VA Department of Veterans Affairs	VA RESEARCH CONSENT FORM

Subject Name: _____ Date: _____

Title of Study: A Neuroprosthesis For Prolonged Standing After SCI Using Multi-Contact Peripheral Nerve Electrodes-Screening and Evaluation Phase I

Principal Investigator: Ronald J. Triolo, Ph.D. VAMC: Cleveland (541)

Consent Version Date: December, 2017

DESCRIPTION OF RESEARCH BY INVESTIGATOR

TO POTENTIAL PARTICIPANTS: Federal regulations require written informed consent before participation in a research study. This is to be certain that research volunteers know the nature and risks of the study, so they can make an informed decision about participation. You are asked to read the following information and discuss it with the investigator, so that you understand this research study and how it may affect you. Your signature on this form means that you have been fully informed and that you freely give your consent to participate. It is also important that you read and understand these principles that apply to all individuals who agree to participate in the research project below:

1. Taking part in the research is entirely voluntary.

2. You may not personally benefit from taking part in the research but the knowledge obtained may help the health care professionals caring for you to better understand the disease/condition and how to treat it.

3. You may withdraw from the study at any time without anyone objecting and without penalty or loss of any benefits to which you are otherwise entitled.

4. If, during your participation in the research project, new information becomes available concerning your condition (disease) or concerning better therapies, which may affect your willingness to continue in the research project, your doctor will discuss the new information with you and will help you make a decision about continuing in the research.

5. The purpose of the research, how it will be done, and what your part in the research will be, is described below. Also described are the risks, inconveniences, discomforts, and other important information, which you need to make a decision about whether or not you wish to participate. You are urged to discuss any questions, concerns, or complaints you have about this research with the research staff members.

Cleveland VAMC IRB approved
the use of this version on 2/13/18

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A description of this study will be available on http://www.ClinicalTrials.gov. 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.

I. PURPOSE OF THE STUDY:

The purpose of this study is to improve the performance of neuroprostheses for standing by developing and testing new advanced methods that use multiple-contact peripheral nerve electrodes to slow the onset of fatigue and increase standing duration. The new advanced methods will take advantage of the ability of multiple-contact nerve cuff electrodes to selectively activate portions of a muscle that perform the same action. Alternating activation to multiple muscles (or parts of the same muscle) rather than continuously activating the entire muscle group constantly should allow them to rest and recover from fatiguing contractions. This should allow users to remain upright for longer periods of time to perform activities of daily living, reduce the risk of falls due to fatigue, and increase the potential of receiving the health benefits of standing.

The device (IRS-8 or IST-16) being studied is experimental. The U.S. Food and Drug Administration (FDA) allows investigational use of the implanted stimulators for limited use in the lower extremities in persons paralyzed from spinal cord injury for research purposes.

This study is supported by the Rehabilitation Research and Development Service of the Veterans Affairs and will take place at the Louis Stokes Cleveland Department of Veterans Affairs Medical Center (LSCVAMC). 100 SCI subjects will be screened. There will be a total of 25 qualifying participants in the implementation phase of the study. Ten of the 25 will be recruited from other studies and already have implanted functional electrical stimulation (FES) systems.

II. DESCRIPTION OF STUDY:

Your participation in this study during the screening phase may take place over several days but should last no more than six weeks depending on your physical and psychosocial status. Screening may take longer depending on your individual circumstances. During the screening and evaluation process you can learn about FES and the research study to help you decide if participation is right for you. In addition, a physical therapist or other member of the research team will be working with you to clarify your personal goals and to identify any physical obstacles to participation.

If you successfully complete the screening and evaluation process as described in this consent form you will be considered for the "Prolonged Standing After SCI Using Multi-Contact Peripheral Nerve Electrode" study. If you have not been previously implanted with an FES device, and you successfully complete the screening and evaluation process, you will be asked to sign a second consent form that will explain surgery, therapy, and all the tests to evaluate standing including follow-up visits.

