose control, and body composition. In a presentation at the 16th Annual International FES Society Conference in 2011, Gibbons et al. reported the only results known to date on the benefits to bone from FES-rowing, but only for a single subject. The remarkable benefit to skeletal health reported for that single individual were in large part the motivation for the present study. However, before FES-rowing can be advocated as a clinical counter-measure for bone loss following SCI we must determine if the results reported by Gibbons and colleagues for a single individual can be repeated in a larger pilot study. That is the goal of our study.

b) Describe any animal experimentation and findings leading to the formulation of the study.

While there are numerous studies that indicate that exercise can elicit an osteogenic response in animals, such as mice and rats, the ultimate translation of those findings must be demonstrated in humans.

4. Radioisotopes or Radiation Machines

- a) **List all standard of care procedures using ionizing radiation (radiation dose received by a subject that is considered part of their normal medical care). List all research procedures using ionizing radiation (procedures performed due to participation in this study that is not considered part of their normal medical care). List each potential procedure in the sequence that it would normally occur during the entire study. More Info**

Identify Week/Month of study	Name of Exam	Identify if SOC or Research
Start of week 0, end of weeks 8, 22 and 36	DXA and pQCT bone density measurements	Research

- b) **For research radioisotope projects, provide the following radiation-related information:**

Identify the radionuclide(s) and chemical form(s).

N/A

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For the typical subject, provide the total number of times the radioisotope and activity will be administered (mCi) and the route of administration.

N/A

If not FDA approved provide dosimetry information and reference the source documents (package insert, MIRD calculation, peer reviewed literature).

N/A

c) For research radiation machine projects, provide the following diagnostic procedures:

For well-established radiographic procedures describe the exam.

Bone density measurements for both the Standard-of-Care group and the FES-rowing group will be performed using Dual energy X-ray Absorptiometry (DXA) and peripheral Quantitative Computed Tomography (pQCT). These scans will take place at VA Palo Alto. Scans will be performed at four time points: baseline (time 0, i.e., at the start of week 1), and at the end of weeks 8, 22 and 36 following baseline. The DXA scans will include a proximal femur scan and a scan starting immediately proximal to the patella and extending proximally 23 cm, ending just distal to the femoral mid-shaft. Those scans will be randomized to one side only. A standard AP spine DXA scan will also be done. The pQCT scans (same side as DXA scans) will entail two image slices in the distal femur (4% and 20% up from the distal limit of the lateral femoral condyle) and three image slices in the tibia (4% and 34% down from the proximal end of the medial tibial plateau and 4% up from the distal end of the tibia, referenced from the distal limit of the tibial subchondral bone at the center of the tibiotalar joint).

For the typical subject, identify the total number of times each will be performed on a single research subject.

Each subject in each group will be scanned using DXA and pQCT on 4 occasions, at 0, 8, 22 and 36 weeks after enrollment in the study.

For each radiographic procedure, provide the setup and technique sufficient to permit research subject dose modeling. The chief technologist can usually provide this information.

Both scanners are well-established and substantial information for both exists in the literature to estimate effective dose levels.

Lewis et al. (Osteoporosis Int, 4:11-15,1994) determined effective dose (ED) levels for a hip and AP spine scans using the QDR-1000 DXA scanner. The ED for one hip scan was 0.1 microSv in males, and 1.4 microSv in females because of additional dose to the ovaries. The ED for an AP spine scan is 0.5 microSv. These dose levels were subsequently incorporated into the "Technical White Paper: Bone Densitometry" developed by the Conference of Radiation Control Program Directors' Task Force on Bone Densitometry (2006). We estimate the DXA dose for the mid-shaft/distal femur scan to be 0.1 microSv, since that scan mimic the hip scan, but with no dose to the ovaries. The total dose for the three DXA scans would be $1.4 + 0.5 + 0.1 = 2.0$ microSv. Accounting for four scan sessions throughout the study (start of week 0, end of weeks 8, 22 and 36), the total cumulative effective dose from the DXA scans would be $4 \times 2.0 = 8$ microSv.

The effective dose for the pQCT scans, based on data reported by Gordon et al. (J Bone Min Res, vol. 18, Suppl 2, p. S314, 2003), is 1.0 microSv for a single scout view plus one CT slice, with 60% of the ED, or 0.6 microSv, due to the scout view and 0.4 microSv due to the CT slice. In our protocol, we will perform 2 scout views (one at the knee; one at the ankle) and 4 CT slices (2 distal femur; 1 proximal tibia; 1 distal tibia). The total ED per scan session will be $(2 \times 0.6) + (4 \times 0.4) = 2.8$ microSv. Accounting for four scan sessions throughout the study, the total cumulative effective dose from the pQCT scans will be $4 \times 2.8 = 11.2$ microSv.

The combined total effective dose from all DXA scans and all pQCT scans will be 19.2 microSv, which is slightly more than 2 days of background radiation based on an average background radiation dose of 3,000 microSv per year in the US (Report in Brief, June 2005, BEIR VII: Health Risks from Exposure to Low Levels of Ionizing Radiation, National Research Council).

For radiographic procedures not well-established, provide FDA status of the machine, and

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information sufficient to permit research subject dose modeling.

Both radiographic procedures (DXA, pQCT) are well-established and both scanners are FDA approved.

d) For research radiation machine projects, provide the following therapeutic procedures:

For a well-established therapeutic procedure, identify the area treated, dose per fraction and number of fractions. State whether the therapeutic procedure is being performed as a normal part of clinical management for the research participants' medical condition or whether it is being performed because the research participant is participating in this project.

N/A

For a therapeutic procedure that is not well-established, provide FDA status of the machine, basis for dosimetry, area treated, dose per fraction and number of fractions.

N/A

5. Devices

a) Please list in the table below all Investigational Devices (including Commercial Devices used off-label) to be used on participants.

5.1 Device Name : Odstock 4 Channel Stimulator, model # O4CHS

Describe the device to be used.

In this study we will use a 4-channel muscle stimulator. This device is made by Odstock Medical Limited, The National Clinical FES Centre, Salisbury District Hospital, Salisbury, Wiltshire, SP2-8BJ, UK. This device is currently used in research facilities in England, Canada and United States in programs that offer FES-rowing exercise to individuals with spinal cord injuries.

The device is described on the website:

<http://www.odstockmedical.com/products/odstock-4-channel-stimulator-kit>

Manufacturer : Odstock Medical Ltd.

Risk : Non-significant

Y I confirm the above are true.

Rationale for the device being non-significant risk:

The manufacturer of the O4CHS stimulator, Odstock Medical Limited, was formed in 2005 in response to demand by researchers and clinicians for neuromuscular stimulators with features that are not available with other commercial stimulator devices, such as the use of manual trigger. Odstock Medical, has obtained CE mark for all of their stimulation devices for sale and use within the European Union.

The Odstock 4-channel muscle stimulator (model O4CHS) has been used for many years in FES-rowing research studies in England, Canada and the United States. Our research consultants in England who are pioneers of FES-

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rowing programs, and who have helped establish FES-rowing programs around the world, have used this exact 4-channel stimulator with approximately 30 subjects with SCI and have never had a serious adverse event related to the use of the O4CHS stimulator. Researchers at Spaulding Rehab in Boston also have never experienced a serious adverse event related to the use of the O4CHS stimulator. Given the long history of safe use of the O4CHS stimulator in other FES-rowing program we believe this device qualifies as a non-significant risk.

Sponsor of Project

Indicate who is responsible for submitting safety reports to the FDA:

Y The sponsor is a non-STANFORD investigator or group.

Ordering, Storage and Control

To prevent the device being used by a person other than the investigator, and in someone other than a research participant: Confirm that the device will be handled according to the SHC/LPCH policy for Investigational New Devices or as appropriate. If no, please provide an explanation. :

Y Confirm?

b) Please list in the table below all IDE Exempt Devices (Commercial Device used according to label, Investigational In Vitro Device or Assay, or Consumer Preference/Modifications/Combinations of Approved Devices) to be used on participants.

6. Drugs, Reagents, or Chemicals

a) Please list in the table below all investigational drugs, reagents or chemicals to be administered to participants.

b) Please list in the table below all commercial drugs, reagents or chemicals to be administered to participants.

7. Medical Equipment for Human Subjects and Laboratory Animals

If medical equipment used for human patients/participants is also used on animals, describe such equipment and disinfection procedures.

N/A

8. Participant Population

a) State the following: (i) the number of participants expected to be enrolled at Stanford-affiliated site(s); (ii) the total number of participants expected to enroll at all sites; (iii) the type of participants (i.e. students, patients with certain cancer, patients with certain cardiac condition) and the reasons for using such participants.

(i) 10
(ii) 10
(III) Subjects with SCI will be enrolled. Subjects with SCI will be used because these subjects exhibit substantial musculoskeletal atrophy in the lower limbs, the prevention of which is the focus of our research.

b) State the age range, gender, and ethnic background of the participant population being recruited.

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Age range: 18-50 years
Gender: both
Ethnic background: subjects of all ethnicities are eligible

- c) State the number and rationale for involvement of potentially vulnerable subjects in the study (including children, pregnant women, economically and educationally disadvantaged, decisionally impaired, homeless people, employees and students). Specify the measures being taken to minimize the risks and the chance of harm to the potentially vulnerable subjects and the additional safeguards that have been included in the protocol to protect their rights and welfare.**

No potentially vulnerable subjects will be enrolled.

- d) If women, minorities, or children are not included, a clear compelling rationale must be provided (e.g., disease does not occur in children, drug or device would interfere with normal growth and development, etc.).**

Our inclusion criteria specifically allows for the inclusion of women and minorities. Children will not be included since the study is funded by the Department of Veterans Affairs, which does not conduct research using children.

- e) State the number, if any, of participants who are laboratory personnel, employees, and/or students. They should render the same written informed consent. If payment is allowed, they should also receive it. Please see Stanford University policy.**

We do not plan to recruit participants who are VA or Stanford laboratory personnel, VA or Stanford employees, or Stanford students.

- f) State the number, if any, of participants who are healthy volunteers. Provide rationale for the inclusion of healthy volunteers in this study. Specify any risks to which participants may possibly be exposed. Specify the measures being taken to minimize the risks and the chance of harm to the volunteers and the additional safeguards that have been included in the protocol to protect their rights and welfare.**

The study will not include healthy volunteers.

- g) How will you identify participants for recruitment? (E.g., by: chart review; referral from treating physician; response to ad). Attach recruitment materials in Section #16 (Attachments). All Final or revised recruitment materials, flyers, etc. must be submitted to the IRB for review and approval before use. You may not contact potential participants prior to IRB approval. See Advertisements: Appropriate Language for Recruitment Material.**

The identification of potential participants from VA Palo Alto will be facilitated by Dr. Graham Creasey, who is an Attending Physician in the Spinal Cord Injury Service at VA Palo Alto, and by Dr. Jenny Kiratli, who is the Director of Clinical Research in the VA Palo Alto Spinal Cord Injury Center. In the course of performing their standard clinical responsibilities, both Dr. Creasey and Dr. Kiratli are in regular contact with inpatients and outpatients in the VA SCI Center. Clinical colleagues of Drs. Creasey and Kiratli whom we will tell about our planned study, will also assist in identifying potential subjects during the course of their standard clinical interactions with patients. A similar situation exists for Dr. James Crew who is the Chief of Spinal Cord Injury at the Santa Clara Valley Medical Center in San Jose. Any patients who appear to be possible candidates for the study will be told briefly about the study by Drs. Creasey and Kiratli, or by their clinical colleagues, and if a patient expresses an interest in the study, they will be given contact information for Dr. Beaupre. Interested patients will be able to ask any additional questions by contacting Dr. Beaupre.

- h) Inclusion and Exclusion Criteria.
Identify inclusion criteria.**

Subjects in the rowing groups:
· male and female SCI outpatients or inpatients
· have a T1 to T12, ASIA-A or ASIA-B, spinal cord injury
· be at least 18 year old

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- have their physician's clearance to exercise
- between 3 and 12 months post spinal cord injury
- minimum passive hip flexion range of motion (ROM) from 20 to 100 deg
- minimum passive knee flexion ROM from 20 to 100 deg
- minimum passive ankle ROM from +10 deg (dorsi-flexion) to -15 deg (plantar-flexion)
- currently use a manual wheelchair
- be able to perform independent and safe transfers to and from their wheelchair

Subjects in the control group:

- male and female SCI outpatients or inpatients
- have a C5 to T12, ASIA-A or ASIA-B, spinal cord injury
- be at least 18 year old
- between 3 and 12 months post spinal cord injury
- be able to perform safe transfers to and from their wheelchair, either independently or with assistance

Identify exclusion criteria.

Exclusion Criteria

- pregnant women
- women of childbearing potential not practicing a reliable method of contraception
- women who are post-menopausal
- have mechanical instability of the spine
- resting blood pressure higher than 140/90
- a grade 1 or greater, sacral, gluteal or ischial pressure ulcer
- history of low trauma, lower limb fracture since SCI
- renal disease
- current osteomyelitis
- current thrombosis/hemorrhage
- cancer
- other neurological disease (i.e. stroke, peripheral neuropathy, myopathy)
- any implanted electronic device
- active treatment for epilepsy
- regular use of tobacco
- known coronary artery disease
- family history of sudden cardiac death
- current use of cardioactive medications, e.g., for treatment of congestive heart failure or arrhythmia
- current use of medications that can affect bone density and fracture risk including:
 - bisphosphonates
 - parathyroid hormone (PTH) and PTH analogs
 - androgenic steroids
 - estrogenic steroids
 - glucocorticoids
 - anti-epileptics

We will also exclude patients with cognitive impairments that will limit understanding of the nature of the project or understanding of the informed consent process.

- i) **Describe your screening procedures, including how qualifying laboratory values will be obtained. If you are collecting personal health information prior to enrollment (e.g., telephone screening), please request a waiver of authorization for recruitment (in section 15).**

Subjects initially identified as potential candidates by Drs. Creasey and Kiratli or their clinical colleagues at VA Palo Alto or Santa Clara Valley Medical Center, will be given contact information for Dr. Beaupre. Interested patients will be told to contact Dr. Beaupre to find out about the study and ask any additional questions.

- j) **Describe how you will be cognizant of other protocols in which participants might be enrolled. Please explain if participants will be enrolled in more than one study.**

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Patients will be asked during recruitment if they are participating in any other studies. Participants will not be eligible for our study if they are already participating in another research study that uses drugs or exercise to maintain skeletal health.

