Title: Patterned FES Ergometry of Arm and Shoulder in individuals with Spinal Cord Injury

PI: Cristina Sadowsky

IRB Number: NA_00014481

NCT01005615

16-Sept-2013

Advanced Restoration Therapies in Spinal Cord Injury. Aim1: Patterned FES Ergometry of Arm and Shoulder in Individuals with Spinal Cord Injury.

I. PROTOCOL INFORMATION

Title: Advanced Restoration Therapies in Spinal Cord Injury. Aim1: Patterned FES Ergometry of Arm and Shoulder in Individuals with Spinal Cord Injury.

Protocol No. Sponsor: Opportunity#W81XWH-BAA07-1
ERMS # 08284002
Sponsor: Opportunity #W81XWH-09-2-0186
ERMS #09181006
Local IRB: NA_00014481

Sponsor: Department of Defense (DOD) Telemedicine and Advanced Technology Research Center (TATRC)

IRB of Record: The Johns Hopkins Medicine Institutional Review Boards (JHM IRBs)
Reed Hall B-130
1620 McElderry Street
Baltimore, Maryland 21205-1911
Phone: (410) 955-3008
Fax: (410) 955-4367 or (443) 287-5353

Phase of study: randomized, controlled, single-blinded trial

Version/Date: 11.0, 16-Sept-2013

The protocol will be conducted in accordance with the protocol submitted to and approved by the Office of Research Protections (ORP), Human Research Protection Office (HRPO) and will not be initiated until written notification of approval of the research project is issued by the ORP HRPO.

II. PRINCIPAL INVESTIGATOR'S INFORMATION

PI Name: Cristina Sadowsky, MD
Title: Assistant Professor, Dept. Physical Medicine & Rehabilitation, The Johns Hopkins University School of Medicine
Director,Paralysis Restoration Clinic, Int. Center for Spinal Cord Injury
Research Institution: Kennedy Krieger Institute

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III. ROLES AND RESPONSIBILITIES

a. study team members

All Study Team Members are employed by the International Center for Spinal Cord Injury at the Kennedy Krieger Institute (KKI).

1. Principal Investigator: Cristina Sadowsky, M.D.

The Principal Investigator will be responsible for:

- Compliance with all the requirements of the IRB on Records and the United States Army Medical Research and Materiel Command's (USAMRMC) Office of Research Protections (ORP), Human Research Protection Office (HRPO).
- Performing screening chart review.
- Consenting the research subjects.
- Conducting some of the assessments as listed in section XI.
- Performing the data analysis.

2. Co-Investigator 1: John McDonald, M.D., Ph.D.

Title: Associate Professor of Neurology and Physical Medicine and Rehabilitation, The Johns Hopkins University School of Medicine
Executive Vice President and Director, Int. Center for Spinal Cord Injury

The Co-Investigator 2 will be responsible for:

- Performing screening chart review.
- Consenting the research subjects.
- Conducting some of the assessments as listed in section XI.
- Performing the data analysis.

3. Co-Investigator 2: Albert Recio, M.D.

Title: Faculty Instructor, Physical Medicine & Rehabilitation, Johns Hopkins University School of Medicine
Physician, Paralysis Restoration Clinic, Int. Center for Spinal Cord Injury

The Co-Investigator 3 will be responsible for:

- Conducting data analysis for some of the assessments as listed in section XI, specifically the Severity of gleno-humeral subluxation.

4. Therapist 1: Rebecca Martin, OTR/L, OTD

Title: Manager, Clinical Training and Education, Int. Center for Spinal Cord Injury

The Therapist 1 (T1) will be responsible for:

- Conducting some of the assessments as listed in section XI.
- .
- Performing the data analysis.

5. *Therapist 5: Marjorie Morgan, AD Physical Therapist Assistant*

Title: Physical Therapist Assistant I, Int. Center for Spinal Cord Injury

The Therapist 5 (T5) will be responsible for:
- Conducting the treatment.

6. *Therapist 6: Kim Perone, OTR/L, M.S*

Title: Occupational Therapist I, Int. Center for Spinal Cord Injury

The Therapist 6 (T6) will be responsible for:
- Conducting some of the assessments as listed in section XI.
- Performing the data analysis.
-

7. *Therapist 6: Heidi Nash, OTR/L, M.S*

Title: Occupational Therapist I, Int. Center for Spinal Cord Injury

The Therapist 6 (T6) will be responsible for:
- Conducting some of the assessments as listed in section XI.
- Performing the data analysis.

8. *Therapist 7: Jennifer Silvestri, OTR/L, M.S.*

Title: Occupational Therapist I, Int. Center for Spinal Cord Injury

The Therapist 7 (T7) will be responsible for:
- Conducting the treatment.

9. *Therapist 8: Cara Felter, BS, DPT, MPH*

Title: Physical Therapist IV (Senior), Int. Center for Spinal Cord Injury

The Therapist 8 (T8) will be responsible for:
- Conducting the treatment.

10. *Therapist 7: Scott Meyer.*

Title: Physical Therapist Assistant II, Int. Center for Spinal Cord Injury

The Therapist 9 (T9) will be responsible for:
- Conducting the treatment.

11. *Nurse 1: Charnan Koller, CRRN, AD, BA, MA*

Title: Nurse Clinician, Int. Center for Spinal Cord Injury

The Nurse 1 (N1) will be responsible for:

- Conducting some of the assessments as listed in section XI.

12. Nurse 2: Grethlyn Orr, BSN, MA

Title: Nurse Clinician, Int. Center for Spinal Cord Injury

The Nurse 2 (N2) will be responsible for:
- Conducting some of the assessments as listed in section XI.

13. Nurse 3: Florence Hanssen, RN

Title: Nurse Clinician, Int. Center for Spinal Cord Injury

The Nurse 3 (N3) will be responsible for:
- Conducting some of the assessments as listed in section XI.

14. Study Coordinator 2: Shannon Inches

Title: Research Assistant I (clinical trial), Int. Center for Spinal Cord Injury

The Study Coordinator 2 (SC2) will be responsible for:
- Preparing all regulatory documentation.
- Compliance with all the requirements of the IRB on Records and the United States Army Medical Research and Materiel Command's (USAMRMC) Office of Research Protections (ORP), Human Research Protection Office (HRPO).
- Conducting the screening phone interview.
- Consenting the research subjects.
- Coordinating subject visits.
- Conducting some of the assessments as listed in section XI.
- Holding the randomization sequence.
- Maintaining study data.

15. Medical Monitor: Daniel Becker, M.D.

Title: Assistant Professor, Physical Medicine & Rehabilitation, Johns Hopkins University School of Medicine
Associate Medical Staff, Paralysis Restoration Clinic, ICSCI

The Medical Monitor(MM) will be responsible for:
- Providing medical care to research volunteers for conditions that may arise during the conduct of the study.
- Monitoring the volunteers' medical status during the conduct of the study.
- Reviewing all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event.

16. Other Staff 1: Edward Hammond, M.D., M.P.H.

Title: Research Coordinator II, Int. Center for Spinal Cord Injury

The Other Staff 1 will be responsible for:
- Performing the data analysis.

b. collaborating institutions

Not applicable

IV. SITE INFORMATION

All the research activity will take place at the Broadway& Fairmount campus of the International Center for Spinal Cord Injury (ICSCI) Paralysis Restoration Clinic at the Kennedy Krieger Institute (KKI).