Subject Name: _____ Date:

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Principal Investigator: Ronald J. Triolo, Ph.D. VAMC: Cleveland (541)

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Screening and Evaluation

Your participation in this screening and evaluation phase of the study is entirely voluntary. You will be asked periodically to describe the study process and your understanding of the risks and benefits of all aspects of the study throughout your participation. You are being considered for this study because you are over 21 years of age, and sustained a spinal cord injury at least 6 months ago resulting in paralysis to the lower extremities.

A study physician and study staff will review your medical history to assure that you meet the inclusion criteria and that you do not have any medical problems that would exclude you from being a candidate.

Pregnant women will be excluded from this study because the effects of electrical stimulation on an unborn child are not known. It is possible that the electrical currents used to stimulate the nerves and muscles of a pregnant woman could affect the health of her developing child. There may be a risk of birth defect, miscarriage or other unanticipated side effect of electrical stimulation during pregnancy. For female volunteers less than 61 years of age pregnancy screening will be done prior to each of the following: motor and sensory evaluation, nerve excitability, cardiovascular and pulmonary evaluation, and movement analysis. A urine test will be used instead of a blood test to decrease the risks of blood draw if no additional laboratory blood tests are being done. Pregnancy testing can be waived if there is acceptable medical evidence of the volunteer's inability to conceive a child. Acceptable evidence includes: proof of surgical sterility such as a tubal ligation or hysterectomy or medically documented evidence of biological sterility.

Determination of candidacy may require evaluation by the candidate's primary care physician (PCP) to determine baseline physical and psychological status and obtain clearance to apply electrical stimulation. These evaluations may include electrocardiograms, radiographs, respirometry, blood chemistry, urine cultures or other clinical tests as indicated. Candidates with brain injuries will be referred to their PCP for neuropsychological evaluation.

In addition to a physical examination and reviewing your medical history, the following evaluations will be done during the screening phase of the study to determine if you would be a good candidate for surgical implantation. Screening will involve a comprehensive review of your medical history and a physical examination to identify any conditions which would rule out your participation in this research study. You may be asked to participate in a number of different tests during the course of this screening evaluation. The specific tests which you may or may not be asked to complete are described below. Each test will be explained before being administered to you. If any incidental findings which affect your general health are discovered during the medical record review or physical exam, the clinical study staff will discuss them with you, and communicate with a physician of your choice for follow-up with your permission.

Motor and Sensory Evaluation:

A doctor or other members of the research team will examine you to assess your current, or "baseline," motor and sensory status. This involves putting your arms and legs in different positions, and asking you to make voluntary movements. If you have sufficient control of your muscles, their strength and endurance will be measured by a special machine called a dynamometer. Similarly, the natural electrical activity of your muscles (the electromyogram, or EMG) will be recorded. EMG recording will be done either with surface or intramuscular electrodes, both of which are commonly used in general medical practice. Surface electrodes are small patches of conductive material that stick to the skin over each muscle to be monitored. Wire electrodes are used when more

specific recording of your muscle activity is required. They are thin, sterile wires that are inserted with a hypodermic needle after the skin has been properly cleaned. They are left in place for the duration of testing and then removed. Test objects will be pressed or brushed against your skin to determine the extent of your sensation. Your reflexes and spasticity will also be evaluated by standard methods such as tendon tapping, moving your joints or EMG recording.

A qualified clinical study staff will perform a physical examination including a full American Spinal Injury Association (ASIA) Impairment Scale Sensory and Motor Evaluation as defined in the International Standards for Neurological and Functioning Classification of Spinal Cord Injury. In addition the motor and sensory exam described, the ASIA involves a rectal exam to measure deep anal pressure awareness necessary to test for intact sensory function and motor sparing.

Nerve Excitability:
The responses of your nerves and muscles to small electrical currents will be tested by applying stimulation to the surface of your skin. A trained therapist or other member of the research staff will conduct these tests. Surface electrodes are small patches (typically 2" x 2") of conductive material that are applied to the surface of the skin, similar to electrodes used to record electrical signals from the heart (the electrocardiogram or EKG). Conductive gels or water will be used to improve the contact between the electrode and the skin surface. One to eight of these electrodes will be applied at a single time to allow the research team to assess the contraction of a single muscle, or to stimulate a group of muscles at the same time. Standing may be tested with surface stimulation as part of the screening process.