- k) Payment/reimbursement. Explain the amount and schedule of payment or reimbursement, if any, that will be paid for participation in the study. Substantiate that proposed payments are reasonable and commensurate with the expected contributions of participants and that they do not constitute undue pressure on participants to volunteer for the research study. Include provisions for prorating payment. See payment considerations**

Subjects in the Standard-of-Care group will receive \$50 after each DXA assessment.

Subjects in the FES-rowing group will receive \$150 after each of three participation milestones as appreciation for their participation, distributed as follows:

- After 8-weeks of participation: \$150
- After 22-weeks of participation: \$150
- After 36-weeks of participation: \$150

We do not consider these payments to be inducements to continue or to influence a subject's desire to withdraw at any point in time. The payments are meant to acknowledge our appreciation for a given subject having achieved key study milestones.

- l) Costs. Please explain any costs that will be charged to the participant.**

No costs will be charged to the participants.

- m) Estimate the probable duration of the entire study. Also estimate the total time per participant for: (i) screening of participant; (ii) active participation in study; (iii) analysis of participant data.**

The duration of the study is expected to be two years. Screening and consenting of each participant is expected to take 1 hour.

Active participation for each subject in the Standard-of-Care group is expected to total 10 hours, associated with four, 2.5-hour visits to VA Palo Alto for DXA and pQCT scans, occurring over a span of 36 weeks.

Active participation in the FES-rowing group is expected to be 10 hours for bone density scans, plus 116 hours for regular sessions of muscle conditioning and FES-rowing, plus 12 hours for motion capture and muscle strength testing. The total time for active participation for the FES-rowing group is expected to be 138 hours, or 17.25 days, occurring over a span of 36 weeks.

9. Risks

- a) For the following categories include a scientific estimate of the frequency, severity, and reversibility of potential risks. Wherever possible, include statistical incidence of complications and the mortality rate of proposed procedures. Where there has been insufficient time to accumulate significant data on risk, a statement to this effect should be included. (In describing these risks in the consent form to the participant it is helpful to use comparisons which are meaningful to persons unfamiliar with medical terminology.)

The risks of the Investigational devices.

This study will use an Odstock 4-channel muscle stimulator (model O4CHS) that has been used for many years in FES-rowing research studies in England, Canada and the United States. This device is powered by a standard, 9-volt battery identical to those used to power a transistor radio or smoke alarm. Our research consultants in England who are pioneers of FES-rowing programs, and who have helped establish FES-rowing programs in several other research laboratories around the world, have used this exact 4-channel stimulator with approximately 30 subjects with SCI and have never had an adverse event related

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to its use. Researchers at Spaulding Rehab in Boston also have never experienced an adverse event related to the use of the O4CHS device. Given the long history of safe use of the O4CHS device in other FES-rowing programs we believe this device qualifies as a non-significant risk.

The Odstock 4-channel muscle stimulator is used during FES muscle conditioning, FES muscle strength testing, and FES rowing.

The risks of the Investigational drugs. Information about risks can often be found in the Investigator's brochure.

None.

The risks of the Commercially available drugs, reagents or chemicals. Information about risks can often be found in the package insert.

None.

The risks of the Procedures to be performed. Include all investigational, non-investigational and non-invasive procedures (e.g., surgery, blood draws, treadmill tests).

Other than the bone density scans for which the risk is described later, there are no other procedures to be performed on the Standard-of-Care (control) group.

For the FES-rowing group, participants will undergo an 8-week, Functional Electrical Stimulation (FES) muscle conditioning program to strengthen the quadriceps and hamstring muscles, followed by a 28-week FES-rowing program. At four time points (0, 8, 22, 36 weeks), participants will perform FES muscle strength testing of the quadriceps and hamstrings.

We have assessed potential risks of these procedures by consulting with other research groups with extensive FES-rowing experience and ongoing FES-rowing programs. Potential risks include the following:

- 1) Soft tissue reaction during FES training
- 2) Muscle strain during muscle conditioning, strength testing or FES-assisted rowing
- 3) Fall during transfer to or from rowing machine
- 4) Serious autonomic dysreflexia during FES training
- 5) Lower limb fracture during muscle conditioning, strength testing or FES-assisted rowing
- 6) Increase in neuropathic pain to an unacceptable level
- 7) Increase in spasticity to an unmanageable level

Based on the experience of other researchers with ongoing FES-rowing programs, only two of the above seven issues have ever occurred. These are: 1) a soft tissue reaction during FES training and rowing; and 2) a muscle strain during FES-rowing. Since those are the only issues experienced in previous FES-rowing projects we will discuss them first.

1) A soft tissue reaction to FES training can be associated with several causes. The first is a local reddening of the skin under the electrodes. This reddening is thought to be due to an increase in blood flow beneath the electrode caused by the electrical stimulation. This reddening typically lasts for less than one hour after stimulation is stopped. This reddening is expected to occur to some degree with all participants in the FES-rowing group.

Reddening may also potentially occur as a result of an allergic reaction to the gel used to adhere the surface electrode to the skin. If reddening of the skin persists for much longer than one hour after removal of the electrode, then an allergic reaction is a possible cause. Our consultants in England who have trained

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approximately 30 individuals to become FES-rowers have never seen a case of an individual who was allergic to the electrode gel, although this remains a potential risk.

The third and final potential skin reaction is reddening suggestive of the initiation of soft tissue breakdown (e.g., a "pressure sore") due to excessive pressure or shear stress. In individuals with SCI, the areas most prone to excessive stress are the sacral, gluteal or ischial regions. This potential for skin breakdown exists for all individuals who utilize a wheelchair or who are bed-bound for prolonged periods. Our consultants in England have never had any participants experience skin breakdown caused by their participation in FES-rowing, although this remains a potential risk.

2) Muscle strain during muscle conditioning, strength testing or FES-assisted rowing: As with participating in any exercise program, there is a risk of experiencing a muscle strain. Based on the experience of other researchers with FES-rowing programs, only two out of thirty FES-rowing participants have ever experienced a muscle strain. Muscle strains have never been observed in the lower limbs. For both participants with muscle strains, the strain occurred in the torso, between innervated and paralyzed muscle. These strains were treated by ceasing FES training for 48 to 72 hours and by the use of ice and over-the-counter analgesics. Neither participant has had a repeat incidence of a muscle strain.

3) Risk of a fall during transfer to or from rowing machine: There is a possibility that a participant may fall while transferring to or from the rowing machine or to or from the table they will lie on while having their bone density scans. The risk of falling can be minimized to a very low level by using safe transfer techniques.

4) Serious autonomic dysreflexia during FES training: Autonomic dysreflexia (AD) is a condition which can occur in people who have sustained a spinal cord injury. Autonomic dysreflexia is more common in individuals with tetraplegia (quadriplegia), but it can also occur in individuals with paraplegia. Autonomic dysreflexia can be brought on by a variety of stimuli, including a full bladder or bowel, a pressure sore or infection, exercise, or by Functional Electrical Stimulation. Possible symptoms of an AD reaction include:

- Severe headache
- Flushing or blotching of the skin above the level of the spinal cord injury
- Profuse sweating, particularly above the level of the spinal cord injury
- Increased blood pressure
- Decreased heart rate

Generally, an AD reaction will quickly diminish once the initiating stimulus that caused the reaction is removed. To reduce the risk of an AD response, all participants will be encouraged to completely empty their bladder prior to each muscle conditioning or rowing session. The risk of an AD response should also decrease as training progresses and a participant's muscles become conditioned from the electrical stimulation. Thus, the risk of AD is highest during the initial muscle conditioning session. During a participant's first muscle conditioning session we will assess the ability of their muscles to respond to the electrical stimulation and we will pay particular attention to any signs of an AD response. It is possible that an AD response that is greater than mild might be identified at a participant's initial session and that could mean that they are not an acceptable candidate for continuation in the study.

It should also be noted that an individual's likelihood of having an AD episode in response to exercising part of the body below the level of a spinal cord injury will be heightened if an individual already has an underlying condition that is perceived by their body as a noxious stimulus. For example, an individual with a bladder infection might be more prone to an AD episode from an additional stimulus, such as Functional Electrical Stimulation of the legs, compared to an individual without a bladder infection. Therefore, it is important that any underlying noxious stimulus that might predispose an individual to an AD response is identified as early as possible and addressed before commencing or continuing with the rowing exercise.

We should note that FES-rowing research groups in England and Boston have never had a participant in their FES-rowing programs experience a severe case of AD, and those participants who have experienced

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mild cases of AD also experience mild cases during their everyday lives. Therefore, we believe the risk of experiencing a severe case of AD from participation in this study is very low, although the possibility of experiencing a mild case of AD is higher. At the first sign of an AD response, electrical stimulation will be stopped. Additional medical treatment in the case of a severe AD response will be available in our testing facilities.

5) Lower limb fracture during muscle conditioning, strength testing or FES-assisted rowing: The use of FES to stimulate paralyzed muscles in individuals with SCI has been studied for more than 50 years. Over that 50-year period there have been two reported cases of a fracture related to the use of functional electrical stimulation. One individual fractured their patella and a second individual fractured their lateral femoral condyle. Although the total number of individuals with SCI who have used functional electrical stimulation to exercise the lower limbs is not known, we believe the risk of a fracture is very low given that there have only been two reported fractures in 50 years of FES use. To further reduce the risk of fracture, only participants who have never experienced a low-energy or fragility fracture will be allowed to take part in this study. In addition, we will measure bone density for each participant at the beginning of the study and those measurements will provide us with an initial assessment of the health of each participant's femur and tibia. If we believe a participant's bones are too weak to safely undergo the muscle conditioning and rowing exercise, that participant will be withdrawn from the study.

6) Increase in neuropathic pain to an unacceptable level: Some spinal cord injured individuals suffer from neuropathic pain which can range from a mild tickling sensation to a severe burning sensation. It is not known what effect, if any, electrical stimulation has on this condition. In addition, some individuals with SCI who have some sensation in their thighs may find the electrical stimulation to be uncomfortable or even intolerable. Any participant who finds the electrical stimulation to produce neuropathic pain or sensation that is unacceptable to them will be withdrawn from the study.

7) Increase in spasticity to an unmanageable level: It is not known what effect FES has on the intensity and frequency of spasticity. In other FES-rowing programs, a few participants have had an increase in spasticity, while some participants have had a decrease. In general, spasticity levels should be reduced after a muscle conditioning or rowing session, since the muscles will be fatigued. If a subject experiences increased spasticity to a level that is unmanageable, they will be withdrawn from the study.

The risks of the Radioisotopes/radiation-producing machines (e.g., X-rays, CT scans, fluoroscopy) and associated risks.

Both of the bone density scanners we will use involve very low exposures to X-ray radiation. The total radiation exposure from all four visits will be 19.2 microSv. For comparison, a person can be expected to receive 8 microSv of natural background radiation per day from the environment. For an additional comparison, a person can be expected to receive approximately 30 microSv of radiation during an airline flight from San Francisco to New York. Therefore, the total additional radiation from the bone density scans is equivalent to slightly more than 2 days of natural background radiation and slightly more than half the radiation from a coast-to-coast airline flight. There are no known hazards from radiation at such a low level. This radiation dose is considered safe to administer to humans except during pregnancy. Although there are no documented risks to a fetus, we will exclude any subject who might be pregnant at the time of the study.

The risks of the Physical well-being.

None other than those described above.

The risks of the Psychological well-being.

We do not anticipate that any research-related procedure will adversely affect the psychological well-being of the participants.

The risks of the Economic well-being.

We do not anticipate that any research-related procedure will adversely affect the economic well-being of the participants.

The risks of the Social well-being.

We do not anticipate that any research-related procedure will adversely affect the social well-being of the

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participants.

Overall evaluation of Risk.

Low - innocuous procedures such as phlebotomy, urine or stool collection, no therapeutic agent, or safe therapeutic agent such as the use of an FDA approved drug or device.

- b) If you are conducting international research, describe the qualifications/preparations that enable you to both estimate and minimize risks to participants. Also complete the International Research Form and attach it in the Attachments section. If not applicable, enter N/A.**

N/A

- c) Describe the planned procedures for protecting against and minimizing all potential risks. Include the means for monitoring to detect hazards to the participant (and/or to a potential fetus if applicable). Include steps to minimize risks to the confidentiality of identifiable information.**

Confidentiality of the identifiable information will be carefully protected and data security measures will be strictly enforced. Any information or data on paper, including signed consents, will be stored in locked cabinets in locked offices in a secure VA building. All electronic data that contain identifiable subject information will be saved on a secure VA file server behind the VA firewall. No data will be maintained on portable electronic devices.

Protecting against and minimizing potential risks: To reiterate, the following are the potential risks to participants in the FES-rowing group.

- 1) Soft tissue reaction during FES training
- 2) Muscle strain during muscle conditioning, strength testing or FES-assisted rowing
- 3) Fall during transfer to or from rowing machine
- 4) Serious autonomic dysreflexia (AD) during FES training
- 5) Lower limb fracture during muscle conditioning, strength testing or FES-assisted rowing
- 6) Increase in neuropathic pain to an unacceptable level
- 7) Increase in spasticity to an unmanageable level

The following paragraphs describe how these risks will be mitigated to reduce them to the lowest possible levels.

1) Soft tissue reaction: Other than the typical reddening beneath the electrodes, which is to be expected, we will be vigilant to look for other types of soft tissue reactions and we will encourage all participants to be vigilant. To the best of our knowledge no prior FES-rowing participants have experienced a skin breakdown or pressure sore caused by their participation in an FES-rowing program. Nevertheless, before and after each session, we will look for any signs of bruising or swelling that might be suggestive of tissue breakdown, paying particular attention to the shoulders, back, buttocks, upper calves and knee areas.

2) Muscle strain: We will inform all participants of the possibility of a muscle strain and encourage participants that it is not necessary to perform at levels which push personal boundaries of performance, especially in terms of the energy which they exert when pulling on the handle of the rowing machine with their arms, since excessive upper body exertion is the more likely cause of muscle strain in the torso. Since subjects with SCI can have normal arm strength it is possible that a subject might believe that intensive arm pulling is required or encouraged. We will make it clear to participants that intensive arm pulling is not required. We will also discuss with each participant the experience of other FES-rowing groups so that our rowers are aware of the possibility of a muscle strain and let them know that they should tell us immediately if they think they have experienced a muscle strain. Since this risk has actually been observed in two

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FES-rowers in another research group, the possibility of a muscle strain is more than a theoretical possibility and we want to minimize that possibility by adequately informing our participants.