The Kennedy Krieger Institute has a Federal Wide Assurance, FWA00005719, expires 09/26/2016.

The Shoulder X-Ray will be done as fee-for-service at the Radiology Services of the Johns Hopkins Hospital, which is accessible through an underground tunnel from KKI. There is no need for the subjects to organize their own transportation and there is no additional travel cost. A study team member will be available to assist the subject if needed.

V. TABLE OF CONTENT

VI. STUDY INFORMATION

a. Type of Research

This is Specific Aim 1 of Proposal 08284002 titled "Advanced Restoration Therapies inSpinal Cord Injury".

Specific Aim 1: To determine whether functional electrical stimulation promotes neurological and physical recovery in patients with Spinal Cord Injury.
We will investigate the extent of functional recovery in patients with Spinal Cord Injury (SCI) who receive Functional Electrical Stimulation (FES) in the upper extremities compared with patients who do not receive FES.

b. Abstract

Background: Recent evidence suggests that FES can improve certain functions in the Central Nervous System (CNS) following injury or disease; it can enhance motor recovery, change H reflex and flexor reflex excitability [1-3]and enhance sensory function in chronic SCI [4].
Using FES-based therapies in our clinic, we have seen neurological, physical, and functional improvements. By systematically measuring the impact of FES on functional recovery in individuals with spinal cord related paralysis, we hope to greatly advance our clinical application of FES.

Objective/Hypothesis: To test the hypothesis that patterned neural activity induced by FES enhances recovery of function in the injured spinal cord patients with paralysis.

Study Design SA1: A randomized, controlled, single-blinded, in-subject controlled (A-B type) trial will be performed in patients with SCI receiving an upper extremities non-FES assisted exercise protocolcompared with patients receiving upper extremities ergometry in combination with FES. Neurological and functional outcome measures will be obtained at baseline (time 0), after 1st4 months of intervention (4 months), after 1 month washout (5 months),after 2nd 4 months intervention (9 months), and 3 month after completing the last intervention (12 months).

Relevance: The studies proposed here will rigorously test the efficacy of FES-based restorative therapies in promoting neurological and functional recovery in patients with SCI. These findings will be applied in a clinical setting to optimize the FES-based therapies.

VII. STUDY DESIGN

a. Background

Overview:Spinal Cord Injury and related paralysis imposeamajor socioeconomic burden on those afflicted with this devastating neurologic deficit. At the society level, the estimated annual aggregate cost is over 7 billion 1992 US dollars [5]. There is no cure, but bench research data point to neuro-restorative potential of different interventions. Several different reports support the hypothesis that plasticity occurs at the spinal cord level [6-8], and that maintenance of neural activity in injured areas influences the nervous system modeling and repair through different mechanisms: 1) new synapse formation and strengthening of existing ones, 2) re-myelination, 3) new cell birth. Neuronal activity is necessary for the full development and maintenance of inhibitory circuitry [9-21]. Chemical inhibition of neural activity in culture and in animals, results in reduced numbers of inhibitory synapse connections and can result in nervous system over-activity (such as spasticity) once the blockade is partially removed. New synapse formation and stabilization of excitatory synapses may also require coincident neural input to refine connection selectivity and to maintain connections. Re-myelination of axons that have

been de-myelinated secondary to injury is dependent on optimal electrical activity [22]. The strongest evidence is in the peripheral nervous system but strong data also exist in the central nervous system [23-25]. Stem cells exist in the ventricle lining of the brain and spinal cord of adults. These stem cells are capable of birthing new neurons, oligodendrocytes and astrocytes [26, 27]. Patterned neural activity created by enhancing walking activity in rodents can lead to overall greater production and survival of newly born cells [27]. The survival of injured or newly developed neurons and glia has been shown to be partly dependent upon optimal levels of neural activity [28].

Most research groups study the acute phase of injury [29]. ButKennedy Krieger's International Center for Spinal Cord Injury (ICSCI)is developing and applying treatments for long-standing SCI. Its central focus is ***Activity-Based Restoration Therapies (RT)***, [30], which have been shown to reduce the risk of cardiovascular disease and diabetes and to lower the incidence of the medical complications of SCI [4, 30]. However, recent research from our group and others has raised the captivating idea that enhancing activity in regions of the nervous system that become dormant after SCI might be critical for spinal cord regeneration [30, 31]. How does functional electrical stimulation enhance neuro-recovery is not entirely clear, but there is evidence that thesensory afferent input provided by peripheral electricalstimulation provides drive to the spared CNS, altering electrophysiologicalparameters of spinal motor pattern-generating circuitry[32-34], altering amino acid neurotransmitter levels in the spinal cord (glycine and taurine) [35], and altering blood flow, both peripherally and centrally [36,37].Direct electrical stimulation of peripheral neuron cell bodies increasesBDNF and TrkB expression and leads to axonal regeneration [38-41].

To build on our success with clinical trials that combined leg cycle ergometry with FES of paralyzed muscles [4, 31, 42], we propose ***to determine whether FES, a major component of RT, can promote regeneration and functional recoveryby enhancing neural activitythrough external electrical stimulation***. The studies will be performed by field leaders, scientists, clinicians, and therapists in ICSCI's three major divisions, which are housed at the same location. With their collective expertise in clinical care, regeneration research, magnetic resonance imaging, and clinical trials, these experts are superbly equipped to perform all of the *in vitro*, *in vivo*, and imaging studies proposed here and to disseminate RT methodology to military and civilian rehabilitation specialists across the United States.

Specific Aim 1:We will test the hypothesis that ***patterned FES of arm and shoulder muscles, via upper extremity FES ergometry, improves physical and neurological function in subjects with chronic tetraplegia due to SCI***. We propose a 12-month randomized, controlled, A-B type, single-blinded trial in which we test the effect of FES used in combination with an ergometer wheel versus an upper extremities non-FES assisted exercise protocol.
This aim builds on our center's success with comparing FES cycle ergometry to standard physical therapy for chronic SCI. Our preliminary data suggests clinically relevant physical, functional, and neurological recovery. Importantly, we found that FES cycle ergometry 3 hours per week doubled thigh muscle volume, halved thigh fat volume, and increased muscle strength while proportionally reducing spasticity. We also demonstrated clinically significant improvements in sensory and motor functions and functional independence. Also, more than half the FES subjects were able to stop using Baclofen, an anti-spasmodic, and 90% reduced the dosage or switched from polytherapy to monotherapy to control spasticity. Moreover, 40% of FES subjects converted from ASIA A to B, C, or D, despite having injuries more than 2 years old. In stark contrast, the control group exhibited the 4% ASIA A conversion rate that is reported in the literature [42].
We now wish to study upper extremity function, which is a major problem for patients with cervical injury and cannot yet be reliably treated. We propose to measure a battery of physical, functional, and neurological domains that are known to respond to FES cycle ergometry or that relate to the common sequelae of the shoulder dysfunction seen in tetraplegia. FDA approval of a recently developed FES/motor ergometer provides the first real opportunity to pursue this Aim.

Military Significance: Traumatic injury to the Central Nervous System (CNS) is an increasing problem for the U.S. military, given the increasing number of soldiers with SCI returning from combat zones. Our proposed project will address this specific need by developing rehabilitative programs and training tools as well as advanced technologies for restoring nerve cell function. Understanding the underlying mechanisms that promote regeneration and recovery, as outlined in this proposal, will contribute to the knowledge base in the field as well as advance current concepts of regeneration. Overall, the aims of this proposal have direct and indirect relevance to military and related civilian populations.