If your response to surface stimulation is weak, painful or includes unwanted reflexes, fine wire or thin needle probes will be inserted into your muscles to deliver stimulation. Electrical pulses will be sent through the probes to test whether or not the nerves can be stimulated to produce useful muscle contractions. The wire or needle probes will be removed after the testing is finished. Depending on your level of sensation you may be given a local anesthetic or mild sedative, either by injection or orally.

Stimulation will be applied while you are lying on an examination table, sitting in a chair, or performing an activity such as reaching or standing. To further document the quality of your stimulated contractions, your muscle strength and endurance will be measured with a dynamometer. The naturally occurring electrical activity of other muscles may also be recorded at the same time to further assess your reflexes.

Psychosocial Status:
A psychological evaluation may be conducted in order to assess your eligibility. Due to the various demands of research (e.g. surgical electrode implantation, long periods of waiting, etc.) it may be necessary to determine your potential to cope with the different stresses resulting from participation. These tests and interviews may take several hours. The results of these evaluations will be strictly confidential.

Cardiopulmonary & Metabolic Status:
Evaluation of your cardiovascular and pulmonary systems will be required. These may include cardiac stress tests, EKGs and/or tests of metabolic energy. Metabolic energy testing will require that you breathe through a mask connected to a respiratory gas analyzer. Tests of your lung capacity and breathing function may also be necessary. These evaluations may be applied with or without stimulation.

Movement Analysis:
Baseline information about how you move will be necessary to determine if you will benefit from participation. Movement data can be collected with a system using lightweight markers or other special sensors taped to your skin or clothing. The position of your limbs will be monitored by a video system and the naturally occurring electrical activity of your muscles may be recorded simultaneously as you make various movements or perform activities such as reaching or standing. The markers and recording devices will be removed at the end of the test, which will last no more than two hours. Your face may appear in the video recordings of these sessions. In this case the videos will remain confidential as part of the record of your participation and will not be reproduced or released to anyone else without your permission. Surface stimulation of key muscles may be incorporated during motion analysis to provide investigators with additional information on the potential of stimulation to correct your particular movement problem.

Participation Timeline
If selected for this study, your participation may continue up to 3 years, or longer until study closure (dependent on available funding).

Discontinuation Visit
If you withdraw from the study prior to completion of the screening process, you will not be invited to participate in the Phase II Surgical Implantation and Evaluation. This will not preclude you from re-entering screening and evaluation for participation in this study or future studies.

End of Screening and Evaluation
If you meet all inclusion criteria at the end of Screening and Evaluation and you are a good surgical candidate you will be invited to participate in the development and evaluation of this study by signing another consent form. In the development and evaluation Phase II of this study you will receive an implanted device to provide electrical stimulation to muscles to help you stand.

During the screening process, the study team may identify that you are eligible for other studies or that you may be a better candidate for a different study. You may be referred to other studies.

III. INCONVENIENCES:

Screening may include getting your medical record released to LSCDVAMC if you were treated elsewhere. You may be required to get additional tests if you had medical problems in the past that increase your risk for elective surgery or may affect you r participation in this study. If agreeing to participate in this study, you may be expected to come to the Motion Study Laboratory at the LSCDVAMC as often as three times per week for certain portions of evaluation. Some sessions may take two to four hours to complete. You also need to keep the research team up to date on how to contact you with accurate and current phone numbers and address.

IV. DISCOMFORTS / RISKS / SIDE EFFECTS:

Your participation in this study may involve the following risks:

Adverse sensation

If you have sensation below the level of your spinal cord injury, you may experience discomfort or pain during electrical stimulation while the proper levels of current are being determined. Finding comfortable stimulus parameters should take no more than several minutes per electrode and involves slowly adjusting the stimulation so you can identify tolerable levels. After comfortable levels are found, there should be no additional discomfort or pain when the stimulation is applied.