3) Risk of a fall during transfers: The risk of falling during transfers can be minimized to a very low level by using safe transfer techniques. Dr. Creasey, who has worked with patients with SCI for more than 30 years, is knowledgeable in what constitutes safe transfer techniques. Dr. Creasey will observe each participant when they are first required to perform transfer in the study and based upon his observations he will recommendation for improving their transfer technique if needed.

4) Serious autonomic dysreflexia (AD) during FES training: To reduce the risk of an AD response, all participants will be encouraged to completely empty their bladder prior to each muscle conditioning or rowing session. We will also inform participants that the risk of an AD response is increased if they have an underlying condition which their body perceives as a noxious stimulus, such as a bladder infection. We will ask each participant to inform us if they have a known or suspected bladder infection. We will also inform participants that it may be necessary for them to take a break from their training or rowing while a bladder infection is treated.

The risk of an AD response should also decrease as training progresses and a participant's muscles become conditioned from the electrical stimulation. Thus, the risk of AD will be highest during the initial muscle conditioning session. During the initial muscle conditioning session for each participant, we will pay particular attention to any signs of an AD response. At the first sign of an AD response, electrical stimulation will be stopped. Additional medical treatment (e.g., the application of Nitropaste) in the case of a severe AD response will be available in our research facilities. Given that no other FES-rowing group has ever reported a severe AD response we believe the likelihood of a participant having a severe AD response is very low, however, all of our research staff and each participant will be informed about the possibility of AD response and we will be vigilant in looking for an AD response.

5) Lower limb fracture during muscle conditioning, strength testing or FES-assisted rowing: To reduce the risk of fracture, only participants who have never experienced a low-energy or fragility fracture will be allowed to take part in this study. In addition, we will measure bone density for each participant at the beginning of the study and those measurements will provide us with an initial assessment of the health of each participant's femur and tibia. If we believe a participant's bones are too weak to safely undergo the muscle conditioning and rowing exercise, we will not allow that participant to continue in the study. In addition, participants will be educated on potential signs of a fracture for a person with SCI who is insensate in the area; these include localized redness and swelling, excess spasticity, possibly excess sweating and/or AD. We believe this is unlikely, but the added precaution of educating the participant will allow him/her to be extra vigilant for this occurrence.

6) Increase in neuropathic pain to an unacceptable level: Some spinal cord injured individuals suffer from neuropathic pain which can range from a mild tickling sensation to a severe burning sensation. It is not known what effect, if any, electrical stimulation has on this condition. In addition, some individuals with SCI who have some sensation in their thighs may find the electrical stimulation to be uncomfortable or even intolerable. Any participant who finds the electrical stimulation to produce neuropathic pain or sensation that is unacceptable to them will be withdrawn from the study.

7) Increase in spasticity to an unmanageable level: It is not known what effect FES has on the intensity and frequency of spasticity. In other FES-rowing programs, a few participants have had an increase in spasticity, while some participants have had a decrease. In general, spasticity levels should be reduced after a muscle conditioning or rowing session, since the muscles will be fatigued. If a subject experiences increased spasticity that is unmanageable, they will be withdrawn from the study.

- d) **Explain the point at which the experiment will terminate. If appropriate, include the standards for the termination of the participation of the individual participant Also discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the participants.**

Given the low risk level and given the success of other FES-rowing research studies, we do not anticipate

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terminating the study before the two-year funding period ends.

However, individual participants may be withdrawn from the study for several reasons, including, but not limited to:

- Inadequate muscle response to electrical stimulation
- Severe AD reaction in response to exercise or electrical stimulation
- Markedly low bone density compared to other individuals with acute and sub-acute SCI
- An increase in neuropathic pain or pain sensation from electrical stimulation to an unacceptable level
- An increase in spasticity to an unmanageable level

e) **Data Safety and Monitoring Plan (DSMP).** See guidance on **Data Safety and Monitoring.**

A Data and Safety Monitoring Plan (DSMP) is required for studies that present Medium or High risk to participants. (See Overall Evaluation of Risk above). If Low Risk, a DSMP may not be necessary. Multi-site Phase III clinical trials funded by NIH require the DSM Plan to have a Data Safety Monitoring Board or Committee (DSMC or DSMB). The FDA recommends that all multi-site clinical trials that involve interventions that have potential for greater than minimal risk to study participants also have a DSMB or DSMC.

The role of the DSMC or DSMB is to ensure the safety of participants by analyzing pooled data from all sites, and to oversee the validity and integrity of the data. Depending on the degree of risk and the complexity of the protocol, monitoring may be performed by an independent committee, a board (DSMC/DSMB), a sponsor's Data Safety Committee (DSC), a Medical Monitor, a sponsor's safety officer, or by the Protocol Director (PD).

Describe the following:

What type of data and/or events will be reviewed under the monitoring plan, e.g. adverse events, protocol deviations, aggregate data?

We will look for and track any adverse events, including unanticipated problems, that may occur during FES muscle-conditioning or FES rowing sessions. We will also be vigilant for any security breaches involving paper or electronic records.

Identify who will be responsible for Data and Safety Monitoring for this study, e.g. Stanford Cancer Institute DSMC, an independent monitoring committee, the sponsor, Stanford investigators independent of the study, the PD, or other person(s).

The PI/PD, Dr. Gary Beaupre and Co-PD & Co-Investigator, Dr. Jenny Kiratli, will be responsible for monitoring the data collected, including data related to unanticipated problems and adverse events.

Provide the scope and composition of the monitoring board, committee, or safety monitor, e.g., information about each member's relevant experience or area of expertise. If the Monitor is the Stanford Cancer Center DSMC or the PD, enter N/A.

PD and co-PD have extensive experience with regards to monitoring and maintaining safety of events/data related to this study.

Confirm that you will report Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Reactions (SUSARs), or Unanticipated Problems (UPs) to the person or committee monitoring the study in accordance with Sponsor requirements and FDA regulations.

Serious Adverse Events (SAEs) and/or Unanticipated Problems (UAPs) are considered unlikely . Given the nature of this study, with each participant closely supervised and monitored regularly during muscle

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conditioning and rowing sessions, there should be minimal delay in reporting if any AE/UAP occur.

If applicable, how frequently will the Monitoring Committee meet? Will the Monitoring Committee provide written recommendations about continuing the study to the Sponsor and IRB?

As needed. As above, these are not considered likely to occur at all nor are they expected to be frequent occurrences. The total number of subjects to be enrolled is small and we plan to make notes of our observations for each subject after each session.

Specify triggers or stopping rules that will dictate when the study will end, or when some action is required. If you specified this in Section 2g [Study Endpoints], earlier in this application enter 'See 2g'.

N/A

Indicate to whom the data and safety monitoring person, board, or committee will disseminate the outcome of the review(s), e.g., to the IRB, the study sponsor, the investigator, or other officials, as appropriate.

If any AE or UAP occurs, we will follow the established timeframes for reporting to the IRB and the VA R&D Committee; i.e., immediately for any SAE or serious UAP and at annual renewal for any non-serious or expected occurrence.

Select One:

- Y The Protocol Director will be the only monitoring entity for this study.
This protocol will utilize a board, committee, or safety monitor as identified in question #2 above.

10. Benefits

- a) **Describe the potential benefit(s) to be gained by the participants or by the acquisition of important knowledge which may benefit future participants, etc.**

It is possible that individuals who participate in the FES-Rowing group will increase (or reduce loss of) bone mass in their legs and/or experience other health/fitness benefits. In addition, findings from this study may contribute to the development of knowledge which may eventually benefit individuals with spinal cord injury.

Subjects in both groups will be provided with the results of their DXA hip scans which they will be encouraged to share with their personal physician. A knowledge of bone density at the hip can be considered a minor benefit experienced by participants.

11. Privacy and Confidentiality

Privacy Protections

- a) **Describe how the conditions under which interactions will occur are adequate to protect the privacy interests of participants (e.g., privacy of physical setting for interviews or data collection, protections for follow-up interactions such as telephone, email and mail communications).**

Initial identification of potential participants will be done by a patient's personal physician who is familiar with our planned study. Follow-up interactions with potential participants will be by telephone for answering any additional questions a potential participant might have, or in person in a private, laboratory setting, for any subject who prefers to meet in person.

Confidentiality Protections

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- b) Specify PHI (Protected Health Information). PHI is health information linked to HIPAA identifiers (see above). List BOTH health information AND HIPAA identifiers. If you are using STARR, use the Data Privacy Attestation to ensure that your request will match your IRB-approved protocol. Be consistent with information entered in section 15a.**

Name, date of birth, telephone number and address will be obtained from each participant. We will also obtain information on injury history, including date of injury for each participant. We may also acquire photographs or video of participants while performing any research-related tasks. This information will be stored on a secure VA server. We will also use the VA Form 10-3203 ("CONSENT FOR USE OF PICTURE AND/OR VOICE") as required by VA (attached).

- c) You are required to comply with University Policy that states that ALL electronic devices: computers (laptops and desktops; OFFICE or HOME); smart phones; tablets; external hard disks, USB drives, etc. that may hold identifiable participant data will be password protected, backed up, and encrypted. See <http://med.stanford.edu/datasecurity/> for more information on the Data Security Policy and links to encrypt your devices.**

Provide any additional information on ALL data security measures you are taking. You must use secure databases such as RedCap <https://med.stanford.edu/researchit/infrastructure/redcap.html>. If you are unsure of the security of the system, check with your Department IT representative. Please see <http://med.stanford.edu/irt/security/> for more information on IRT Information Security Services and http://www.stanford.edu/group/security/securecomputing/mobile_devices.html for more information for securing mobile computing devices. Additionally, any PHI data on paper must be secured in a locked environment.

By checking this box, You affirm the aforementioned. Y

Any data on paper will be kept in a locked filing cabinet in Dr. Beaupre's locked office or in a locked filing cabinet in a locked room designated for the storage of human subjects documents, such as signed informed consent forms. These rooms are located in a secure VA building accessible only by VA badge access. De-identified, electronic information will be stored on a secure VA server. Data analysis will only occur on de-identified data and will occur on password-protected computers.

- d) Describe how data or specimens will be labeled (e.g. name, medical record number, study number, linked coding system) or de-identified. If you are de-identifying data or specimens, who will be responsible for the de-identification? If x-rays or other digital images are used, explain how and by whom the images will be de-identified.**

Each subject will be given a code number and data for each subject will be identified by code number only. The electronic file that links the code number with a subject's name will be kept on a secure VA server. Dr. Beaupre will be responsible for de-identification and coding of all data files.

- e) Indicate who will have access to the data or specimens (e.g., research team, sponsors, consultants) and describe levels of access control (e.g., restricted access for certain persons or groups, access to linked data or specimens).**

Only members of the research team will have access to the data.

- f) If data or specimens will be coded, describe the method in which they will be coded so that study participants' identities cannot be readily ascertained from the code.**

Data for each subject will be given a unique code number that is unrelated in any way to a subject's III or PHI.

- g) If data or specimens will be coded, indicate who will maintain the key to the code and describe how it will be protected against unauthorized access.**

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Dr. Beaupre will maintain the key to the code. The key to the code will be kept on a secure VA server.

- h) If you will be sharing data with others, describe how data will be transferred (e.g., courier, mail) or transmitted (e.g., file transfer software, file sharing, email). If transmitted via electronic networks, describe how you will secure the data while in transit. See <http://www.stanford.edu/group/security/securecomputing/> <http://www.stanford.edu/group/security/securecomputing/>. Additionally, if you will be using or sharing PHI see <https://uit.stanford.edu/security/hipaa> <https://uit.stanford.edu/security/hipaa>.**

Data will not be shared outside of the investigator group.

- i) How will you educate research staff to ensure they take appropriate measures to protect the privacy of participants and the confidentiality of data or specimens collected (e.g. conscious of oral and written communications, conducting insurance billing, and maintaining paper and electronic data)?**

All members of the research team will complete all trainings required by VA Research Administration, including all human subjects related trainings. In his weekly meeting with study staff, Dr. Beaupre will discuss and reinforce the importance of privacy.

12. Potential Conflict of Interest

Investigators are required to disclose any financial interests that reasonably appear to be related to this protocol.

Financial Interest Tasks

Investigators	Role	Email	Has Financial Interest?	Date Financial Interest Answered	Date OPACS Disclosure Submitted	Date OPACS Review Completed
Gary Scott Beaupre	PD	Gary.Beaupre@va.gov	N	07/15/2014	N/A	N/A
Graham Harold Creasey	OC	gcreasey@stanford.edu	N	07/15/2014	N/A	N/A

13. Consent Background

13.1 Waiver of Documentation Phone screening

Check if VA related

- a) Describe the informed consent process. Include the following.**
- i) Who is obtaining consent? (The person obtaining consent must be knowledgeable about the study.)**
 - ii) When and where will consent be obtained?**
 - iii) How much time will be devoted to consent discussion?**
 - iv) Will these periods provide sufficient opportunity for the participant to consider whether or not to participate and sign the written consent?**
 - v) What steps are you taking to minimize the possibility of coercion and undue influence?**

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vi) If consent relates to children and if you have a reason for only one parent signing, provide that rationale for IRB consideration.

Dr. Beaupre or a member of his study team will obtain consent from participants. Consent for the phone screen will be done over the phone. The subject will be assured that he/she has as much time as necessary to review the consent document and ask any questions.

b) What is the Procedure to assess understanding of the information contained in the consent? How will the information be provided to participants if they do not understand English or if they have a hearing impairment? See HRPP Chapter 12.2 for guidance.

The person obtaining consent will ask the participant if he/she has questions about the information contained in the consent or about the study. We do not expect to enroll anyone with whom there will be difficulty communicating nor will we enroll any non-English speakers and this will be determined from the initial contact.

c) What steps are you taking to determine that potential participants are competent to participate in the decision-making process? If your study may enroll adults who are unable to consent, describe (i) how you will assess the capacity to consent, (ii) what provisions will be taken if the participant regains the capacity to consent, (iii) who will be used as a legally authorized representative, and (iv) what provisions will be made for the assent of the participant.

Subjects will arrange for their own transportation to the study location. There is therefore sufficient reason to believe that they will be participating at their own free will. The research team will repeatedly remind the subject that they may withdraw at any time.