Public Purpose:SCI is a devastating condition that imposes major costs on individuals and society. Close to 12,000 traumatic injuries occur each year in the United States, and approximately 1 million people live with SCI. Moreover, military personnel have returned from combat zones with SCI in the past years. Estimates for lifetime financial burden per individual range from $500,000 to $2 million, and costs for SCI patient care in the United States exceed $7 billion dollars. Including non-traumatic spinal-cord lesions, such as those associated with multiple sclerosis, would quadruple the number and annual cost of U.S. SCI cases [43]. However, virtually all current treatments must be applied shortly after the onset of SCI, as there are not yet effective treatments for the chronic phase of injury [4]. Effective treatment and therapeutic strategies geared toward the chronic injury phase would both improve the lifestyles of people with SCI and decrease their financial burden.

b. Study Design, Research Objectives

Study Design:A 12 months randomized, controlled, single-blinded, in-subject controlled (A-B type) trial will be performed in patients with SCI receiving upper extremity ergometry in combination with FESversus an upper extremities non-FES assisted exercise protocol. Neurological and functional outcome measures will be used at 0, 4, 5, 9, and 12 months to test the efficacy of each intervention.

Specific Aim: Does FES of the upper extremities promote neurological and functional recovery?

Hypothesis 1: Patterned FES of arm and shoulder muscles, via upper extremity ergometry, will improve physical and neurological function in individuals with paralysis resulting from spinal cord injury.
Expected Result: An FES paradigm involving ergometry of the upper extremities will enhance subjects' functional recovery, as measured in the clinic by neurological and anatomical indices.

VIII. INCLUSION / EXCLUSION CRITERIA

a. Inclusion criteria:

a. Male, Female, age 18-55, all ethnic groups.
b. Spinal Cord Injury, traumatic and non-traumatic.
c. C1-C6 neurological level.
d. ASIA class A or B.
e. Chronic injury,>12 months and < 20 years from the injury.
f. No upper-extremity electrical stimulation in the previous 4 weeks.
g. Subjects are medically stable, with no recent (1 month or less) inpatient admission for acute medical or surgical issues.
h. Baseline physical activity will be kept stable during the study.
i. Pain and antispasticity medications dose will be kept stable during the study.
j. Subjects are legally able to make their own health care decisions.

b. Exclusion criteria:

a. Associated lower motor neuron/peripheral nerve injury in the C1-C6 levels.
b. Presence of pacemaker.
c. Presence of cancer.
d. History of seizures.
e. Women who are pregnant.

IX. SUBJECT RECRUITMENT & SCREENING

a. Subject recruitment & screening:

Recruitment scenario 1:
Patients of the ICSCI, and prior study participantswill be identified as meeting the inclusion criteria by reviewing the medical records held by the ICSCIand filling out a Medical Chart Review Form. A waiver of privacy authorization will be obtained from the local IRB of Record [HIPAA Form4] prior to chart review. Patients will be told about the studyduring a clinical visit;they will be given aSubject Recruitment Flyer with contact information; a note of this communication will be made in the patient's medical record. Those who are interested can meet privately with, or contact later the principal investigator or study coordinator who will explain in simple terms: 1) the purpose of the research and the procedures involved, 2) potential benefits, 3) potential risks, 4) the subject's right to withdraw at any time without penalty of any sort, and 5) assurance of anonymity.If a patient indicates that he/she is no longer interested or is not eligible, the Medical Chart Review Form will be shredded.

Recruitment scenario 2:
Subject Recruitment Flyers will be posted at KKI and outside medical facilities who have agreed to do so. Physicians at KKI and these outside facilities will be provided with a guide to inform them generally of the exclusion/inclusion criteria for the study, and extra copies of the flyer to give out to potential subjects. The Subject Recruitment Flyer will be posted on the ICSCI website (www.spinalcordrecovery.org) and 3rd party websites who have agreed to do so.The Study will also be listed on the newsletter published periodically by ICSCI and KKI. The Study will also be listed on KKI Facebook social networking page (http://www.facebook.com/kennedykrieger)and other social network sites as appropriate.This study will also be registered onwww.clinicaltrials.gov within one year from initial IRB approval.This study can also be posted on and www.centerwatch.com. This study will also advertisedon the KKI on-hold message phone system. This study will be also discussed in an Press Release. All potential subjects who contact us in respond to the recruitment flyers will be called back by the study coordinator to complete a phone screening interview todetermine initial eligibility documented in a Phone Screening Form. A waiver of privacy authorization will be obtained from the local IRB of Record [HIPAA Form4] prior to phone screening interview. The study coordinator will explain in simple terms: 1) the purpose of the research and the procedures involved, 2) potential benefits, 3) potential risks, 4) the subject's right to withdraw at any time without penalty of any sort, and 5) assurance of anonymity. If the potential subject is interested in participating, study coordinator will ask the potential subject questions about his/her medical history. The principal investigator or co-investigators will review the potential subject's medical history to ascertain if inclusion criteria are met and that there are no obvious exclusions. The potential subject will be called back to indicate if they are eligible to participate. If a potential subject indicates that he/she is no longer interested or is not eligible, the Phone Screening Form will be shredded.

For all recruitment scenarios:
If the potential subject meets the inclusion criteria and agrees to participate, the subject will receive a copy of the Informed Consent Form. The potential subject will be allowed as much time as needed (up to 1 month) to

make a decision to participate in the study. In addition, the candidate will be allowed to discuss the study's appointment logistics with their own care providers. Any questions the potential subject has about the study will answered. Once the potential subject agrees to participate, the subject will be enrolled andan initial visit will be set up. The subject consent will be obtained during this initial visit before the post-consent screening is performed.

In the 3 years since opening the International Center for Spinal Cord Injury (ICSCI) in 2005 (05'-08'), we have evaluated and treated over 600 new patients with longstanding SCI (White 63.57%, Black 31.69%, American Indian 0.91%, Hispanic 0.36%, Asian 0.18%, Other 3.28%). Currently we evaluate and treat over 250 new patients annually. Of the new patients with long-standing SCI, 50% are ASIA A and B and of this subgroup, over 10% have a neurological level between C1 and C6. Using projections through 08' and bases of 850 system clients, approximately 85 patients will meet the entry criteria of ASIA A-B, neurological level C1-6 proposed in our study. Furthermore, study entry does not have to be limited to clients already within our ICSCI system. Therefore, based on this availability, we do not anticipate the recruitment of patients to be a substantive barrier to recruitment for this study.

b. Target Population:

We plan to enroll up to 30 subjects with an expected accrued number of subjects of 24 (screening failure of 6). The 24 accrued subjects will be randomized in 2 groups of 12. We are anticipating an attrition rate of 4 subjects maximum.

We plan to enroll both male and female subject, all ethnic groups.
No specific racial or ethnic groups will be targeted by our recruitment process.
Non-English speaking subjects will not be targeted by our recruitment process.

No vulnerable population is specifically targeted by our recruitment process.
Pregnant womenwill be excluded from this study.

c. Recruitment Material:

Subject Recruitment Flyer: form given to ICSCI patients that fit the study criteria during a clinic visit, and posted on the ICSCI website (www.spinalcordrecovery.org).
Inclusion/Exclusion Index Card: Laminated index cards with inclusion/exclusion criteria that physician can carry.
Inclusion/Exclusion Wall Listing: Laminated listing with inclusion/exclusion criteria posted in ICSCI clinic rooms that physician can refer to.
ICSCI & KKI Newsletter: IRB approved language that will be inserted in the ICSCI and KKI Newsletter.
KKI Facebook: IRB approved language that will be inserted on the KKI Facebook page.
KKI On-Hold Phone Message: IRB approved script that will be played on the KKI On-Hold phone system.
ICSCI Press Release: IRB approved press release.