Burns and electrical hazards

There is a possibility of electrical shock whenever electricity is used to stimulate or to power the instruments necessary to record test results. There is also a possibility of electrical burn. Stimulators and measurement instruments are designed to prevent any current flow at levels that could produce tissue damage to minimize these risks. A safety officer associated with the research group checks all laboratory instrumentation, including stimulation systems, before they are applied.

It is also possible to receive a chemical burn if the material inside the stimulator batteries comes in contact with your skin. The batteries are sealed inside of the external stimulators to minimize these risks.

Risks to the heart and nervous system

There is a risk of heart or nervous system problems such as abnormal rhythms or autonomic dysreflexia (sudden increases in blood pressure) with electrical stimulation. The electrical stimulation used in this study is similar to that routinely used on a therapeutic basis in the general medical practice. If you have had a history of cardiac problems, you should not be a candidate without consulting your cardiologist and informing the research team.

Nerve or vessel injury

If nerve excitability or muscle activity is tested with fine wire or needle probes, the usual dangers of any hypodermic injection are present. These include puncture of a blood vessel, irritation of a nerve or breaking of the needle inside the body. Individuals taking blood-thinning agents such as coumadin or aspirin may have increased risk of bleeding. Although it is possible to injure a nerve during probing, there have been no instances of permanent nerve damage from the procedure.

Skin irritation

The conductive gels and adhesives used with surface electrodes or body-mounted sensors can irritate your skin. You may experience a temporary redness of your skin from either the tapes used to secure surface electrodes or sensors to your body or the heat generated by electrical stimulation. This redness should fade within a few hours of testing and there should be no long-term effects of the heating. There is also a risk of abrasion or pressure from the surface electrodes, sensors, or the straps and pads used to secure your limbs in measurement devices. The research staff will check your skin at regular intervals and discontinue testing if there is any evidence of irritation or potential skin breakdown.

Bone or joint injury

There is a risk of fracture, sprain, and joint or ligament damage during some of the testing procedures. All testing is designed to minimize the stress on the bones, joints, and soft tissues and will be performed by trained professionals experienced with the testing equipment and knowledgeable about the precautions to take while manipulating your extremities. There is also a risk of injury from a fall during maneuvers that might be part of the evaluation procedure, but you will be closely supervised by the research staff.

Metabolic testing

Metabolic testing involves using a nose clip and mouthpiece that might cause claustrophobia or discomfort in some individuals. The metabolic tests will be short and they will be stopped if you find them to be intolerable.

Pregnancy risks

The effects of electrical stimulation on an unborn child or a pregnant woman are unknown. It is possible that the electrical currents used to stimulate the nerves and muscles of a pregnant woman could induce premature labor contractions or a miscarriage, cause a birth defect in the unborn child, or result in other unknown or unanticipated side effects in the unborn child and/or mother. For these reasons, female subjects under the age of 61 years will be screened for pregnancy as explained above under the "DESCRIPTION OF STUDY" section. If you know or suspect you are pregnant, notify a member of the research team immediately."

Blood Draws

The insertion of the needle to draw blood is painful; however, this discomfort is brief. For most people, needle punctures to get blood samples do not cause any serious problems; however, they may cause bleeding, bruising, discomfort, infections, dizziness, or fainting.

Other Discomfort

A qualified clinical study staff will perform the ASIA exam to measure your level of intact movement and sensation. A rectal exam is included to test for sensation and contraction. The clinical study staff will insert a gloved finger into the rectum. This portion of the exam will only take seconds to complete. You may feel a slight momentary discomfort during the test. The exam is not expected to cause any significant pain or damage.

Unanticipated risks

You are being screened to participate in an investigational study, there are unknown risks. The investigators will inform you if any new information that would possibly influence your decision to participate in this study becomes available. On your part, you agree to report any problems that you may have with the study to a member of the research team.

To better analyze and collect baseline information about your physical condition, your screening and evaluation visits may be recorded. Only the research staff will have access to the recordings. Your face may appear in the video recordings of these sessions and you will be asked to sign a VA audiotape/videotape consent form (VA Form 10-3203).

V. BENEFITS:

You will not directly benefit from participating in this study. This program is only in the research stage and this evaluation is to determine your candidacy for various research projects. The procedures described in this consent form will not improve your condition. Your participation may help the investigators develop newer technologies that may help paralyzed people to move and exercise in the future.