Select one of the following regulatory criteria for a waiver of documentation (signature) and provide a protocol-specific justification:

- 1) 45 CFR 46.117(c)(i). For research that is not subject to FDA regulation, the only record linking the participants and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality; each participant will be asked whether he/she wants documentation linking the participant with the research, and the participant's wishes govern.
- 2) 45 CFR 46.117(c)(ii). For research that is not subject to FDA regulation, presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context.
- 3) 45 CFR 46.117(c)(iii). For research not subject to FDA regulation, if subjects or legally authorized representatives (LAR) are members of a distinct cultural group in which signing forms is not the norm, the research presents no more than minimal risk and there is an appropriate alternative mechanism for documenting that informed consent was obtained.
- 4) Y 21 CFR 56.109(c)(1). For research that is subject to FDA regulation, presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context.

Rationale for above selection:

The phone screen asks minimal risk questions that relate to their eligibility for the study.

13.2 Consent FES-Rowing Group Consent Sept 29-2014

Check if VA related Y

a) Describe the informed consent process. Include the following.

- i) Who is obtaining consent? (The person obtaining consent must be knowledgeable about the study.)
- ii) When and where will consent be obtained?
- iii) How much time will be devoted to consent discussion?
- iv) Will these periods provide sufficient opportunity for the participant to consider whether or not to participate and sign the written consent?
- v) What steps are you taking to minimize the possibility of coercion and undue influence?
- vi) If consent relates to children and if you have a reason for only one parent signing, provide that rationale for IRB consideration.

(i) Dr. Beaupre or a member of his study team will obtain consent from participants. (ii) Consent will be obtained upon arrival of the subject at the study location. (iii) As much time as necessary to address any questions. (iv) Yes. (v) The subject will be assured that he/she has as much time as necessary to review the consent document and ask any questions. (vi) N/A

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- b) **What is the Procedure to assess understanding of the information contained in the consent? How will the information be provided to participants if they do not understand English or if they have a hearing impairment? See HRPP Chapter 12.2 for guidance.**

The person obtaining consent will ask the participant if he/she has questions about the information contained in the consent or about the study. We do not expect to enroll anyone with whom there will be difficulty communicating nor will we enroll any non-English speakers and this will be determined from the initial contact.

- c) **What steps are you taking to determine that potential participants are competent to participate in the decision-making process? If your study may enroll adults who are unable to consent, describe (i) how you will assess the capacity to consent, (ii) what provisions will be taken if the participant regains the capacity to consent, (iii) who will be used as a legally authorized representative, and (iv) what provisions will be made for the assent of the participant.**

Subjects will arrange for their own transportation to the study location. There is therefore sufficient reason to believe that they will be participating at their own free will. The research team will repeatedly remind the subject that they may withdraw at any time.

Additional VA questions:

- i) **List the people to whom you have formally delegated responsibility to obtain informed consent, and state whether they have the appropriate training to perform this activity.**

Dr. Beaupre, Dr. Kiratli, Dr. Creasey, or Dr. Lambach will obtain all consents. These people have or will have completed appropriate training and each will have prior experience or specific training in performing consents.

- ii) **Will legally effective informed consent be obtained from the participant or the participant's legally authorized representative (LAR) or both? If LAR, is it clear who can serve as LAR?**

Legally effective informed consent will be obtained from each participant. No LARs will be used.

- iii) **Will the circumstances of the consent process minimize the possibility of coercion or undue influence and provide the prospective participant or their representative sufficient opportunity to consider whether to participate?**

Yes

- iv) **Will the circumstances of the consent process minimize the possibility of coercion or undue influence?**

Yes

- v) **Will the information being communicated to the participant or the representative during the consent process exclude any exculpatory language through which the participant or the representative is made to waive or appear to waive the participant's legal rights, or release or appear to release the investigator, the sponsor, the institution, or its agent from liability for negligence (e.g. I give up any property rights I may have in bodily fluids or tissue samples obtained in the course of the research)?**

Yes

- vi) **Please confirm the following:**

- a. A witness to the participant's signature or the participant's legally authorized representative's signature will sign and date the consent document.
- b. If the sponsor or the IRB requires a witness to the consenting process in addition to the witness to the participant's signature and if the same person is needed to serve both capacities, a note to that effect is placed under the witness's signature line.
- c. A copy of the signed and dated consent document will be given to the person signing the consent document.
- d. The consent form is on the VA Form 10-1086.

13.3 Consent Control Group Consent Sept 29-2014

Check if VA related Y

- a) **Describe the informed consent process. Include the following.**

- i) **Who is obtaining consent? (The person obtaining consent must be knowledgeable about the study.)**
- ii) **When and where will consent be obtained?**
- iii) **How much time will be devoted to consent discussion?**
- iv) **Will these periods provide sufficient opportunity for the participant to consider whether or not to participate and sign the written consent?**

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v) What steps are you taking to minimize the possibility of coercion and undue influence?

vi) If consent relates to children and if you have a reason for only one parent signing, provide that rationale for IRB consideration.

(i) Dr. Beaupre or a member of his study team will obtain consent from participants. (ii) Consent will be obtained upon arrival of the subject at the study location. (iii) As much time as necessary to address any questions. (iv) Yes. (v) The subject will be assured that he/she has as much time as necessary to review the consent document and ask any questions. (vi) N/A

b) What is the Procedure to assess understanding of the information contained in the consent? How will the information be provided to participants if they do not understand English or if they have a hearing impairment? See HRPP Chapter 12.2 for guidance.

The person obtaining consent will ask the participant if he/she has questions about the information contained in the consent or about the study. We do not expect to enroll anyone with whom there will be difficulty communicating nor will we enroll any non-English speakers and this will be determined from the initial contact.

c) What steps are you taking to determine that potential participants are competent to participate in the decision-making process? If your study may enroll adults who are unable to consent, describe (i) how you will assess the capacity to consent, (ii) what provisions will be taken if the participant regains the capacity to consent, (iii) who will be used as a legally authorized representative, and (iv) what provisions will be made for the assent of the participant.

Subjects will arrange for their own transportation to the study location. There is therefore sufficient reason to believe that they will be participating at their own free will. The research team will adequately remind each subject that they may withdraw at any time.

Additional VA questions:

i) List the people to whom you have formally delegated responsibility to obtain informed consent, and state whether they have the appropriate training to perform this activity.

Dr. Beaupre, Dr. Kiratli, Dr. Creasey, or Dr. Lambach will obtain all consents. These people have or will have completed appropriate training and each will have prior experience or specific training in performing consents.

ii) Will legally effective informed consent be obtained from the participant or the participant's legally authorized representative (LAR) or both? If LAR, is it clear who can serve as LAR?

Legally effective informed consent will be obtained from each participant. No LARs will be used.

iii) Will the circumstances of the consent process minimize the possibility of coercion or undue influence and provide the prospective participant or their representative sufficient opportunity to consider whether to participate?

Yes

iv) Will the circumstances of the consent process minimize the possibility of coercion or undue influence?

Yes

v) Will the information being communicated to the participant or the representative during the consent process exclude any exculpatory language through which the participant or the representative is made to waive or appear to waive the participant's legal rights, or release or appear to release the investigator, the sponsor, the institution, or its agent from liability for negligence (e.g. I give up any property rights I may have in bodily fluids or tissue samples obtained in the course of the research)?

Yes

vi) Please confirm the following:

- a. A witness to the participant's signature or the participant's legally authorized representative's signature will sign and date the consent document.
- b. If the sponsor or the IRB requires a witness to the consenting process in addition to the witness to the participant's signature and if the same person is needed to serve both capacities, a note to that effect is placed under the witness's signature line.
- c. A copy of the signed and dated consent document will be given to the person signing the consent document.
- d. The consent form is on the VA Form 10-1086.

13. 4 Consent Experienced Rower Consent Sept 29-2104

Check if VA related Y

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- a) Describe the informed consent process. Include the following.
 - i) Who is obtaining consent? (The person obtaining consent must be knowledgeable about the study.)
 - ii) When and where will consent be obtained?
 - iii) How much time will be devoted to consent discussion?
 - iv) Will these periods provide sufficient opportunity for the participant to consider whether or not to participate and sign the written consent?
 - v) What steps are you taking to minimize the possibility of coercion and undue influence?
 - vi) If consent relates to children and if you have a reason for only one parent signing, provide that rationale for IRB consideration.

(i) Dr. Beaupre or a member of his study team will obtain consent from participants. (ii) Consent will be obtained upon arrival of the subject at the study location. (iii) As much time as necessary to address any questions. (iv) Yes. (v) The subject will be assured that he/she has as much time as necessary to review the consent document and ask any questions. (vi) N/A

- b) What is the Procedure to assess understanding of the information contained in the consent? How will the information be provided to participants if they do not understand English or if they have a hearing impairment? See HRPP Chapter 12.2 for guidance.

The person obtaining consent will ask the participant if he/she has questions about the information contained in the consent or about the study. We do not expect to enroll anyone with whom there will be difficulty communicating nor will we enroll any non-English speakers and this will be determined from the initial contact.

- c) What steps are you taking to determine that potential participants are competent to participate in the decision-making process? If your study may enroll adults who are unable to consent, describe (i) how you will assess the capacity to consent, (ii) what provisions will be taken if the participant regains the capacity to consent, (iii) who will be used as a legally authorized representative, and (iv) what provisions will be made for the assent of the participant.

Subjects will arrange for their own transportation to the study location. There is therefore sufficient reason to believe that they will be participating at their own free will. The research team will adequately remind each subject that they may withdraw at any time.

Additional VA questions:

- i) List the people to whom you have formally delegated responsibility to obtain informed consent, and state whether they have the appropriate training to perform this activity.

Dr. Beaupre, Dr. Kiratli, Dr. Creasey, or Dr. Lambach will obtain all consents. These people have or will have completed appropriate training and each will have prior experience or specific training in performing consents.

- ii) Will legally effective informed consent be obtained from the participant or the participant's legally authorized representative (LAR) or both? If LAR, is it clear who can serve as LAR?

Legally effective informed consent will be obtained from each participant. No LARs will be used.

- iii) Will the circumstances of the consent process minimize the possibility of coercion or undue influence and provide the prospective participant or their representative sufficient opportunity to consider whether to participate?

Yes

- iv) Will the circumstances of the consent process minimize the possibility of coercion or undue influence?

Yes

- v) Will the information being communicated to the participant or the representative during the consent process exclude any exculpatory language through which the participant or the representative is made to waive or appear to waive the participant's legal rights, or release or appear to release the investigator, the sponsor, the institution, or its agent from liability for negligence (e.g. I give up any property rights I may have in bodily fluids or tissue samples obtained in the course of the research)?

Yes

- vi) Please confirm the following:
 - a. A witness to the participant's signature or the participant's legally authorized representative's signature will sign and date the consent document.
 - b. If the sponsor or the IRB requires a witness to the consenting process in addition to the witness to the participant's signature and if the same person is needed to serve both capacities, a note to that

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effect is placed under the witness's signature line.

- c. A copy of the signed and dated consent document will be given to the person signing the consent document.
- d. The consent form is on the VA Form 10-1086.

14. Assent Background (less than 18 years of age)

15. HIPAA Background

15.1 Waiver of Authorization for pre-screening of potential participants

Recruitment

- a) Describe the protected health information (PHI) needed to conduct screening or recruitment. PHI is health information linked to HIPAA identifiers. List BOTH health information AND HIPAA identifiers. If you are using STARR, use the Data Privacy Attestation to ensure that your request will match your IRB-approved protocol.

Potential participants will typically make their first contact with Dr. Beaupre by phone. During that initial phone call, Dr. Beaupre will provide potential participants with a general overview of the project, including the two possible groups to participate in, the total duration of the study and the time commitment. During that phone call, Dr. Beaupre will also make an initial assessment of potential participants from the perspective of the inclusion and exclusion criteria. This initial assessment is particularly important in terms of convenience to potential participants since all participants will have spinal cord injuries which may make it difficult for them in terms of transportation to and from the VA. The investigators do not want to inconvenience a potential subject by requiring them to come to the VA only to learn after one or two minutes of discussion that the subject is not really interested in the study or does not qualify, say, because of age, or because of the time commitment, or because of one of the inclusion or exclusion criteria. During the initial phone conversation with a potential participant, it is possible that the individual calling will provide his or her name or reveal other III or PHI, such as the city where they live or some health information such as the date or level of their spinal cord injury. It is not possible to have that phone conversation without there being a reasonable likelihood that the individual will reveal some III or PHI. It is not practical or reasonable to require that an individual make a special trip to the VA, sign an informed consent, and only thereafter to determine if they are interested in the study or if they potentially qualify for inclusion.

- b) Please Answer:
 - Y Do you certify that the use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals?
 - Y Do you certify that the research could not practically be conducted with out the waiver?
 - Y Do you certify that you have adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted?
 - Y Do you certify that the research could not practically be conducted with out access to and use of the protected health information?
- c) Please describe an adequate plan to protect any identifiers from improper use and disclosure.

During the initial phone call by potential participants to Dr. Beaupre during which the potential participant might disclose PHI or III, Dr. Beaupre will typically take hand-written notes about the potential participant. After the phone conversation, those notes will be transcribed to a WORD document and stored on a secure server at the VA. At that point the handwritten notes will be depositing in a secure bin for shredding. If it is

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subsequently determined that a subject is not a candidate for inclusion or potential inclusion in the study the electronics notes will be permanently deleted from the VA server. Candidates who ultimately do become participants will have any PHI or III appended to their information in the file that contains the code number for participants, which will only be stored on the secure VA server behind the VA firewall.

- d) **Please describe an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.**

All VA research records will be maintained consistent with existing VA record retention policies.

16. Attachments

Attachment Name	Attached Date	Attached By	Submitted Date
VA Required Questions	08/29/2013	beaupre1	
VA Consent for use of photos, etc.	08/29/2013	beaupre1	
VA Proposal	09/26/2013	beaupre1	
Phone Script	09/29/2013	beaupre1	

Obligations

The Protocol Director agrees to:

- Adhere to principles of sound scientific research designed to yield valid results
- Conduct the study according to the protocol approved by the IRB
- Be appropriately qualified to conduct the research and be trained in Human Research protection, ethical principles, regulations, policies and procedures
- Ensure all Stanford research personnel are adequately trained and supervised
- Ensure that the rights and welfare of participants are protected including privacy and confidentiality of data
- Ensure that, when de-identified materials are obtained for research purposes, no attempt will be made to re-identify them.
- Disclose to the appropriate entities any potential conflict of interest
- Report promptly any new information, modification, or unanticipated problems that raise risks to participants or others
- Apply relevant professional standards.