X. INFORMED CONSENT PROCESS

a. Consent Process:

For all eligible participants, informed consent will be obtained at the ICSCI by the PI, Co-Investigator 1, or Study Coordinator during their initial (screening) study visit. The meeting will take place privately in one of the clinic rooms. The informed Consent Form will be read to the subject explaining the following in simple terms:
(1) the criteria for participation.
(2) the purpose of the research and the procedures involved.
(3) the subject's right to withdraw at any time without penalty of any sort.
(4) potential benefits to the subject.
(5) potential risks.
(6) assurance of anonymity.
(7) terms of remuneration.

Questions will be asked about the purpose of the study, procedures, risk and benefits to study participants to assess understanding. All participant questions will be answered and he/she will be asked to sign the consent document in the presence of one of the study team members.

Only individuals that are legally able to make their own health care decisions will be enrolled.

For individuals that do not speak English, a "short form" consent document will be used in conjunction with an oral presentation of the full English version consent form to the subject in his or her language by a translator fluent in both English and the subject's spoken language.

A "short form" is a written document stating that the elements of informed consent required by 45CFR46.116 have been presented to and are understood by the subject or the subject's legally authorized representative. The IRB of Record provides an English version of the "short form" and the following approved translations of the "short form" (Arabic, Chinese, Haitian, Italian, Korean, Polish, Portuguese, Russian, Spanish, Vietnamese).

b. Subject Identification/Randomization:

Once consented and qualified, subject will be assigned a study number in the format "14481nnn", where nnn is a sequential 3 digit number starting with 001.

The randomized sequencewill be generated by using the Web site Randomization.com (http://www.randomization.com) using the Random Block Size method for 24 subjects in two groups.The sequence will be stored electronically in a password-protected document.

The Research Coordinator 1is assigned to:
- Manage the randomized sequence electronic file.
- Assign participants to subgroups according to the randomized sequences.

c. HIPAA Compliance

As per the Local IRB of Record Consent Form Template, the HIPAA compliance/authorization language is included in the Consent Form.

d. Pregnancy:

As per the local IRB of Record, pregnant participants are typically excluded from protocols using ionizing radiation. Also, while there are no known risks to an embryo or fetus associated withFES during pregnancy, this research may hurt an embryo or fetus in ways we do not currently know. For this reason, pregnant women cannot take part in this study. If a woman is capable of having children, shemust have a pregnancy test. The pregnancy test will be performed during the post-consent screening. If the subject become pregnant (or suspect pregnancy) before this study is completed, the subject must inform the study team immediately.

XI. DATA COLLECTION and ANALYSIS

a. Study Procedures

1. *Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).*

The study subjects will engage in an A (upper extremities FES assisted ergometry)-B (upper extremities non-FES assisted exercises) type protocol intervention in which they undergo either 4 months of FES assisted upper extremity ergometry followed by 1 month wash out period, then by 4 months of a specific, individualized, non FES assisted exercise regimen (strengthening, stretching, splinting) or 4 months of an upper extremities non-FES assisted exercise protocol followed by 1 month wash out period, then by 4 months of FES assisted upper extremity ergometry. 12 subjects randomly selected will start with the FES assisted intervention and the other 12 subjects will start with the non FES assisted regimen. FES will be delivered using the RT300-SLSA Cycle Ergometer, Restorative Therapies, Inc.The subjects will be assessed using a battery of physical and neurological indicators before starting the intervention (time 0), after completing first 4 months of intervention (4 months), after the 1 month wash out (5 months), after completing the second 4 month of intervention (9 months) and 3 months after completing the last intervention (12 months).The evaluator will be blinded to group assignment, but we cannot use true blinding due to the intervention's sensory component. The Study Time Line is found in Figure 1.

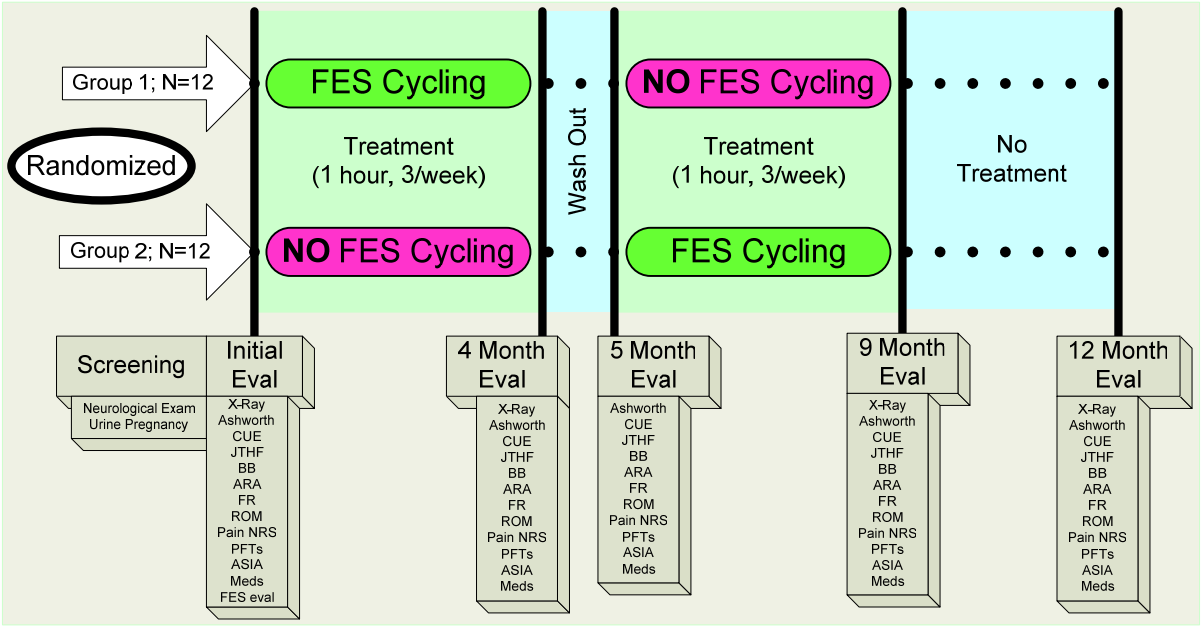

Figure 1: Study Time Line

(1) Assessment:

The tests listed below will be performed for all subjects.The data collection schedule in Table 1.

a) Neurological Exam: This is a routine exam performed to rule out any associated lower motor neuron/peripheral nerve injury in the C1-C6 levels. Subjects will undergo testing of the deep tendon reflexes at the biceps, brachio-radialis and triceps level. This involves tapping of each specified muscle tendon with a neurologic reflex hammer.

b) Fast Urine Pregnancy Test: This is a routine exam performed for women of child bearing age who do not take any birth control prophylaxis.

c) Severity of gleno-humeral subluxation: This is a routine exam performed to assess shoulder subluxation. The space between the glenoid and head of the humerus can be visualized on plain X-rays and measured, in centimeters, to grade severity. This test is done bilaterally.