VI. ALTERNATIVE PROCEDURE(S) / TREATMENT(S):

You have the alternative to not participate in these screening procedures. This will in no way effect your current treatment, the possibility of future research participation or the availability of FES technology to you as it is further developed.

VII. PRIVACY, CONFIDENTIALITY, AND USE OF RESEARCH RESULTS:

Any information obtained about you in this study will be treated as confidential and will be safeguarded in accordance with the Privacy Act of 1974.

Participation in this study will involve a loss of privacy, but information about you will be handled as confidentially as possible. Your research records will be labeled with a code number. The list that matches your name with the code number will be kept in a locked file in the research team's office. The research records will be kept in a password-protected computer file that only the study team has access to. The paper research records will be kept in a locked filing cabinet in a locked office. Your information will be combined with information from other people taking part in the study. We will write about the combined information we have gathered. Any presentations or publications from this information will not identify you.

VA policy requires us to keep study records indefinitely. However, protections will be put in place to be sure that this information is kept confidential.

By joining this study, you give the investigators your permission for them to collect data from your medical records to determine if you are eligible to participate in the study.
In order to comply with federal regulations, research records identifying you may be reviewed by the following:

- Representatives of the sponsor of this study, Louis Stokes Cleveland VA Medical Center
- Authorized representatives of the LSCDVAMC Institutional Review Board and VA

- Federal Agencies such as the Government Accounting Office (GAO), the Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP)

Because this research involves articles regulated by the FDA, the FDA may choose to inspect and copy medical or research records that identify individual research participants.

VIII. SPECIAL CIRCUMSTANCES:

New Findings

You will be told by the study doctor or Principal Investigator of any significant new findings during the course of the study, which may affect your willingness to continue to participate.

Financial Considerations

Your participation in this portion of the research will be done at no cost to you, nor will you receive any payment for your participation. Some veterans are required to pay co-payments for medical care and services provided by VA. These co-payment requirements will continue to apply to medical care and services provided by VA that are not part of this study.

If you are selected to participate in this study and you agree to participate in the regularly scheduled aspects of this research project, you will receive no special compensation. You will receive no special compensation for participating in the regularly scheduled aspects of this research project required to install, maintain or monitor the performance of the system. You will only be reimbursed for legitimate travel expenses up to a maximum of $2,000.

When you participate in follow-up testing, experiments, teaching sessions or demonstrations other than what is required to install, maintain or monitor the performance of the system, you will receive either $50.00 per session or reimbursement for legitimate travel expenses. You can expect this to be less than $1,000 per year. Total annual reimbursement received greater than $600.00 will be reported to the IRS.

Ending Participation

The investigators may stop your participation in this study without your consent, for example, if they think that it will be in your best interest, if you do not follow the study plan, if you experience a study-related injury, or for any other reason.

Participation in this research project is designed to last for up to three years, or longer until study closure (dependent on available funding). If you know now that you may not be able to participate for this length of time, you should discuss your situation with the investigators. You have the right to refuse to participate in this or any other research study without any negative consequences and you can withdraw from the study at any time. If your muscle strength and fatigue resistance do not increase as expected, you may be asked to withdraw from the study. If you are unable to continue following the prescribed exercise program, including regular visits to the LSCDVAMC, you may be asked to withdraw from the study. If your participation is no longer mutually beneficial to you and the investigators, you may be asked to withdraw from the study.

The implanted system is for your private use only. You should not attempt to demonstrate the system to the media, for payment, or in any official capacity representing the VA, MetroHealth, or Case Western Reserve University without the knowledge or assistance of the investigators and program staff.

If you successfully complete the study, you can retain and continue to use your system as long as the research staff is able to provide continued support and you can comply with routine follow-up and maintenance procedures. If you do not or cannot comply with the laboratory schedule but also do not wish to withdraw from the study, you will be placed on inactive status. This means that you will not stimulate and you must have your implanted system, electrodes and incisions examined regularly by a doctor or research study staff associated with the research project. All equipment (which are not implanted) you receive during the course of participation are on loan to you and must be returned if you withdraw from the study or are placed on inactive status. You will be required to sign a separate document to that effect.