Any change in the research protocol must be submitted to the IRB for review prior to the implementation of such change. Any complications in participants or evidence of increase in the original estimate of risk should be reported at once to the IRB before continuing with the project. Inasmuch as the Institutional Review Board (IRB) includes faculty, staff, legal counsel, public members, and students, protocols should be written in language that can be understood by all Panel members. The investigators must inform the participants of any significant new knowledge obtained during the course of the research.

IRB approval of any project is for a maximum period of one year. For continuing projects and activities, it is the responsibility of the investigator(s) to resubmit the project to the IRB for review and re-approval prior to

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the end of the approval period. A Notice to Renew Protocol is sent to the Protocol Director 7 weeks prior to the expiration date of the protocol.

Department Chair must approve faculty and staff research that is not part of a sponsored project. VA applicants must have Division Chief or Ward Supervisor approval. E-mail the Department Chair approval to IRBCoordinator@lists.stanford.edu.

All data including signed consent form documents must be retained for a minimum of three years past the completion of the research. Additional requirements may be imposed by your funding agency, your department, or other entities. (Policy on Retention of and Access to Research Data, Research Policy Handbook, <http://doresearch.stanford.edu/policies/research-policy-handbook/conduct-research/retention-and-access-research-data>)

PLEASE NOTE: List all items (verbatim) that you want to be reflected in your approval letter (e.g., Amendment, Investigator's Brochure, consent form(s), advertisement, etc.) in the box below. Include number and date when appropriate.

Consent Form for Control Group
Consent Form for FES-Rowing Group
Consent Form for Experienced Rowers
Determination of non-significant risk with the use of Odstock O4CHS stimulator
Waiver of Individual Authorization for recruitment under 45 CFR 164.512(i)(2)(ii)(A),(B),(C), pursuant to information provided in the HIPAA section of the protocol application.
Includes grant title: Using Musculoskeletal Models to Assess FES Rowing for Skeletal Health After SCI

Y By checking this box, I verify that I, as the Protocol Director (PD) responsible for this research protocol, have read and agree to abide by the above obligations, or that I have been delegated authority by the PD to certify that the PD has read and agrees to abide by the above obligations.



RESEARCH CONSENT FORM

Title of Study: Skeletal Health in the Lower Limbs Following Spinal Cord Injury

Title of Consent: Skeletal Benefits from FES-Rowing in Individuals with Spinal Cord Injuries

Principal Investigator: Gary Beaupre

VAMC: VA Palo Alto HCS

Are you participating in any other research studies? _____ yes _____ no

PURPOSE OF RESEARCH

You are invited to participate in a research study to determine if a 36-week rowing exercise program can help to prevent the loss of bone in your lower limbs that typically accompanies a spinal cord injury (SCI). You were selected as a possible participant in this study because you sustained a spinal cord injury more than 3 months ago, but less than 24 months ago. This research study is looking for a total of five people with a spinal cord injury in the 3 to 24-month time frame who will participate in the rowing exercise program.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care you are entitled to.

DURATION OF STUDY INVOLVEMENT

This research study is expected to take approximately two years in total. Each participant will be enrolled in the study for approximately 36 weeks or 9 months. During this approximately 36-week period, each participant will make multiple visits to the VA Palo Alto Health Care System campus. The approximate schedule of weekly visits is outlined near the end of the next section (**PROCEDURES**).

PROCEDURES

If you choose to participate in this study, you will be enrolled in a 36-week exercise program that may decrease bone loss in your legs. Weeks of participation will be measured based on completion of 3 training sessions per week with 85% compliance resulting in a minimum of 92 exercise sessions over at least 36 weeks. It may take longer than 36 consecutive calendar weeks to complete the 36-week exercise program. During part of this exercise program you will be trained to exercise using a rowing machine. Before you will be able to use the rowing machine, however, you will participate in an approximately 8-week muscle conditioning program that will strengthen your thigh muscles. Both the muscle conditioning phase and the subsequent rowing phase will require the use of a device called a muscle stimulator. This device uses a technology known as Functional Electrical Stimulation or FES. The muscle stimulator is a battery-powered device that delivers a small electrical signal to your muscles from electrodes



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VAMC: VA Palo Alto HCS

that are placed on the surface of the skin overlying your thigh muscles on both the front of your thighs (quadriceps muscles) and the back of your thighs (hamstrings muscles). These electrodes are connected by electrical cables to the battery-powered FES stimulator. The stimulator unit we will use is currently designated as an investigation device, however the exact model of stimulator has been used successfully for many years and continues to be used by a number of research laboratories throughout the world. Since your leg muscles will likely be weak from lack of use since your spinal cord injury, the purpose of the 8-week muscle conditioning phase is to strengthen your thigh muscles so that you are subsequently able to perform the rowing exercise.

During the first four weeks of the muscle conditioning phase you will visit VA Palo Alto three times per week, typically Monday, Wednesday and Friday. Each training session will last for up to 60 minutes. During weeks 5 through 8 of participation, your muscle conditioning sessions may be increased to five sessions per week, provided you are able to attend that often. At a minimum, you are expected to have three muscle conditioning sessions each week during weeks 5 through 8.

During the muscle conditioning phase, you will sit in your wheelchair or on the edge of a raised padded exam table with your knees flexed (bent) at 90 degrees. The muscle stimulator is initially programmed to provide stimulation for 5 seconds to activate the front thigh muscles in one leg, then stimulation to that leg is turned off. Following 1 second of rest, the stimulator will apply stimulation for 5 seconds to activate the front thigh muscles of your other leg. When the stimulation is turned off to the front muscles of one leg, that leg will return to the 90 degree flexed position due to gravity. A pillow placed under your leg will cushion your leg when the stimulation to that leg is turned off. The goal of strengthening the front thigh muscles is to be able to raise your lower leg and fully extend your knee, such that is your knee can maintain a non-bent or extended position while the stimulation is turned on. This alternate leg extension exercise delivers 5 repetitions per leg per minute.

Similarly, the main muscles on the back of your thighs (hamstrings) will be incorporated into the leg muscle conditioning once the quadriceps have undergone initial strengthening. The hamstrings are activated in each leg only when the stimulation to the quadriceps is turned off. During hamstring stimulation, the knee will remain in the bent, 90° flexed position. A pillow placed between your lower leg and a fixed support will prevent any additional flexion of your knee during hamstrings stimulation. Again, stimulation will alternate between legs (with stimulation to the quadriceps turned off), with 5 seconds of stimulation for one leg, followed by a 1 second rest and then 5 seconds of stimulation for the other leg.

Each session of muscle conditioning will last up to 60 minutes.



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You will be ready to progress to the rowing exercise as soon as your front thigh muscles are able to extend one knee fully during 5 seconds of stimulation, and then extend the other knee fully during 5 seconds of stimulation and to repeat this alternating process for 30 minutes. The muscle conditioning phase of the exercise program typically takes 8 weeks, although not all individuals respond at the same rate, and a given individual may take less or more time. It should be remembered that until your thigh muscles are adequately conditioned you will not be able to progress to the rowing phase, since rowing will not produce a skeletal benefit without adequate thigh muscle strength.

Once you have achieved adequate muscle conditioning, the Functional Electrical Stimulation (FES) rowing phase can begin. During FES-rowing, the stimulation electrodes are placed over the same muscles that were strengthened during the muscle condition phase. In the case of rowing, you will be sitting on the seat of a rowing machine and your feet will be secured to foot plates on the stationary part of the rowing machine. The rowing machine is a commercial exercise machine that has been adapted for use by individuals with spinal cord injury. The FES-rowing machine that we will use is the same as machines in current use in multiple research laboratories around the world, including England, Boston and Alberta, CA. The seat on the rower has a backrest and a harness system. The seat, backrest and harness system will provide stability for your torso during rowing. You will use your hands to hold the handle of the rowing machine. The handle attaches via a chain to the part of the machine that uses resistance to exercise your arms as you pull.

During rowing, the muscles on the front and back of your thigh will be alternately simulated by pressing and releasing a push button on the rowing handle. This button controls which muscles are being stimulated. When the push button is pressed, the muscles on the front of your thighs (quadriceps) are stimulated; when the button is released, the muscles on the back of your thigh (hamstrings) will be stimulated. This will cause your knees to automatically extend and flex in a cyclic pattern as the push button is pressed and released. With practice you will quickly learn to pull on the rower handle while pressing the push button to extend your legs, to push the seat rearwards, and extend your arms while releasing the push button, to flex your legs, moving the seat forwards. This technique will mimic the pattern used by experienced rowers. The ultimate goal of your rowing exercise is for you to be able to row for 30 minutes without stopping and to do this on alternate days, three times per week.

At four points during the course of your participation, we will measure the bone density in your thigh bone (upper leg bone) and shank bone (lower leg bone) using two bone scanners that provide complimentary information on the health of your skeleton. These measurements are non-invasive and painless.



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Your bone density measurements will take place at two laboratories located on the campus of the VA Palo Alto Health Care System. Prior to your visits we will provide you with instructions on where to meet a member of our staff who will escort you to the two laboratories. The measurements we will make are designed to give us a very precise assessment of how much bone there is in key parts of your skeleton; the quantity we will measure is called ‘bone mineral density.’ We will determine the bone mineral density for your spine, one of your hips, as well as locations above and below your knee, and above your ankle.

The first scanner that we will use is called a Dual energy X-ray Absorptiometry scanner, often referred to as DXA scanner. This scanner provides us with a two-dimensional image of your bone and a quantitative bone density “score” for your spine and hip which can be used to compare your bone density to the bone density in young individuals with healthy skeletons. We will also use this scanner to measure the bone density above your knee, which is a region that is susceptible to fracture in individuals with long-standing spinal cord injuries. During DXA scanning you will on your back on a padded table while a scan arm passes above the region of your body being scanned.

The second scanner we will use is called a peripheral Quantitative Computed Tomography scanner, often referred to as a pQCT scanner. This scanner provides use with three-dimensional information, which compliments the information from the two-dimensional DXA scan, and which we can use to estimate the strength of your bones. We will use this scanner to measure the bone density and bone geometry at two sites above your knee, one site just below your knee and one site just above your ankle. As stated previously, these regions are considered key skeletal sites since they are susceptible to fracture in individuals with long-standing spinal cord injuries. During pQCT scanning you will lie on your back on a padded table with one leg placed in the bore of the pQCT scanner. Since this scanner is designed to scan only peripheral sites, such as the legs, no part of the scanner will cover any other part of your body and there will be no sense of claustrophobia, like there could be with a whole-body CT scanner.

At four times during your approximately 36-week participation we may conduct strength testing of your quadriceps and hamstrings. This will be done using the same muscle stimulator that you will use during muscle conditioning and rowing. The goal of this testing is to assess how strong your quadriceps and hamstrings muscles are at different phases of the exercise program. For these strength tests, we will use a strap around your ankle to prevent your leg from moving and we will use a force sensor connected to the strap to determine how much force you generate when your quadriceps and hamstrings are individually activated.

The final measurements we will make involve a procedure called motion capture. For these tests we will tape a number of small (5/8” diameter) reflective markers to various



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parts of your body and we will have you perform FES rowing while we capture the motion of the reflective markers using a series of special digital cameras. We will also record the forces that are created under your feet and in the chain that connects the handle to the rowing machine. With the motion and force data we will be able to estimate the internal forces that exist within your ankles and knees using three-dimensional computer models while you are rowing. We believe that the magnitude of the estimated forces will provide us with new insights into how skeletal health can be maintained in individuals following a spinal cord injury.

Visit Schedule: Your visits to VA Palo Alto will take place on the following schedule:

- Weeks 1-4: 3 visits per week
- Weeks 5-8: 3 to 5 visits per week
- Weeks 9-36: 3 visits per week

The majority of visits will last approximately 1.5 hours. The four visits involving bone density measurements and muscle strength testing will last approximately 3.5 hours. The three visits involving motion capture experiments will last approximately 4 hours.

Women of Childbearing Potential

If you are a woman who is able to become pregnant, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk. 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 begin the study after the onset of your next menstrual period. You must agree to avoid sexual intercourse or use a birth control method judged to be effective by the investigator and which will not interfere with the proposed investigation. You must accept the risk that pregnancy could still result despite the responsible use of a reliable method of birth control. You agree to notify the investigator as soon as possible of any failure of proper use of your birth control method, or if you become pregnant, either of which may result in your being withdrawn from the study.

Access to Medical Records:

We may access your medical records in order to identify any medical conditions that could be relevant to the research study and/or which may influence the safety of your participation.

PARTICIPANT RESPONSIBILITIES



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As a participant, your responsibilities include:

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

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are **free to withdraw** your consent and stop your participation at any time. If you decide to withdraw from the study, you will not lose any benefits to which you would otherwise be entitled.

If you want to stop being in the study you should tell the investigators or study staff. You can do this by phone by calling Dr. Beaupre at (650) 493-5000 extension 64272.

The investigators 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 investigators and/or study staff.
- The investigators decide that continuing your participation could be harmful to you.
- Pregnancy (if applicable).
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES



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This study involves the following risks, discomforts, and possible inconveniences:

Inconveniences and discomforts:

1. Time required for participation in the study
2. Travel to and from our study site
3. Time lying still for the bone density scans
4. Muscle strain
5. Mild autonomic dysreflexia
6. Increase in neuropathic (“nerve”) pain
7. Increase in spasticity
8. High physical exertion when rowing

Risks:

Privacy Risk: Though all possible precautions will be followed to ensure your privacy, there is a very small risk of privacy loss. This could have legal, employment, and social consequences.

Risks of Radiation: This research study involves exposure to radiation from bone density scanners. This radiation exposure is not necessary for your medical care and is for research purposes only. The additional amount of radiation is approximately equal to 2 days of radiation exposure from natural sources like the sun, ground and water. This amount of radiation involves minimal risk and is necessary to obtain the research information desired.

Risk of a fall during transfer to or from rowing machine: There is a possibility that you may fall while transferring to or from the rowing machine or to or from the table you will lie on while having your bone density scans. The risk of falling can be minimized to a very low level by using safe transfer techniques. You will be required to demonstrate the use of a safe transfer technique during your initial assessment visit.