d) Spasticity measurement: This is a routine exam performed for people with spinal cord injury.The Modified Ashworth Scale assesses muscle resistance to passive movement. The evaluator moves the joint through the available range of motion and assigns a score from 0–4, where 0 is no tone and 4 is fixed limb (ordinal scale, [44]).Subjects are tested in a seated position preferably in their wheelchairs. The subjects' upper extremity is stabilized by the examiner above and below the joint to be tested. Then the joint is quickly moved through the previously determined subjects' maximum range of motion.

e) Capabilities of the Upper Extremity (CUE) test: This is a routine exam performed for people with spinal cord injury.The CUE test is a 32-item interview. It is designed to self-assess upper extremity performance on a 7-point scale (nominal scale, [45]).Subjects are questioned while sitting in their wheelchairs. A brief description of the test will be read to the subjects and then questions asked, one at a time. Subjects will give verbal responses on a 7-point likert scale.

f) Jebsen-Taylor Hand Function(JTHF) test: This is a routine exam performed for people with spinal cord injury.The JTHF test is a 7-item test designed to objectively assess various hand functions and speed of performance (ordinal scale, [46]). Subjects are tested in a seated position, preferably from their wheelchairs, in front of a table. Test items will be laid out on the table and the test conducted per the standardized instructions. The JTHF requires subjects to reach for, lift, and in some cases manipulate small objects.

g) Box and Blocks (BB) test: This is a routine exam performed for people with spinal cord injury.The BB assesses gross hand function (ordinal scale, [47]). Subjects are tested in a seated position, preferably from their wheelchairs, in front of a table. Test items will be laid out on the table and the test conducted per the standardized instructions. The BB requires subjects to reach for, lift, and move one inch cubes across a divider inside a wooden box.

h) Action Research Arm (ARA) test: This is a routine exam performed for people with spinal cord injury.The ARA test observationally assesses upper extremity function (20 items, ordinal scale [57]).Subjects are tested in a seated position, preferably from their wheelchairs, in front of a table. Test items will be laid out on the table and the test conducted per the standardized instructions. The ARA requires subjects to handle objects differing in size, weight and shape.

i) Functional Reach (FR) test: This is a routine exam performed for people with spinal cord injury to evaluate trunk balance. The test is performed by patient reaching forward as far as they can while seated in their wheelchair. The distance traveled by the top of the reference shoulder is measured. 2 practice trials and 1 actual reach test is performed for the purpose of the study.

j) Range Of Motion (ROM)of the upper extremity joints: This is a routine exam performed for people with spinal cord injury.The Range Of Motion of the shoulder, elbow, wrist, and metacarpal-phalangeal joints will be measured via goniometry.Subjects are tested in a seated position, preferably in their wheelchairs. The desired joint is isolated and moved through the maximum available range of motion. Once the end range is reached, joint excursion is measured with a goniometer.

k) Numerical Rating Scale (NRS) for pain: This is a routine exam performed for people with spinal cord injury.Subjects report how much pain they are having by choosing a number from 0 (no pain) to 10 (the worst pain imaginable) (ordinal scale, [48]).

l) Pulmonary Function Test (PFTs): This is a routine exam performed for people with spinal cord injury.Three respiratory functions will be measured. Vital Capacity (VC) is the maximal amount of air that can be exhaled after a maximal inhalation. Negative Inspiratory Force (NIF) is the ability to take a deep breath in and to generate a cough strong enough to clear secretions. Peak Cough Flow (PCF) measures the expiratory muscle force and the ability to cough.

m) American Spinal Injury Association (ASIA) exam: This is a routine exam performed for people with spinal cord injury.The ASIA exam assesses motor function at 10 key muscles in the body and light touch and pinprick sensation at 28 key points on each side of the body. It is also used to classify injury level and severity (ordinal scale, [49]).

n) Pain and Spasticity Medication inventory: This is a routine exam performed for people with spinal cord injury. Pain and antispasticity medications dose will recorded.

o) FES Evaluation: This is a routine exam performed for people with spinal cord injury prior to receiving FES.Therapist 1 or 6 will test the different muscles that are targeted for this study to achieve the best motor response to FES, and maintain subject comfort. Depending on the neurological level of the subject, the muscles are: supraspinatus; infraspinatus; teres major and minor; anterior, middle, or posterior deltoid; biceps; and triceps.

(2) Intervention:

The subjects will be randomly assigned, in a one-to-one ratio, either to group 1, which will first engage in the FES assisted ergometry followed by the non-FES assisted exercise, or to group 2, which will first engage in the non-FES assisted exercise followed by the FES assisted ergometry.

p) FES Upper Extremity Cycle Ergometry: While undergoing the FES assisted ergometry intervention, the subjects will use an RT300-SLSA upper extremity ergometer configured with FES. Electrode placement will be individually optimized to produce smooth cycling, as measured by crank symmetry, average stimulation level, expended energy per hour, and muscle stiffness. Parameters of stimulation current will also be individually optimized to achieve the best motor response (frequency of 10 to 100 Hz, pulse duration of 50 to500 μs, and amplitude of 10 to140 mA). Silver mesh self-adhesive surface electrodes will be used to conduct the stimulation. They will activate some combination of the following muscles,depending on the neurological level at which they are applied: supraspinatus; infraspinatus; teres major and minor; anterior, middle, or

posterior deltoid; biceps; and triceps. Target cycling speed will be 20 rpm, with a resistance of0.965Nm. The subjects will warm up between2 and 10 minutes depending on muscle stiffness or spasms, actively cycle with FES for 1 hour, and cool down of 2 minutes. The ergometer software will be set to provide motor support once muscle fatigue has been reached so the subjects can continue. The subjects will remain seated in their primary wheelchair throughout the treatment. The subjects will cycle for 60 minutes/session, three times a week for 4 months.

q)Non-FES Upper Extremity Exercise: While undergoing the non-FES exercise intervention, the subjects will receive a specific, individualized exercise regimen, consisting of strengthening, stretching, splintingand any other therapeutic interventions that do not use electrical stimulation.. The subjects will remain seated in their primary wheelchair throughout the treatment. The subjects will exercise for 60 minutes/session, three times a week for 4 months.

2. Study duration and number of study visits required of research participants.

The study will last 12 months. The Study Time Line is found in Figure 1, and the Data Collection Schedule in Table 1.

(1) Assessment:

The following post-consent screening will be performed at the Initial visit:

a. Neurological Exam (about 30 minutes)
b. Fast Urine Pregnancy Test (about 15 minutes)

The following assessments will be performed at the Initial Visit:

o. FESEvaluation (about 15 minutes)

The following assessments will be performed at the Initial, 4th month, 9th month, and 12thmonth Visits:

c. Severity of gleno-humeral subluxation (about 30 minutes)

The following assessments will be performed at the Initial, 4th month, 5th month, 9th month, and 12th month Visits:

d. Spasticity measurement (about 15 minutes)
e. Capabilities of the Upper Extremity test (about 10 minutes)
f. Jebsen-Taylor Hand Function test (about 15 minutes)
g. Box and Blocks test (about 15 minutes)
h. Action Research Arm test (about 20 minutes)
i. Functional Reach test (about 5 minutes)
j. Range Of Motion of the upper extremity joints (about 30 minutes)
k. Numerical Rating Scale (NRS) for pain (about 1 minutes)
l. Pulmonary Function Test (PFTs) (about 5 minutes)
m. American Spinal Injury Association (ASIA) exam (about 60 minutes)
n. Pain and Spasticity Medication inventory (about 10 minutes)