Participation requires a clear mind, normal reaction time, and unimpaired judgment. Use of stimulation while under the influence of any mind-altering drug, including alcohol, heightens the potential risks. In the interest of the welfare of study participants, random drug screening may be performed. Participants testing positive for controlled substances may be retested on a regular basis. Continued positive screening or refusing to be tested is grounds for dismissal from the research project.

Compensation for Research-Related Injury

If you sustain an injury as a direct result of your study participation, medical care will be provided by the LSCDVAMC at no cost to you. Financial compensation for such things as lost wages, disability, or discomfort due to an injury is not available.

Financial Conflict of Interest

This study is being sponsored by grants and awards from the US Department of Veterans Affairs or other agencies. Portions of the salaries of Dr. Triolo and his research team are being paid by these grants. The research team has no financial conflicts of interest with these studies.

Subject Name: _____ Date:

Title of Study: A Neuroprosthesis For Prolonged Standing After SCI Using Multi-Contact Peripheral Nerve Electrodes-Screening and Evaluation Phase I

Principal Investigator: Ronald J. Triolo, Ph.D. VAMC: Cleveland (541)

Consent Version Date: December, 2017

IX.CONTACT INFORMATION

To answer questions about the research or if you sustain a research related injury contact the following:

- During the Day: Ronald J. Triolo, Ph.D.at (216) 791-3800 ext. 4138 or
  Lisa Lombardo, PT at (216) 791-3800 ext. 4909 or
  Dr. Stephen Selkirk at (216) 791-3800 ext. 6076

- After Hours: Lisa Lombardo, PT at (216) 402-0190 or
  page Dr. Stephen Selkirk at (440) 562-0243

For answers to questions about rights as a research participant or to voice a concern or complaint contact the following:

- The Research Administrative Officer at (216) 791-3800 ext. 4657
- The LSCDVAMC Patient Representative at (216) 791-3800 ext. 4026

If you wish to speak with someone other than study staff to provide input concerning the research process, check whether a study is being conducted at the LSCDVAMC, and if study staff are permitted to represent the study contact :

- The LSCDVAMC Institutional Review Board Office at (216) 791-3800 ext. 4658

Subject Name: _____ Date:

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Principal Investigator: Ronald J. Triolo, Ph.D. VAMC: Cleveland (541)

Consent Version Date: December, 2017

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

Dr./Mr./Ms. _____has explained the study to me and answered all of my questions. I have been told of the risks or discomforts and possible benefits of the study. I have been told of other choices of treatment available to me.

I understand that I do not have to take part in this study, and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw from this study at any time without penalty or loss of VA or other benefits to which I am entitled.

The results of this study may be published, but I will not be identified in publications by name, photograph, or other identifiers. My records, including my name and results of my participation, may be revealed as required by laws and regulations of state and federal agencies.

I understand my rights as a subject, and I voluntarily consent to participate in this study. I understand what the study is about and how and why it is being done. I will receive a signed consent form or a photocopy of it. I understand that in signing this consent form I do not waive my legal rights nor release the LSCDVAMC from liability for negligence.

Subject's Signature_____ Date __ / __ /__

Signature of Subject's Representative _____ Date __ / __ /__
(if subject not competent)

Printed name_____

Signature of Person Obtaining Consent_____ Date __ / __ /__

VA RESEARCH CONSENT FORM

Subject Name: _____ Date: _____

Title of Study: A Neuroprosthesis For Prolonged Standing After SCI Using Multi-Contact Peripheral Nerve Electrodes-Implant Phase II

Principal Investigator: Ronald J. Triolo, Ph.D. VAMC: Cleveland (541)

Consent Version Date: December, 2017

DESCRIPTION OF RESEARCH BY INVESTIGATOR

TO POTENTIAL PARTICIPANTS: Federal regulations require written informed consent before participation in a research study. This is to be certain that research volunteers know the nature and risks of the study, so they can make an informed decision about participation. You are asked to read the following information and discuss it with the investigator, so that you understand this research study and how it may affect you. Your signature on this form means that you have been fully informed and that you freely give your consent to participate. It is also important that you read and understand these principles that apply to all individuals who agree to participate in the research project below:

1. Taking part in the research is entirely voluntary.

2. You may not personally benefit from taking part in the research but the knowledge obtained may help the health care professionals caring for you to better understand the disease/condition and how to treat it.