Soft tissue reaction during FES training: A soft tissue reaction to muscle conditioning and FES-rowing can be associated with several causes. The first is a local reddening of the skin under the electrodes. This reddening is thought to be due to an increase in blood flow beneath the electrode caused by the electrical stimulation. This reddening typically lasts for less than one hour after stimulation is stopped. This reddening is expected to occur to some degree with all participants.

Reddening may also potentially occur as a result of an allergic reaction to the gel used to adhere the surface electrode to the skin. If reddening of the skin persists for much longer than one hour after removal of the electrode, then an allergic reaction is a



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possible cause. If a participant has an allergic reaction to the gel, we can try a different electrode with a different gel.

The third and final potential skin reaction is reddening suggestive of the initiation of soft tissue breakdown (e.g., a "pressure sore") due to excessive pressure or shear stress. This potential for skin breakdown exists for all individuals who utilize a wheelchair for prolonged periods. To the best of our knowledge no prior FES-rowing participants have experienced a skin breakdown or pressure sore caused by their participation in an FES-rowing program. Nevertheless, before and after each session, we will look for any signs of bruising or swelling that might be suggestive of tissue breakdown, paying particular attention to the shoulders, back, buttocks, upper calves and knee areas.

Serious autonomic dysreflexia during FES training: Autonomic dysreflexia (AD) is a condition which can occur in people who have sustained a spinal cord injury. Autonomic dysreflexia is more common in individuals with tetraplegia (quadriplegia), but it can also occur in individuals with paraplegia. Autonomic dysreflexia can be brought on by a variety of stimuli, including a full bladder or bowel, a pressure sore or infection, exercise, or by Functional Electrical Stimulation. Possible symptoms of an AD reaction include:

- Severe headache
- Flushing or blotching of the skin above the level of the spinal cord injury
- Profuse sweating, particularly above the level of the spinal cord injury
- Increased blood pressure
- Decreased heart rate

Generally, an AD reaction will quickly diminish once the initiating stimulus that caused the reaction is removed. To reduce the risk of an AD response, all participants will be encouraged to completely empty their bladder prior to each muscle conditioning or rowing session. The risk of an AD response should also decrease as training progresses and your muscles become conditioned from the electrical stimulation. Thus, the risk of AD is highest during the initial muscle conditioning session. During your first muscle conditioning session we will assess the ability of your muscles to respond to the electrical stimulation and we will pay particular attention to any signs of an AD response. It is possible that an AD response that is greater than mild might be identified at your initial session and that could mean that you are not an acceptable candidate for continuation in the study.

It is important to note that FES-rowing researchers in England and Boston have never had a participant in their FES-rowing programs experience a severe case of AD, and those participants who have experienced mild cases of AD also typically experience mild cases of AD during their everyday lives. Therefore, we believe the risk of



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experiencing a severe case of AD from participation in this study is very low, although the possibility of experiencing a mild case of AD is higher. At the first sign of an AD response, electrical stimulation will be stopped. Additional medical treatment in the case of a severe AD response will be available in our testing facilities.

It should also be noted that an individual's likelihood of having an AD episode in response to exercising part of the body below the level of a spinal cord injury will be heightened if an individual already has an underlying condition that is perceived by their body as a noxious stimulus. For example, an individual with a bladder infection might be more prone to an AD episode from an additional stimulus, such as Functional Electrical Stimulation of the legs, compared to an individual without a bladder infection. Therefore, it is important that any underlying noxious stimulus that might predispose an individual to an AD response is identified as early as possible and addressed before commencing or continuing with the rowing exercise.

Muscle strain during muscle conditioning, strength testing or FES-assisted rowing: As with participating in any exercise program, there is a risk of experiencing a muscle strain. Based on the experience of other researchers with FES-rowing programs, only two out of thirty FES-rowing participants have ever experienced a muscle strain. Muscle strains have never been observed in the lower limbs. For both participants with muscle strains, the strain occurred in the torso, between innervated and paralyzed muscle. These strains were treated by ceasing FES training for 48 to 72 hours and by the use of ice and over-the-counter analgesics. Neither of the two individuals who experienced a muscle strain has had a repeat incident and we believe the risk of a muscle strain is low.

Lower limb fracture during muscle conditioning, strength testing or FES-assisted rowing: The use of FES to stimulate paralyzed muscles in individuals with SCI has been studied for more than 50 years. Over that 50-year period there have been two reported cases of a fracture related to the use of functional electrical stimulation. One individual fractured their knee cap and a second individual fractured their thigh bone. Although the total number of individuals with SCI who have used functional electrical stimulation to exercise the lower limbs is not known, we believe the risk of a fracture is very low given that there have only been two reported fractures in 50 years of FES use. To further reduce the risk of fracture, only participants who have never experienced a low-energy fracture will be allowed to take part in this study. In addition, we will measure your bone density at the beginning of the study and those measurements will provide us with an initial assessment of the health of your bones. If we believe your bones are too weak to safely undergo the muscle conditioning and rowing exercise, you will not be able to continue in the study.



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Increase in neuropathic (“nerve”) pain or an increase in sensory pain from FES: Some individuals with spinal cord injuries individuals have what is known as neuropathic pain. Neuropathic pain can range from a mild tickling sensation to a severe burning sensation. It is not known what effect, if any, electrical stimulation has on this condition. In addition, some individuals with SCI who retain some sensation in their thighs may find the electrical stimulation to be uncomfortable or even intolerable. If you experience an increase in neuropathic pain to an unacceptable level or if the electrical stimulation produces a sensation which you find unacceptable, it may be necessary for you to withdraw from the study.

Increase in spasticity to an unmanageable level: It is not known what effect FES has on the intensity and frequency of muscle spasticity. In other FES-rowing programs, a few participants have had an increase in spasticity, while some have had a decrease. In general, spasticity levels should be reduced after a muscle conditioning or rowing session, since the muscles will be fatigued. However, if you experience increased spasticity that is unmanageable, it may be necessary for you to withdraw from the study.

Unforeseen Risks: There may be other risks to participating in this study that are not foreseeable.

POTENTIAL BENEFITS

We cannot and do not guarantee that you will received any benefits from this study. Nevertheless, it is possible that participating in an FES-rowing exercise program may reduce bone loss in parts of your legs. Since the spine and hip DXA scans that we will perform represent a clinical standard by which osteoporosis is assessed, we will provide you with copies of the results of your spine and hip DXA scans which you are free to share with your personal physician, who should be able to help you interpret your bone density results.

Please note that at the present time rowing with FES is not available within the VA clinical facility, and stimulators are not available for distribution outside of research use. However, the VA Palo Alto SCI Center is developing a program to support adaptive rowing under the auspices of recreation therapy, and so in the future there may be opportunities for veterans with SCI to access this program as part of inpatient or outpatient therapy.

ALTERNATIVES

Your alternative is simply to not participate in this study.



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PARTICIPANT'S RIGHTS

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

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

We will keep your name and all the information you tell us in this study as confidential as possible. We may publish the results of this study for others to read about, but you will not be identified in any articles about the study by name, social security number, address, telephone number, or any other direct personal identifier. Also, other federal agencies as required, such as the VA Office of Research Oversight and the VA Office of the Inspector General may have access to your information.

FINANCIAL CONSIDERATIONS

Payment

As a token of our appreciation for your participation, you will receive a total of \$450 for your full participation in this study. You will receive a \$150 payment after you complete each of three phases of the study, according to the following milestones:

- Milestone 1) 12-weeks of participation and completion of 31 exercise sessions: \$150
- Milestone 2) 24-weeks of participation and completion of 61 exercise sessions: \$150
- Milestone 3) 36-weeks of participation and completion of 92 exercise sessions: \$150

Payments may only be made to U.S. citizens, legal resident aliens, and those who have a work eligible visa.



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Costs

There will be no costs to you for any of the treatment or testing done as part of this research study. However, medical care and services provided by the VA that are not part of this study (e.g., normal hospital and prescription expenses which are not part of the research study) may require co-payments if your VA-eligibility category requires co-payment for VA services.

You will not have to pay anything to be in this study, although you will have to provide for your own transportation to and from the VA Palo Alto Campus.

Sponsor

The Department of Veterans Affairs is providing financial support and/or material for this study.

COMPENSATION for Research Related Injury

If you are injured as a direct result of being in this study, medical treatment will be available. If you are eligible for veteran's benefits, the cost of such treatment will be covered by the VA. If not, the cost of such treatments may still be covered by the VA depending on a number of factors. In most circumstances, the treatment must be provided in a VA medical facility. No other form of compensation for injuries is available. However, by signing this form you have not released the VA from liability for negligence. For further information, you may call the Human Protections Administrator at (650) 493-5000, ext. 67593 or the V.A. Regional Counsel at (415) 750-2288.

CONTACT INFORMATION

Questions, Concerns, or Complaints: 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 principal investigator, Dr. Beaupre at (650) 493-5000 extension 64272. You should also contact him 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, 3000 El Camino Real, Five Palo Alto Square, 4th Floor, Palo Alto, CA 94306..



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Appointment Contact: If you need to change your appointment, please contact Dr. Lambach at (650) 493-5000 extension 69411.

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 (by phone or mail) about future research studies that may be of interest to you? Yes No

Signing your name means you agree to be in this study and that you were given a copy of this consent form.

Signature of Participant

Date



IRB Use Only

Approval Date: September 1, 2015

Expiration Date: August 31, 2016

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VAMC: VA Palo Alto HCS

Print Name of Participant

Signature of Person Obtaining Consent

Date

Print Name of Person Obtaining Consent

*This page separates the
Informed Consent Document (above)
from the
HIPAA Authorization document
(below)*

*To preserve formatting, please
DO NOT DELETE this page*

VA Palo Alto Health Care System – HIPAA Authorization Form

Protocol Title: Skeletal Health in the Lower Limbs Following Spinal Cord Injury

Principal Investigator: Gary Beaupre

Date of Review: October 1, 2013

HIPAA (Health Insurance Portability & Accountability Act) is a federal privacy law that protects the confidentiality of health information collected about you. The following explains how health information collected about you will be used by the investigators and who they may share your health information with as part of this research.

What is the purpose of the research study, and how will my health information be utilized in the study?

In this study we hope to determine if the amount of bone loss at skeletal locations in the lower limbs in individuals with a spinal cord injury can be positively influenced by participating in a 36-week FES muscle conditioning and rowing program. We plan to use the information obtained in this study to compare to the results in a companion study of individuals with SCI who are not participating in an FES exercise program.

What Personal Health Information Will Be Used or Shared?

The following health information, linked to you by name, address, e-mail address, phone number and/or date of birth, will be used for this research:

- Medical history and physical examination information
- Bone density scans
- Photographs, videotapes, other images

Who May Use or Share Your Health Information?

By signing this document, you allow the following individuals and entities to obtain, use and share your health information for this research study:

- The Principal Investigator, Gary Beaupre, and members of the VA research team.
- Departments within the VA Health Care System responsible for the oversight, administration, or conduct of research.
- The Stanford University Administrative Panel on Human Subjects in Medical Research and other Stanford University Officials responsible for the oversight, administration, or conduct of research.

VA Palo Alto Health Care System – HIPAA Authorization Form

Protocol Title: Skeletal Health in the Lower Limbs Following Spinal Cord Injury

Principal Investigator: Gary Beaupre

Date of Review: October 1, 2013

Who May Receive and Use Your Health Information

The investigators may share your health information with the following individuals/entities as part of this research study.

- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- The Food and Drug Administration

Health information shared pursuant to this authorization may no longer be protected by Federal laws or regulations and may be further shared by the above individuals/entities who receive the health information.

Do I have to sign this form?

No. Signing this form is voluntary. The VA may not condition treatment, payment, enrollment or eligibility for benefits based on signing this form. If you decide not to sign the form, you will not be able to take part in this study.

If I sign now, can I decide later not to continue in the study?

Yes. You are free to take back your permission and stop being in the study. The investigators will not collect any more information about you after you take back your permission, but they can continue to use your information that was collected before you took back your permission.

Your request to take back your permission must be done in writing. Either give or send your written request to the investigator:

Dr. Gary S. Beaupre
Musculoskeletal Research Laboratory (Mail Code 153)
VA Palo Alto Health Care System
3801 Miranda Avenue
Palo Alto, CA 94304

VA Palo Alto Health Care System – HIPAA Authorization Form

Protocol Title: Skeletal Health in the Lower Limbs Following Spinal Cord Injury

Principal Investigator: Gary Beaupre

Date of Review: October 1, 2013

Does My Permission for the use my Personal Health Information Expire?

Yes. Your information cannot be used forever. Your permission related to the use and sharing of your health information expires on 12/31/2023.

HIPAA regulations require you to give separate written permission (signature) for the use of your protected health information.

Signature of Participant

Date

Printed Name of Participant



RESEARCH CONSENT FORM

Title of Study: Skeletal Health in the Lower Limbs Following Spinal Cord Injury	
Title of Consent: Bone Changes in the Lower Limbs in Individuals with Spinal Cord Injuries	
Principal Investigator: Gary Beaupre	VAMC: VA Palo Alto HCS

Are you participating in any other research studies? _____ yes _____ no

PURPOSE OF RESEARCH

You are invited to participate in a research study to monitor changes to the skeleton in the lower limbs after spinal cord injury and with participation in a program of rowing with electrical stimulation of the legs. You are not a participant in the rowing exercise part of the study either because you did not want to participate or because of a medical reason that prevented you from qualifying. We hope to determine whether the rowing exercise may slow the rate of bone loss in the legs. You were selected as a possible subject in this study because you had a spinal cord injury more than 3 months ago, but less than 24 months ago, and your information can be used for comparison with information from the individuals who do participate in the rowing program. We are hoping to enroll five people in the rowing study and five people who are not participating in rowing.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care you are entitled to.

DURATION OF STUDY INVOLVEMENT

This research study is expected to take approximately two years in total. Each participant will be enrolled in the study for approximately 36 weeks or 9 months. During this approximately 36-week period, each participant will have a total of four visits to the VA Palo Alto Health Care System campus. Your first visit will take approximately 3.5 hours, including the time to assess your enrollment eligibility, to complete the informed consent process, and to complete your initial bone density scans if you are eligible and elect to participate in the study. The subsequent three visits should take no more than 2.5 hours each. Your total participation time for the four visits combined will be about 11 hours. After your first visit, we will schedule you for return visits approximately 12 weeks, 24 weeks, and 36 weeks later.

PROCEDURES

If you choose to participate, the investigators will measure the bone density in your thigh bone (upper leg bone) and shank bone (lower leg bone) using two bone scanners that provide complimentary information on the health of your skeleton. These measurements are non-invasive and painless.