	Initial	4th Month	5th Month	9th Month	12th Month	Test Evaluator*	Blinded
	5 hours	4 ½ hours	3 2/3 hours	4 ¼ hours	4 ¼ hours		
Neurological Exam	√					PI, CoI1	No
Fast Urine Pregnancy	√					N1, N2, N3	No
Shoulder X-Ray	√	√		√	√	PI, CoI3	Yes
Modified Ashworth	√	√	√	√	√	PI, CoI1	Yes
CUE	√	√	√	√	√	T1,T6	Yes
JTHF	√	√	√	√	√	T1,T6	Yes
BB	√	√	√	√	√	T1,T6	Yes
ARA	√	√	√	√	√	T1,T6	Yes
FR	√	√	√	√	√	T1,T6	Yes
ROM	√	√	√	√	√	T1,T6	Yes
Pain NRS	√	√	√	√	√	PI, CoI1, SC2	No
PFTs	√	√	√	√	√	N1, N2, N3	No
ASIA	√	√	√	√	√	PI, CoI1	Yes
Meds Inventory	√	√	√	√	√	PI, CoI1, N1, N2, N3, SC2	No
FES Eval	√					T1,T6	No

* PI: Principal Investigator, CoI1: Co-Investigator 1, CoI3: Co-Investigator 3, T1-7: Therapist 1-7, N1: Nurse 1, N2: Nurse 2, N3: Nurse 3, SC2: Study Coordinator2.

Table 1: Data Collection Schedule

(2) Intervention:

There are a total of 96 visits: 48 FES assisted intervention visits scheduled 1 hour, 3 times a week for 4 months, and 48 non-FES assisted exercise regimen visits scheduled 1 hour, 3 times a week for 4 months.

3. Blinding, including justification for blinding or not blinding the trial, if applicable.

The evaluator will be blinded to group assignment for the following assessment, but we cannot use true blinding due to the intervention's sensory component:

c. Severity of gleno-humeral subluxation
d. Spasticity measurement
e. Capabilities of the Upper Extremity test
f. Jebsen-Taylor Hand Function test
g. Box and Blocks test
h.Action Research Arm test
i. Functional Reach test
j. Range Of Motion of the upper extremity joints
m. American Spinal Injury Association (ASIA) exam

4. *Justification of why participants will not receive routine care or will have current therapy stopped.*

All subjects will continue to consistently perform their usual ("baseline") amount of physical activity throughout the study, including performance of lower extremities assisted FES ergometry, home exercise stretching program, cardiovascular conditioning, etc. "Baseline" activity is defined as amount of physical activity performed for at least 1 month prior to enrollment. Routine care will not be interrupted.

5. *Justification for inclusion of a placebo or non-treatment group.*

Both groups will receive some type of intervention: upper extremity passive ergometry or FES assisted upper extremity ergometry. This way, the effect of FES application will be extracted.

6. *Definition of treatment failure or participant removal criteria.*

Treatment failure constitutes of:
- Increased pain (more than 3 points increase on the NRS).
- Increased shoulder subluxation (more than 1 cm).
- Decreased range of motion (more than 15 deg).

Subjects will be removed from the study if they:
- Requires significant hospitalization (that would interfere with physiologic processes proposed to be studied through the protocol, i.e. e-stim) – at the discretion of PI.
- Become pregnant.

7. *Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.*

We will be offering FES assisted upper extremity ergometry through our Open Gym program or, if rehabilitative care requires it, though an ongoing, patient tailored program.

b. Devices

1. *Name of Test Device:*

RT300-SLSA
Manufactured by: Restorative Therapies, Inc
907 South Lakewood Ave
Baltimore, MD 21224
Phone:(800) 609-9166
Fax:(410) 878-2466

2. *Schedule/duration/administration of test device:*

The RT300-SLSA Cycle Ergometer is the only device capable of upper extremity cycle ergometry with and without FES, for use in the study.

The device will be used for 1 hour, three times a week, for 4 month,, by both the FES and Control group.For the Treatment group, the device will be program to delivered synchronized electrical pulses to the upper extremities.For the Control group, the device will be programmed to drive thecycling of the upper extremities.

Device Risk Assessment: The RT300-SLSA cycle ergometer is a motorized system that allow for purely passive, active, or assisted control over leg or arm cycling. The stimulation system is fully integrated with leg and arm motors ("dynamic motor support") with unilateral or bilateral stimulation option, allowing for individualized usage for upper and lower extremities. The systems allow for the individual to remain in his/her wheelchair, insuring easy usage across subjects without transfer of the subjects. The speed of cycling can be changed from zero to sixty revolutions per minute (rev/min) and the load (resistance) can be adjusted from zero to 17 Newton-meters (Nm). The system has numerous safety features, such as muscle spasm detection and arm guides, that make it ideal for use in this study. The system have internet connectivity allowing the retrieval of subject settings and the automatic collection of cycling data, ensuring easy use across subjects in this study.

All the ergometers that will be used for this study will be checked and tagged by Johns Hopkins Hospital Clinical Engineering Services (CES). The local IRB of Record does require an approval letter from CES regarding the use of the device in the study. The approval letter is part of the application to the local IRB of Record.

3. FDA Status:

The device is classified as an external functional neuromuscular stimulator (CFR 882.5810).The device is FDA cleared under section 510(k). The device clearance number is K072398.

The device will be used in a research mode that:
1] allows the stimulation of our proposed list of upper extremity muscles (supraspinatus; infraspinatus; teres major and minor; anterior, middle, or posterior deltoid; biceps; and triceps), which is more that the standard set of muscles (bilateral biceps, triceps and supraspinatus).
2] allows to change the timing of the stimulation (On/Off) to produce a smooth cycling motion.

4. FDA approved use description:

The device FDA indication for use are:
1. Relaxation of muscle spasms
2. Prevention or retardation of disuse atrophy
3. Increasing local blood circulation
4. Maintaining or increasing range of motion

5. IDE Info:

Not applicable

c. Study Statistics

1. Primary outcome variable.

Independent Variables
FES or no FES

Dependent Variables: to be measured at 0, 4, 5, 9 and 12months
Severity of gleno-humeral subluxation, measured by X-ray (not measured at 5 months).
Spasticity of the pectoralis, biceps, triceps, and long finger flexor muscles, measured with the Modified Ashworth.
Functional movement of the shoulder, measured with the Capabilities of the Upper Extremity (CUE) test.

Hand function, measured with the Jebsen-Taylor Hand Function (JTHF) and Box and Blocks (BB) tests.
Upper limb function measured with the Action Research Arm test (ARA) test.
Range Of Motion of the upper extremity joints (of the shoulder, elbow, wrist, and fingers/thumbs), measured with goniometry.
Pain, measured with the Numerical Rating Scale (NRS).
Neurological function, measured with the American Spinal Injury Association (ASIA) exam.

2. Secondary outcome variables.

Not applicable

3. Statistical plan including sample size justification and interim data analysis.

Data Analysis: Data will be collected in accordance with each instrument's standardized instructions, with the evaluator being blinded to group assignment. To obtain consistency and facilitate interpretation of the data, we will use means and standard deviations (SDs) to describe normally as well as non-normally distributed variables. Appropriate post-hoc statistical analysis will be used to compare between group means and repeated measures. Baseline tests of homogeneity will be used *a priori*. If statistically significant differences are found after the subjects are randomized to the two groups, they will be corrected in the post-hoc analysis. Results will be considered significant at $P<0.05$.