3. You may withdraw from the study at any time without anyone objecting and without penalty or loss of any benefits to which you are otherwise entitled.

4. If, during your participation in the research project, new information becomes available concerning your condition (disease) or concerning better therapies, which may affect your willingness to continue in the research project, your doctor will discuss the new information with you and will help you make a decision about continuing in the research.

5. The purpose of the research, how it will be done, and what your part in the research will be, is described below. Also described are the risks, inconveniences, discomforts, and other important information, which you need to make a decision about whether or not you wish to participate. You are urged to discuss any questions, concerns, or complaints you have about this research with the research staff members.

Subject Name: _____ Date:

Title of Study: A Neuroprosthesis For Prolonged Standing After SCI Using Multi-Contact Peripheral Nerve Electrodes-Implant Phase II

Principal Investigator: Ronald J. Triolo, Ph.D. VAMC: Cleveland (541)

Consent Version Date: December, 2017

A description of this study will be available on http://www.ClinicalTrials.gov . 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.

I. PURPOSE OF THE STUDY:

The purpose of this study is to improve the performance of neuroprostheses for standing by developing and testing new advanced methods that use multiple-contact peripheral nerve electrodes to slow the onset of fatigue and increase standing duration. The new advanced methods will take advantage of the ability of multiple-contact nerve cuff electrodes to selectively activate portions of a muscle that perform the same action. Alternating activation to multiple muscles (or parts of the same muscle) rather than continuously activating the entire muscle group constantly should allow them to rest and recover from fatiguing contractions. This should allow users to remain upright for longer periods of time to perform activities of daily living, reduce the risk of falls due to fatigue, and increase the potential of receiving the health benefits of standing.

The device (IRS-8 or IST-16) being studied is experimental. The U.S. Food and Drug Administration (FDA) allow investigational use of the implanted stimulators for limited use in the lower extremities in persons paralyzed from spinal cord injury for research purposes.

This study is supported by the Rehabilitation Research and Development Service of the Veterans Affairs and will take place at the Louis Stokes Cleveland Department of Veterans Affairs Medical Center (LSCVAMC). There will be a total of 25 qualifying participants in the implementation phase of the study. Ten of the 25 will be recruited from other studies and already have implanted functional electrical stimulation (FES) systems.

II. DESCRIPTION OF STUDY:

Your participation in this study will last approximately 3 years, or longer until study closure (dependent on available funding), with optional yearly exams for your safety.

As a participant in this study, you will be asked to come to the LSCDVAMC for implantation, or surgical implantation may take place at MetroHealth Medical Center. This study involves surgically implanting electrodes to excite the muscles that move your paralyzed legs. These electrodes are connected to a small implanted stimulator/s that deliver of electrical pulses to the nerves. These pulses cause the muscles to contract to perform functional movements or to exercise. One implanted stimulator can activate up to sixteen separate muscles or muscle groups and is generally sufficient for exercise,

You will be required to exercise with surface electrodes prior to implant surgery. These are small patches (typically 2" x 2") of conductive material that are applied to the surface of the skin similar to electrodes used to record the electrical activity of the heart (EKG). Conductive gels or water are often used to improve the contact between the electrode and the skin surface.

Anywhere between two and sixteen of these electrodes may be applied at a single time to exercise the muscles that will receive the implanted electrodes. To prepare for the implant, you will be given a muscle stimulator and instructed about how to exercise with FES at home. The equipment provided to you is on loan and must be returned when you complete the study, discontinue your participation, or are asked to withdraw from the study. You are expected to follow the prescribed home exercise program. The strength and endurance of your muscles may be measured prior to surgery and on a regular basis after implantation with a special machine called a dynamometer.