RESEARCH CONSENT FORM

Title of Study: Skeletal Health in the Lower Limbs Following Spinal Cord Injury	
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Your bone density measurements will take place at two laboratories located on the campus of the VA Palo Alto Health Care System. Prior to your visits we will provide you with instructions on where to meet a member of our staff who will escort you to the two laboratories. The measurements we will make are designed to give us a very precise assessment of how much bone there is in key parts of your skeleton; the quantity we will measure is called ‘bone mineral density.’ We will determine the bone mineral density for your spine, one of your hips, as well as locations above and below your knee, and above your ankle.

The first scanner that we will use is called a Dual energy X-ray Absorptiometry scanner, often referred to as DXA scanner. This scanner provides us with a two-dimensional image of your bone and a quantitative bone density “score” for your hip which can be used to compare your bone density to the bone density in young individuals with healthy skeletons. We will also use this scanner to measure the bone density above your knee, which is a region that is susceptible to fracture in individuals with long-standing spinal cord injuries. During DXA scanning you will lie on your back on a padded table while a scan arm passes above the region of your body being scanned.

The second scanner we will use is called a peripheral Quantitative Computed Tomography scanner, often referred to as a pQCT scanner. This scanner provides use with three-dimensional information, which compliments the information from the DXA scan, and which we can use to estimate the strength of your bones. We will use this scanner to measure the bone density and bone geometry at two sites above your knee, one site just below your knee and one site just above your ankle. As stated previously, these regions are key skeletal sites since they are susceptible to fracture in individuals with long-standing spinal cord injuries. During pQCT scanning, you will lie on your back on a padded table with one leg placed in the pQCT scanner. Since this scanner is designed to scan only peripheral sites, such as the legs, no part of the scanner will cover any other part of your body and there will be no sense of claustrophobia, like there could be with a whole-body CT scanner.

Although bone density measurements are typically not done as part of the standard of care following a spinal cord injury, we require bone density measurements in both the non-exercise group and in the exercise group in order for us to determine if exercising has any benefit to bone health compared to not exercising.

Visit Schedule: Your bone density measurements will take place during four visits to VA Palo Alto at the following time points: 1) at your first visit, after signing an informed consent; 2) approximately 12 weeks later; 3) approximately 24 weeks after your first visit; and 4) approximately 36 weeks after your first visit.



RESEARCH CONSENT FORM

Title of Study: Skeletal Health in the Lower Limbs Following Spinal Cord Injury	
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Women of Childbearing Potential

If you are a woman who is able to become pregnant, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk. 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 begin the study after the onset of your next menstrual period. You must agree to avoid sexual intercourse or use a birth control method judged to be effective by the investigator and which will not interfere with the proposed investigation. You must accept the risk that pregnancy could still result despite the responsible use of a reliable method of birth control. You agree to notify the investigator as soon as possible of any failure of proper use of your birth control method, or if you become pregnant, either of which may result in your being withdrawn from the study.

Access to Medical Records:

We may access your medical records in order to identify any medical conditions that could be relevant to the research study and/or which may influence the safety of your participation.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

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



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Title of Study: Skeletal Health in the Lower Limbs Following Spinal Cord Injury	
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WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are **free to withdraw** your consent and stop your participation at any time. If you decide to withdraw from the study, you will not lose any benefits to which you would otherwise be entitled.

If you want to stop being in the study you should tell the investigators or study staff. You can do this by phone by calling Dr. Beaupre at (650) 493-5000 extension 64272.

The investigators 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 investigators and/or study staff.
- The investigators decide that continuing your participation could be harmful to you.
- Pregnancy (if applicable).
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

This study involves the following risks, discomforts, and possible inconveniences:

Inconveniences and discomforts:

1. Time required for participation in the study
2. Travel to and from our study site
3. Time lying still for the bone density scans

Risks:

Privacy Risk: Though all possible precautions will be followed to ensure your privacy, there is a very small risk of privacy loss. This could have legal, employment, and social consequences.

Risks of Radiation: This research study involves exposure to radiation from bone density scanners. This radiation exposure is not necessary for your medical care and is



RESEARCH CONSENT FORM

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for research purposes only. The additional amount of radiation is approximately equal to 2 days of radiation exposure from natural sources like the sun, ground and water. This amount of radiation involves minimal risk and is necessary to obtain the research information desired.

Unforeseen Risks: There may be other risks to participating in this study that are not foreseeable.

POTENTIAL BENEFITS

We cannot and do not guarantee that you will receive any benefits from this study. Since the hip DXA scans that we will perform represent a clinical standard by which osteoporosis is assessed, we will provide you with copies of the results of your hip DXA scans which you are free to share with your personal physician, who should be able to help you interpret your bone density results.

ALTERNATIVES

Your alternative is simply to not participate in this study.

PARTICIPANT'S RIGHTS

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

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

We will keep your name and all the information you tell us in this study as confidential as possible. We may publish the results of this study for others to read about, but you will not be identified in any articles about the study by name, social security number,



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address, telephone number, or any other direct personal identifier. Also, other federal agencies as required, such as the VA Office of Research Oversight and the VA Office of the Inspector General may have access to your information.

FINANCIAL CONSIDERATIONS

Payment

As a token of our appreciation for your participation, you will receive a \$50 payment after you complete each of the four DXA assessments.

Payments may only be made to U.S. citizens, legal resident aliens, and those who have a work eligible visa.

Costs

There will be no costs to you for any of the treatment or testing done as part of this research study. However, medical care and services provided by the VA that are not part of this study (e.g., normal hospital and prescription expenses which are not part of the research study) may require co-payments if your VA-eligibility category requires co-payment for VA services.

You will not have to pay anything to be in this study, although you will have to provide for your own transportation to and from the VA Palo Alto Campus.

Sponsor

The Department of Veterans Affairs is providing financial support and/or material for this study.

COMPENSATION for Research Related Injury

If you are injured as a direct result of being in this study, medical treatment will be available. If you are eligible for veteran's benefits, the cost of such treatment will be covered by the VA. If not, the cost of such treatments may still be covered by the VA depending on a number of factors. In most circumstances, the treatment must be provided in a VA medical facility. No other form of compensation for injuries is available. However, by signing this form you have not released the VA from liability for negligence. For further information, you may call the Human Protections Administrator at (650) 493-5000, ext. 67593 or the V.A. Regional Counsel at (415) 750-2288.

CONTACT INFORMATION



RESEARCH CONSENT FORM

Title of Study: Skeletal Health in the Lower Limbs Following Spinal Cord Injury	
Title of Consent: Bone Changes in the Lower Limbs in Individuals with Spinal Cord Injuries	
Principal Investigator: Gary Beaupre	VAMC: VA Palo Alto HCS

Questions, Concerns, or Complaints: 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 principal investigator, Dr. Beaupre at (650) 493-5000 extension 64272. You should also contact him 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, 3000 El Camino Real, Five Palo Alto Square, 4th Floor, Palo Alto, CA 94306..

Appointment Contact: If you need to change your appointment, please contact Dr. Lambach at (650) 493-5000 extension 69411.

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.



IRB Use Only

Approval Date: September 1, 2015

Expiration Date: August 31, 2016

RESEARCH CONSENT FORM

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Principal Investigator: Gary Beaupre	VAMC: VA Palo Alto HCS

May we contact you (by phone or mail) about future research studies that may be of interest to you? ___ Yes ___ No

Signing your name means you agree to be in this study and that you were given a copy of this consent form.

Signature of Participant

Date

Print Name of Participant

Signature of Person Obtaining Consent

Date

Print Name of Person Obtaining Consent

*This page separates the
Informed Consent Document (above)
from the
HIPAA Authorization document
(below)*

*To preserve formatting, please
DO NOT DELETE this page*

VA Palo Alto Health Care System – HIPAA Authorization Form

Protocol Title: Skeletal Health in the Lower Limbs Following Spinal Cord Injury

Principal Investigator: Gary Beaupre

Date of Review: October 1, 2013

HIPAA (Health Insurance Portability & Accountability Act) is a federal privacy law that protects the confidentiality of health information collected about you. The following explains how health information collected about you will be used by the investigators and who they may share your health information with as part of this research.

What is the purpose of the research study, and how will my health information be utilized in the study?

In this study we hope to determine the rate of bone loss at skeletal locations in the lower limbs that are susceptible to fracture as an individual with a spinal cord injury ages. We plan to use this information to compare with the results in a companion study to determine the extent to which a new exercise program may reduce the amount of bone loss after sustaining a spinal cord injury.

What Personal Health Information Will Be Used or Shared?

The following health information, linked to you by name, address, e-mail address, phone number and/or date of birth, will be used for this research:

- Medical history and physical examination information
- Bone density scans

Who May Use or Share Your Health Information?

By signing this document, you allow the following individuals and entities to obtain, use and share your health information for this research study:

- The Principal Investigator, Gary Beaupre, and members of the VA research team.
- Departments within the VA Health Care System responsible for the oversight, administration, or conduct of research.
- The Stanford University Administrative Panel on Human Subjects in Medical Research and other Stanford University Officials responsible for the oversight, administration, or conduct of research.

Who May Receive and Use Your Health Information

VA Palo Alto Health Care System – HIPAA Authorization Form

Protocol Title: Skeletal Health in the Lower Limbs Following Spinal Cord Injury

Principal Investigator: Gary Beaupre

Date of Review: October 1, 2013

The investigators may share your health information with the following individuals/entities as part of this research study.

- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- The Food and Drug Administration

Health information shared pursuant to this authorization may no longer be protected by Federal laws or regulations and may be further shared by the above individuals/entities who receive the health information.

Do I have to sign this form?

No. Signing this form is voluntary. The VA may not condition treatment, payment, enrollment or eligibility for benefits based on signing this form. If you decide not to sign the form, you will not be able to take part in this study.

If I sign now, can I decide later not to continue in the study?

Yes. You are free to take back your permission and stop being in the study. The investigators will not collect any more information about you after you take back your permission, but they can continue to use your information that was collected before you took back your permission.

Your request to take back your permission must be done in writing. Either give or send your written request to the investigator:

Dr. Gary S. Beaupre
Musculoskeletal Research Laboratory (Mail Code 153)
VA Palo Alto Health Care System
3801 Miranda Avenue
Palo Alto, CA 94304

Does My Permission for the use my Personal Health Information Expire?

VA Palo Alto Health Care System – HIPAA Authorization Form

Protocol Title: Skeletal Health in the Lower Limbs Following Spinal Cord Injury

Principal Investigator: Gary Beaupre

Date of Review: October 1, 2013

Yes. Your information cannot be used forever. Your permission related to the use and sharing of your health information expires on 12/31/2023.

HIPAA regulations require you to give separate written permission (signature) for the use of your protected health information.

Signature of Participant

Date

Printed Name of Participant



RESEARCH CONSENT FORM

Title of Study: Skeletal Health in the Lower Limbs Following Spinal Cord Injury	
Title of Consent: Measuring Motion, Forces, and Bone Density in an Experienced FES-Rower	
Principal Investigator: Gary Beaupre	VAMC: VA Palo Alto HCS

Are you participating in any other research studies? _____ yes _____ no

PURPOSE OF RESEARCH

You are invited to participate in a research study to measure the motions and forces during Functional Electrical Stimulation (FES)-assisted rowing, as well as bone density. You were selected as a possible participant in this study because you sustained a spinal cord injury and you already have more than one year of experience performing FES-rowing. This research study is looking for at least one individual with a spinal cord injury who has at least one year of FES-rowing experience.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care you are entitled to.

DURATION OF STUDY INVOLVEMENT

This research study is expected to take approximately two years in total. Your participation will last approximately one week. During this week you will make several visits to the VA Palo Alto Health Care System campus. The approximate schedule of your visits is outlined near the end of the next section (**PROCEDURES**).

PROCEDURES

If you choose to participate in this study, we will measure your bone mineral density and we will perform movement and force measurements while you perform FES-rowing.

We will measure the bone density in your thigh bone (upper leg bone) and shank bone (lower leg bone) using two bone scanners that provide complimentary information on the health of your skeleton. These measurements are non-invasive and painless.

Your bone density measurements will take place at two laboratories located on the campus of the VA Palo Alto Health Care System. The measurements we will make are designed to give us an accurate assessment of how much bone there is in key parts of your skeleton; the quantity we will measure is called 'bone mineral density.' We will determine the bone mineral density for your spine and hips, as well as locations just above and just below your knees, and just above your ankles.



RESEARCH CONSENT FORM

Title of Study: Skeletal Health in the Lower Limbs Following Spinal Cord Injury	
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The first scanner that we will use is called a Dual energy X-ray Absorptiometry scanner, often referred to as DXA scanner. This scanner provides us with a two-dimensional image of the spine and hip region and a quantitative bone density “score” which can be used to compare your bone density to the bone density in young individuals with healthy skeletons. We will also use this scanner to measure the bone density above your knees, which is a region that is susceptible to fracture in individuals with long-standing spinal cord injuries. We will scan you left and right sides separately. During DXA scanning you will on your back on a padded table while a scan arm passes above the region of your body being scanned.

The second scanner we will use is called a peripheral Quantitative Computed Tomography scanner, often called a pQCT scanner. This scanner provides us with three-dimensional information, which complements the information from the two-dimensional DXA scan. We will use this information to estimate the strength of your bones. We will use this scanner to measure the bone density and bone geometry at two sites slightly above your knees, one site just below your knees and one site just above your ankles. As stated previously, these regions are considered key skeletal sites since they are susceptible to fracture in individuals with long-standing spinal cord injuries. During pQCT scanning you will lie on your back on a padded table with one leg placed in the bore of the pQCT scanner. We will scan your left and right sides separately. Since this scanner is designed to scan only peripheral sites, such as the legs, no part of the scanner will cover any other part of your body and there will be no sense of claustrophobia, like there could be with a whole-body CT scanner.

The final measurements we will make involve a procedure called motion capture. For these tests we will tape a number of small (5/8” diameter) reflective markers to various parts of you body and we will have you perform FES rowing while we capture the motion of the reflective markers using special digital cameras. We will also record the forces that are created under your feet and in the chain that connects the handle of the rower to the rowing machine. With the motion and force data we will be able to estimate the internal forces that are created within your ankles and knees using three-dimensional computer models. We believe that the magnitude of the estimated forces will provide us with new insights into how skeletal health can be maintained in individuals following a spinal cord injury.