Power analysis:Because upper extremity, FES-assisted ergometry training is a new intervention, we based our power analysis on previously completed studies that looked at the effect of FES on muscle mass (50, 51) and cardio-vascular conditioning (52-56). A sample size of 24 will allow us to detect a mean difference between the pre- and post-measures. Some of our outcome measures (CUE, JTHF, BB tests) have been shown to respond to many types of rehabilitative interventions, and we believe they will be particularly responsive to the type of training used here. One of our goals is to use the data obtained in this study to determine the magnitude of the effect so we can design future trials. If the magnitude is very small, however, it is unlikely to be clinically relevant. We would then be more likely to propose intensifying the intervention (e.g., by lengthening the periods of cycling) than to suggest increasing sample size.

4. Early stopping rules.

* Subject medical status:
  - Requires significant hospitalization (that would interfere with physiologic processes proposed to be studied through the protocol, i.e. e-stim) – at the discretion of PI.
  - Increased pain (more than 3 points increase on the NRS).
  - Increased shoulder subluxation (more than 1 cm).
  - Decreased range of motion (more than 15 deg).
* Subject not compliant:
  - Fails to follow directions.
  - Become pregnant.

XII. LABELING & STORAGE OF DATA & SPECIMENS

All paper study documents are stored in locked cabinets at the Broadwaycampus of the KKI-ICSCI. Access to the locked cabinets is strictly limited to the study team members listed on this protocol. The documents with identifiers (such as the consent forms, phone screening forms, and the document that links the subject study # to the identity of the subject) are stored in a study binder in a separate locked cabinet from hard copy data collection forms.

All electronic study documents are saved on KKI-ICSCI departmental shared networked drives, and access is strictly limited to the study team members listed on this protocol. The share drives are managed by KKI's Information Systems Department, and housed in a Data Center at KKI's Green Spring Campus. The Data Center is all Card Swipe and Key Pad protected. Access to the Data Center is strictly limited to Director Level and System Administrators. The Data Center is monitored using APC Data Center Monitoring System. We monitor the location with Camera's that store the Video on a Central Server. We monitor the Data Center for Temperature, Humidity and Water as well. All of the Institute's Data is backed to tape on a daily basis and the Tapes are shipped to Iron Mountain, a Data Storage facility. All of the Data on the tapes is encrypted and very secure. All of the Institute Data is also replicated Real Time to our Disaster Recovery site in Baltimore.

All the procedures listed below will be used to protect the confidentiality of data and samples collected and stored for research purposes:

- Only authorized persons will be granted access
- Only authorized persons may enter and view study data
- Passwords and system IDs will not be shared
- Physical security of the workstations/files will be maintained
- Adequate back-up plan is in effect
- Staff trained on data entry system and importance of security procedures
- Workstations with databases will not be left unattended

Authorized persons include:

- the study team members listed on this protocol.
- QA/QI and other regulatory personnel at KKI and the local IRB of Record.

For compliance with 45 CFR 164.528, the local IRB of Record requires investigators to retain study records, along with records of all disclosures of study information, for the following time periods:
1) At least 7 years after the last subject has completed his or her participation in the study, or
2) The date of the last disclosure of identifiable health information from study records, if disclosures continue after all subjects have completed the study.

Accurate and complete study records will be maintained and made available to representatives of the U.S. Army Medical Research and Materiel Command. These representatives are authorized to review research records as part of their responsibility to protect human research volunteers. Research records will be stored in a confidential manner so as to protect the confidentiality of subject information.

XIII. RISK AND INJURY

a. Risks, Risk Management:

All assessments and intervention sessions will be supervised by the Principal Investigator.

For all the study procedures, the risks and risk management are defined in the sections bellow.

1. Assessment Risks:

a) Neurological Exam: During testing, the subject might experience pain induced by hitting/tapping of the arm, but usually, the sensation experienced is a quick, non-painful touching sensation.To**minimize the risk**,one of the study team member trainedin the procedure will perform the test.

b) Fast Urine Pregnancy Test: There is the possibility of psychological stress occurring if testing shows that the subject may be pregnant. To **minimize the risk** in the event that pregnancy test results are positive, the result will be disclosed to the subject. If the subject is uncomfortable with this arrangement, his/her consent to participate in this study is not recommended.

c) Severity of gleno-humeral subluxation: The subjects receive ionizing radiation due to the diagnosticbilateral shoulder X-ray procedures they receive at the Initial, 4th Month, 9th Month, and 12th Month visit.The Total Effective Dose from the procedures is 0.4 rem.This ismore than the 0.3 rem that the average person in the United States gets each year from natural sources like the sun, outer space, air, food and soil. It is less than the 5 rems of radiation that is allowed each year for people who are exposed to radiation in their jobs.To **minimize the risk**,pregnant women are excluded from the study.

d) Spasticity Measurement: There is a risk of eliciting spasmsduring the test.Subjects will feel a quick pull of the muscle, which might be painful at times.To**minimize the risk**,one of the study team member trainedin the procedure will perform the test.

e) Capabilities of the Upper Extremity (CUE) test: There are no known risks associated with this test.

f) Jebsen-Taylor Hand Function (JTHF) test: Patients may feel some discomfort associated with fatigue in the shoulder, elbow, wrist or hand.To**minimize the risk**,one of the study team member trainedin the procedure will perform the test.

g) Box and Blocks (BB) test: Patients may feel some discomfort associated with fatigue in the shoulder, elbow, wrist or hand.To**minimize the risk**,one of the study team member trainedin the procedure will perform the test.

h) Action Research Arm (ARA) test: Patients may feel some discomfort associated with fatigue in the shoulder, elbow, wrist or hand. To**minimize the risk**,one of the study team member trainedin the procedure will perform the test.

i) Functional Risk (FR) test: Patients may feel anxiety related to loss of balance. To**minimize the risk**, one of the study team member trained in the procedure will perform the test and will position themselves in the direction of the lean so subject does not fall.

j) Range Of Motion (ROM)of the upper extremity joints: Subjects may feel a stretch near the end range, which could be painful.To**minimize the risk**,one of the study team member trainedin the procedure will perform the test.

k) Numerical Rating Scale (NRS) for pain: There are no known risks associated with this measurement.

l) Pulmonary Function Test (PFTs): The risk is minimal for most people. Since the test involves some forced breathing and rapid breathing, patients may have some temporary shortness of breath or light-headedness. Patients breathe through a tight-fitting mouthpiece, and will have nose clips. To**minimize the risk**, one of the study team member trained in the procedure will perform the test.

m) American Spinal Injury Association (ASIA) exam: There is a risk of discomfort at the site of the pin prick during the ASIA Exam.To**minimize the risk**,one of the study team member trainedin the procedure will perform the ASIA exam.

n) Pain and Spasticity Medication inventory: Aside from the risk associated with disclosing personnel or protected health information outside the research study, there are no known risks associated with this measurement.

2. Intervention Risks:

o) FES: The risk associated with FES is pain at the stimulation site. To **minimize the risk**, stimulation will only be done to the participant's tolerance level.There is a minimal risk of skin burn. To further **minimize the risk** of skin burn, only appropriate size electrodes will be used and they will replaced as per the manufacturer's recommendations.