Visit Schedule: Your visits to VA Palo Alto will take place on the following schedule:

- Day 1 visit, lasting 4 to 8 hours
- Day 2 visit, lasting 4 to 8 hours

Women of Childbearing Potential

If you are a woman who is able to become pregnant, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk. If you are pregnant or currently breast feeding, you may not



RESEARCH CONSENT FORM

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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 begin the study after the onset of your next menstrual period. You must agree to avoid sexual intercourse or use a birth control method judged to be effective by the investigator and which will not interfere with the proposed investigation. You must accept the risk that pregnancy could still result despite the responsible use of a reliable method of birth control. You agree to notify the investigator as soon as possible of any failure of proper use of your birth control method, or if you become pregnant, either of which may result in your being withdrawn from the study.

Access to Medical Records:

We may access your medical records in order to identify any medical conditions that could be relevant to the research study and/or which may influence the safety of your participation.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

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



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WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are **free to withdraw** your consent and stop your participation at any time. If you decide to withdraw from the study, you will not lose any benefits to which you would otherwise be entitled.

If you want to stop being in the study you should tell the investigators or study staff. You can do this by phone by calling Dr. Beaupre at (650) 493-5000 extension 64272.

The investigators 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 investigators and/or study staff.
- The investigators decide that continuing your participation could be harmful to you.
- Pregnancy (if applicable).
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

This study involves the following risks, discomforts, and possible inconveniences:

Inconveniences and discomforts:

1. Time required for participation in the study
2. Travel to and from our study site
3. Time lying still for the bone density scans
4. Muscle strain
5. Mild autonomic dysreflexia
6. Increase in neuropathic (“nerve”) pain
7. Increase in spasticity
8. High physical exertion when rowing

Risks:



RESEARCH CONSENT FORM

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Title of Consent: Measuring Motion, Forces, and Bone Density in an Experienced FES-Rower	
Principal Investigator: Gary Beaupre	VAMC: VA Palo Alto HCS

Privacy Risk: Though all possible precautions will be followed to ensure your privacy, there is a very small risk of privacy loss. This could have legal, employment, and social consequences.

Risks of Radiation: This research study involves exposure to radiation from bone density scanners. This radiation exposure is not necessary for your medical care and is for research purposes only. The total amount of additional radiation from all scans combined is approximately equal to 2 days of radiation exposure from natural sources like the sun, ground and water. This amount of radiation involves minimal risk and is necessary to obtain the research information desired.

Risk of a fall during transfer to or from rowing machine: There is a possibility that you may fall while transferring to or from the rowing machine or to or from the table you will lie on while having your bone density scans. The risk of falling can be minimized to a very low level by using safe transfer techniques. You will be required to demonstrate the use of a safe transfer technique during your initial assessment visit.

Soft tissue reaction during FES training: A soft tissue reaction to muscle conditioning and FES-rowing can be associated with several causes. The first is a local reddening of the skin under the electrodes. This reddening is thought to be due to an increase in blood flow beneath the electrode caused by the electrical stimulation. This reddening typically lasts for less than one hour after stimulation is stopped. This reddening is expected to occur to some degree with all participants.

Reddening may also potentially occur as a result of an allergic reaction to the gel used to adhere the surface electrode to the skin. If reddening of the skin persists for much longer than one hour after removal of the electrode, then an allergic reaction is a possible cause. If a participant has an allergic reaction to the gel, we can try a different electrode with a different gel.

The third and final potential skin reaction is reddening suggestive of the initiation of soft tissue breakdown (e.g., a "pressure sore") due to excessive pressure or shear stress. This potential for skin breakdown exists for all individuals who utilize a wheelchair for prolonged periods. To the best of our knowledge no prior FES-rowing participants have experienced a skin breakdown or pressure sore caused by their participation in an FES-rowing program. Nevertheless, before and after each session, we will look for any signs of bruising or swelling that might be suggestive of tissue breakdown, paying particular attention to the shoulders, back, buttocks, upper calves and knee areas.

Serious autonomic dysreflexia during FES training: Autonomic dysreflexia (AD) is a condition which can occur in people who have sustained a spinal cord injury. Autonomic dysreflexia is more common in individuals with tetraplegia (quadriplegia), but it can also



RESEARCH CONSENT FORM

Title of Study: Skeletal Health in the Lower Limbs Following Spinal Cord Injury	
Title of Consent: Measuring Motion, Forces, and Bone Density in an Experienced FES-Rower	
Principal Investigator: Gary Beaupre	VAMC: VA Palo Alto HCS

occur in individuals with paraplegia. Autonomic dysreflexia can be brought on by a variety of stimuli, including a full bladder or bowel, a pressure sore or infection, exercise, or by Functional Electrical Stimulation. Possible symptoms of an AD reaction include:

- Severe headache
- Flushing or blotching of the skin above the level of the spinal cord injury
- Profuse sweating, particularly above the level of the spinal cord injury
- Increased blood pressure
- Decreased heart rate

Generally, an AD reaction will quickly diminish once the initiating stimulus that caused the reaction is removed. To reduce the risk of an AD response, all participants will be encouraged to completely empty their bladder prior to each muscle conditioning or rowing session. The risk of an AD response should also decrease as training progresses and your muscles become conditioned from the electrical stimulation. Thus, the risk of AD is highest during the initial muscle conditioning session. During your first muscle conditioning session we will assess the ability of your muscles to respond to the electrical stimulation and we will pay particular attention to any signs of an AD response. It is possible that an AD response that is greater than mild might be identified at your initial session and that could mean that you are not an acceptable candidate for continuation in the study.

It is important to note that FES-rowing researchers in England and Boston have never had a participant in their FES-rowing programs experience a severe case of AD, and those participants who have experienced mild cases of AD also typically experience mild cases of AD during their everyday lives. Therefore, we believe the risk of experiencing a severe case of AD from participation in this study is very low, although the possibility of experiencing a mild case of AD is higher. At the first sign of an AD response, electrical stimulation will be stopped. Additional medical treatment in the case of a severe AD response will be available in our testing facilities.

It should also be noted that an individual's likelihood of having an AD episode in response to exercising part of the body below the level of a spinal cord injury will be heightened if an individual already has an underlying condition that is perceived by their body as a noxious stimulus. For example, an individual with a bladder infection might be more prone to an AD episode from an additional stimulus, such as Functional Electrical Stimulation of the legs, compared to an individual without a bladder infection. Therefore, it is important that any underlying noxious stimulus that might predispose an individual to an AD response is identified as early as possible and addressed before commencing or continuing with the rowing exercise.

Muscle strain during muscle conditioning, strength testing or FES-assisted rowing: As with participating in any exercise program, there is a risk of experiencing a muscle



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strain. Based on the experience of other researchers with FES-rowing programs, only two out of thirty FES-rowing participants have ever experienced a muscle strain. Muscle strains have never been observed in the lower limbs. For both participants with muscle strains, the strain occurred in the torso, between innervated and paralyzed muscle. These strains were treated by ceasing FES training for 48 to 72 hours and by the use of ice and over-the-counter analgesics. Neither of the two individuals who experienced a muscle strain has had a repeat incident and we believe the risk of a muscle strain is low.

Lower limb fracture during muscle conditioning, strength testing or FES-assisted rowing:

The use of FES to stimulate paralyzed muscles in individuals with SCI has been studied for more than 50 years. Over that 50-year period there have been two reported cases of a fracture related to the use of functional electrical stimulation. One individual fractured their knee cap and a second individual fractured their thigh bone. Although the total number of individuals with SCI who have used functional electrical stimulation to exercise the lower limbs is not known, we believe the risk of a fracture is very low given that there have only been two reported fractures in 50 years of FES use. To further reduce the risk of fracture, only participants who have never experienced a low-energy fracture will be allowed to take part in this study.

Increase in neuropathic (“nerve”) pain or an increase in sensory pain from FES: Some individuals with spinal cord injuries individuals have what is known as neuropathic pain. Neuropathic pain can range from a mild tickling sensation to a severe burning sensation. It is not known what effect, if any, electrical stimulation has on this condition. In addition, some individuals with SCI who retain some sensation in their thighs may find the electrical stimulation to be uncomfortable or even intolerable. If you experience an increase in neuropathic pain to an unacceptable level or if the electrical stimulation produces a sensation which you find unacceptable, it may be necessary for you to withdraw from the study.

Increase in spasticity to an unmanageable level: It is not known what effect FES has on the intensity and frequency of muscle spasticity. In other FES-rowing programs, a few participants have had an increase in spasticity, while some have had a decrease. In general, spasticity levels should be reduced after a muscle conditioning or rowing session, since the muscles will be fatigued. However, if you experience increased spasticity that is unmanageable, it may be necessary for you to withdraw from the study.

Unforeseen Risks: There may be other risks to participating in this study that are not foreseeable.

POTENTIAL BENEFITS



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We cannot and do not guarantee that you will received any benefits from this study. Nevertheless, it is possible that participating in an FES-rowing exercise program may reduce bone loss in parts of your legs. Since the spine and hip DXA scans that we will perform represent a clinical standard by which osteoporosis is assessed, we will provide you with copies of the results of your spine and hip DXA scans which you are free to share with your personal physician, who should be able to help you interpret your bone density results.

Please note that at the present time rowing with FES is not available within the VA clinical facility, and stimulators are not available for distribution outside of research use. However, the VA Palo Alto SCI Center is developing a program to support adaptive rowing under the auspices of recreation therapy, and so in the future there may be opportunities for veterans with SCI to access this program as part of inpatient or outpatient therapy.

ALTERNATIVES

Your alternative is simply to not participate in this study.

PARTICIPANT'S RIGHTS

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

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

We will keep your name and all the information you tell us in this study as confidential as possible. We may publish the results of this study for others to read about, but you will not be identified in any articles about the study by name, social security number, address, telephone number, or any other direct personal identifier. Also, other federal



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agencies as required, such as the VA Office of Research Oversight and the VA Office of the Inspector General may have access to your information.

FINANCIAL CONSIDERATIONS

Payment

You will not be paid to participate in this study.

Costs

There will be no costs to you for any of the treatment or testing done as part of this research study. However, medical care and services provided by the VA that are not part of this study (e.g., normal hospital and prescription expenses which are not part of the research study) may require co-payments if your VA-eligibility category requires co-payment for VA services.

You will not have to pay anything to be in this study, although you will have to provide for your own transportation to and from the VA Palo Alto Campus.

Sponsor

The Department of Veterans Affairs is providing financial support and/or material for this study.

COMPENSATION for Research Related Injury

If you are injured as a direct result of being in this study, medical treatment will be available. If you are eligible for veteran's benefits, the cost of such treatment will be covered by the VA. If not, the cost of such treatments may still be covered by the VA depending on a number of factors. In most circumstances, the treatment must be provided in a VA medical facility. No other form of compensation for injuries is available. However, by signing this form you have not released the VA from liability for negligence. For further information, you may call the Human Protections Administrator at (650) 493-5000, ext. 67593 or the V.A. Regional Counsel at (415) 750-2288.

CONTACT INFORMATION

Questions, Concerns, or Complaints: 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 principal investigator, Dr. Beaupre at (650) 493-5000



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extension 64272. You should also contact him 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, 3000 El Camino Real, Five Palo Alto Square, 4th Floor, Palo Alto, CA 94306..

Appointment Contact: If you need to change your appointment, please contact Dr. Lambach at (650) 493-5000 extension 69411.

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.



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May we contact you (by phone or mail) about future research studies that may be of interest to you? ___ Yes ___ No

Signing your name means you agree to be in this study and that you were given a copy of this consent form.

Signature of Participant Date

Print Name of Participant

Signature of Person Obtaining Consent Date

Print Name of Person Obtaining Consent

*This page separates the
Informed Consent Document (above)
from the
HIPAA Authorization document
(below)*

*To preserve formatting, please
DO NOT DELETE this page*

VA Palo Alto Health Care System – HIPAA Authorization Form

Protocol Title: Skeletal Health in the Lower Limbs Following Spinal Cord Injury

Principal Investigator: Gary Beaupre

Date of Review: October 1, 2013

HIPAA (Health Insurance Portability & Accountability Act) is a federal privacy law that protects the confidentiality of health information collected about you. The following explains how health information collected about you will be used by the investigators and who they may share your health information with as part of this research.

What is the purpose of the research study, and how will my health information be utilized in the study?

In this study we plan to measure the motions, forces and bone density in individuals with more than one-year of experience using FES-rowing exercise program. We plan to use the information obtained in this study to compare to the results in a companion study of individuals with SCI who are not participating in an FES exercise program.

What Personal Health Information Will Be Used or Shared?

The following health information, linked to you by name, address, e-mail address, phone number and/or date of birth, will be used for this research:

- Medical history and physical examination information
- Bone density scans
- Photographs, videotapes, other images

Who May Use or Share Your Health Information?

By signing this document, you allow the following individuals and entities to obtain, use and share your health information for this research study:

- The Principal Investigator, Gary Beaupre, and members of the VA research team.
- Departments within the VA Health Care System responsible for the oversight, administration, or conduct of research.
- The Stanford University Administrative Panel on Human Subjects in Medical Research and other Stanford University Officials responsible for the oversight, administration, or conduct of research.

Who May Receive and Use Your Health Information

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The investigators may share your health information with the following individuals/entities as part of this research study.

- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- The Food and Drug Administration

Health information shared pursuant to this authorization may no longer be protected by Federal laws or regulations and may be further shared by the above individuals/entities who receive the health information.

Do I have to sign this form?

No. Signing this form is voluntary. The VA may not condition treatment, payment, enrollment or eligibility for benefits based on signing this form. If you decide not to sign the form, you will not be able to take part in this study.

If I sign now, can I decide later not to continue in the study?

Yes. You are free to take back your permission and stop being in the study. The investigators will not collect any more information about you after you take back your permission, but they can continue to use your information that was collected before you took back your permission.

Your request to take back your permission must be done in writing. Either give or send your written request to the investigator:

Dr. Gary S. Beaupre
Musculoskeletal Research Laboratory (Mail Code 153)
VA Palo Alto Health Care System
3801 Miranda Avenue
Palo Alto, CA 94304

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Does My Permission for the use my Personal Health Information Expire?

Yes. Your information cannot be used forever. Your permission related to the use and sharing of your health information expires on 12/31/2024.

HIPAA regulations require you to give separate written permission (signature) for the use of your protected health information.

Signature of Participant

Date

Printed Name of Participant