3. Other Risks:

p) Time Commitment: The time commitment to the 3 visits per week for 4 months may be inconvenient. To **minimize the risk**: 1] The subject should contact the study coordinator if having problems scheduling the visits; 2] If we feel that the subject can not commit the time and effort, he/she will be excluded from the study; 3] The visits may cause moderate social, school and work disruption. The start of the study will be scheduled to lessen the disruption.

b. Medical Care For Research Related Injury:

For greater than minimal risk studies, the USAMRMC can commit to providing treatment to research volunteers free of charge in an Army medical facility, therefore the ORP HRPO mandated language shall be included in the consent form.

XIV. BENEFIT(S)

There are no known benefits for those who participate in this study. The possible benefits to the participant from upper extremity FES ergometry include muscle mass and strength increase, muscle tone decrease, cardiovascular conditioning. This study may benefit others in the future by helping understand how upper extremity ergometry with FES might contribute to an improved quality of life for people with cervical spinal cord injuries.

XV. COMPENSATION

a. Payment and Remuneration:

Subjects will be paid a total of $250.00 if they complete the study. Of this amount, $20.00 is a bonus, which the subjects will be eligible to receive if they have shown up on time for all study visits as scheduled, and followed the directions of the study staff.

If the subjects do not finish the study, they will be paid only for the amount completed as follows:
$30.00 for the Initial Visit
$25.00 for the 1st month of FES treatment
$25.00 for the 2nd month of FES treatment
$25.00 for the 3rd month of FES treatment
$25.00 for the 4th month visit
$25.00 for the 5thmonth visit
$25.00 for the 9th month visit
$50.00 for the 12th month visit

Payment will be made by check at the final visit.

b. Costs

There is no cost to study participants for any of the study tests. Subjects will be responsible for the cost of travel to and from the Institute (Valet parking is available at no cost to study participant), as well as any food/meals purchased throughout the day while engaged in study procedures.

XVI. CONFIDENTIALITY

All the procedures listed below will be used to protect the confidentiality of data and samples collected and stored for research purposes:

- Only authorized persons will be granted access
- Only authorized persons may enter and view study data
- Passwords and system IDs will not be shared
- Physical security of the workstations/files will be maintained
- Adequate back-up plan is in effect
- Staff trained on data entry system and importance of security procedures
- Workstations with databases will not be left unattended

Accurate and complete study records will be maintained and made available to representatives of the U.S. Army Medical Research and Materiel Command. These representatives are authorized to review research records as part of their responsibility to protect human research volunteers. Research records will be stored in a confidential manner so as to protect the confidentiality of subject information.

XVII. ADVERSE EVENTS

"Unanticipated problems involving risks to participants or others" is defined as:

- The information is unexpected in terms of nature, severity, or frequency, given: a) the research procedures described in the protocol and informed consent document; and b) the characteristics of the subject population being studied; and
- The information indicates that participants or others are at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized."

All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and subject deaths related to participation in the study should be promptly reported by phone (301-619-2165), by email (hsrrb@det.amedd.army.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZB-PH, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

The Medical Monitor is required to review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the medical monitor must comment on the outcomes of the event or problem and in case of a serious adverse event or death, comment on the relationship to participation in the study. The medical monitor must also indicate whether he/she concurs with the details of the report provided by the principal investigator. Reports for events determined by either the investigator or medical monitor to be possibly or definitely related to participation and reports of events resulting in death must be promptly forwarded to the ORP HRPO.

XVIII. CHANGES TO PROTOCOL

a. Protocol Modifications:

Major modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the USAMRMC ORP HRPO for approval prior to implementation. All other amendments will be submitted with the continuing review report to the USAMRMC ORP HRPO for acceptance.

b. Protocol Deviations:

Any deviation to the protocol that may have an effect on the safety or rights of the subject or the integrity of the study must be reported to the USAMRMC ORP HRPO as soon as the deviation is identified.

XIX. CONTINUING REVIEW & FINAL REPORT

a. Continuing Review Reports:

A copy of the continuing review report for the research study will be submitted to the local IRB of Record. A copy of the approved continuing review report and the local IRB of Record approval notification must be submitted to the ORP HRPO as soon as these documents become available. PI will report progress of the approved research to the local IRB of Record and the ORP HRPO as often as requested, but not less frequently than once per year.

c. Final Study Report:

A copy of the final study report will be submitted to the local IRB of Record. A copy of the approved/accepted final study report and the local IRB of Record approval/acceptance notification will be submitted to the ORP HRPO as soon as these documents become available.

XX. LITERATURE REVIEW

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XXI. Appendix: Study Related Documents

a. Recruitment forms:

Subject Recruitment Flyer:File is "*14481 Subject Recruitment Flyer 2010-09-07.docx*"
ICSCI Newsletter language:File is "*14481 Newsletter language 2010-09-07.docx*"
KKI Facebook page language: File is "*14481 KKI Facebook language 2001-03-24.docx*"
KKI On-Hold phone message: File is "*14481 KKI On-Hold Message 2011-03-23.docx*"
KKI Press Release: File is "*ICSCI DoD Research Release 2011-June.docx*"

Waiver of privacy authorization from the IRB on Record: File is "*14481 HIPAA Form4 2010-09-07.docx*"
Medical Chart Review Form:File is "*14481 Medical Chart Review Form 2010-09-07.docx*"
Phone Screening Form:File is "*14481 Phone Screening Form 2010-09-07.docx*"
Inc/Exclusion Criteria Index Card: File is "*14481 Index Card 2010-09-03.docx*"
Inc/Exclusion Wall Index: File is "*14481 Wall Listing 2010-09-03.docx*"
Cover letter: File is "*14481 Inclusion-Exclusion guide 2010-09-07.docx*"

b. Informed Consent forms:

File is "*14481 Consent Form 2011-06-10.docx*"

c. Case Report Forms:

File is "*14481 Case Report Form 2011-03-24.docx*"
File is "*14481 Test 0 Screening Form 2008-09-15.doc*"
File is "*14481 Test 1 Subluxation 2009-05-01.doc*"
File is "*14481 Test 2 Modified Ashworth 2009-05-01.doc*"
File is "*14481 Test 3 CUE 2009-05-01.doc*"
File is "*14481 Test 4 Jebsen-Taylor 2009-05-01.doc*"
File is "*14481 Test 5 Box & Blocks 2009-05-01.doc*"
File is "*14481 Test 6 ROM 2009-05-01.doc*"
File is "*14481 Test 7 NRS 2009-05-01.doc*"
File is "*14481 Test 8 ASIA 2009-05-01.doc*"
File is "*14481 Test 9 Meds 2009-05-01.doc*"
File is "*14481 Test 10 Functional Reach 2009-05-01.doc*"
File is "*14481 Test 11 PFTs 2009-05-01.doc*"
File is "*14481 Test 12 ARAT 2010-01-15.doc*"
File is "*14481 Test 13 FES Eval 2010-02-18.doc*"
File is "*14481 Payment Form 2010-08-16.docx*"

d. Serious Adverse Event report forms:

Any adverse event is reported to the IRB of record electronically as a Further Study Action(FSA), using the local IRB of Record website (https://e-irb.jhmi.edu).
The report will be printed and forwarded to the ORP HRPO as described in section 0. of this protocol.A template of the IRB Problem/Event Report Form is provided.
File is "*IRB Problem Event Report Form Template.pdf*"

XXII. Appendix: Medical Device Related Documents

The device is FDA cleared under section 510(k). The device, RT300-SLSA, clearance number is K072398. File is "*K072398.pdf*"