Three types of stimulating electrodes may be used with the implanted FES system: one is sewn on the muscle, one is inserted into the muscle, and the third is attached directly around a nerve. These three electrodes activate your paralyzed muscles. Another electrode records the natural electrical activity of your muscle, which the system uses to control the stimulation. The type of electrodes chosen for your specific system depends on the pre-surgical testing results and the quality of the stimulated responses from your muscles during the implant procedure. On the wire coming from each electrode is a small connector, which will make it possible to attach it to an implanted stimulator.

All of the electrodes are usually placed at the same time as an implanted stimulator/s, but can also be installed in separate surgical procedures. If necessary the electrodes can be temporarily connected to thin wire leads that come through the skin. When this is the case, you will need to take special precautions to keep the skin exit sites clean and dry until the temporary leads are removed and the electrodes are connected to the implanted stimulator. The surgeon associated with the study has the option to use commercially available protective materials used for tissue repair to cover the connectors. This protective material, such as GoreTex®, AlloDerm® or NeuraWrap™ would help minimize the potential for scar formation and facilitate any revision surgery for repair or revision of the individual system component. Alternatively, the connector pins can be capped to protect them until they are retrieved and connected to the implant.

Prior to implantation, you will provide a comprehensive medical history and will be given a physical examination to identify any conditions that would rule out the surgery. Blood analysis, urine analysis, electrocardiogram (EKG or ECG; a record of the electrical activity of the heart) and a chest X-ray may be required prior to surgery, along with X-rays of your hips, knees, and ankles or a test using equipment called dual-energy x-ray absorptiometry (DEXA) will be used to scan either the neck or lower end of your thigh bone or the upper end of your lower leg bone to assess the strength (mineral density) of your bones.

Surgery

You will be asked to sign an additional informed consent form (the hospital's standard document for any surgery or anesthesia) prior to the operation. You will be admitted to the hospital shortly before the operation (usually the day before) and not be permitted to eat or drink anything the night before surgery. You will be asked to wash with a germicidal soap before surgery, to reduce chances of infection.

Implantation of the stimulator (s) requires a surgical procedure performed in the operating room. The surgery could take up to eight hours. Any temporary lead wires that exit the skin will require special daily care. You will receive written instructions about the care of these leads with your home-going instructions.

These temporary leads will be removed and the electrodes connected to the implanted stimulator in a second surgical procedure once they are no longer needed.

If the surgery cannot be completed in one procedure, a second operation may be necessary. You will receive antibiotics just prior to the surgery and for several days afterwards. You will be given general anesthesia and will be asleep for the entire procedure. Up to 40 incisions ranging from one to approximately six inches in length will be necessary to insert the electrodes and connect them to each stimulator. Incisions for inserting the electrodes will be on the front and back of each leg (upper thigh and/or calf), across the middle of each buttock, and on the lower back on either side of the spine. Two small incisions between the lower rib and the hip on each side will also be necessary to pass the electrode lead wires under the skin from the back of the body so they can be connected to the implant. An incision approximately six inches long will be made in the lower part of the abdomen where the stimulator will be placed under the skin and sewn in place. The connectors between the stimulator and electrodes will be located under separate incisions on the lower abdomen a short distance away from the implant. The incisions will be stitched closed and reinforced with adhesive skin closures. The incisions will be covered with dry sterile dressings. X-rays may be taken to document placement of the stimulator before you leave the operating room. You will then be taken to a recovery room where specially trained nurses will care for you until you are fully awake from the anesthesia.

At the time of the implant, it is necessary to test the responses of the electrodes before securing them in place and connecting them to the stimulator. Selectivity testing may be performed utilizing needle EMG recording electrodes. Electrodes may be installed temporarily and removed if better contractions are obtained at different locations. It may also be necessary to replace an electrode(s) that was installed at an earlier time, or to implant a new electrode(s) to make the system work better. Because of the modular design of the system, old electrodes can be disconnected and removed individually at a later date in a minor surgical procedure. Similarly, new electrodes can be added individually and reconnected to the stimulator at a time after the initial implant.

After the surgery, you will be hospitalized for up to 9 days or until the surgeon clears you for discharge. During this time your system will be checked to make sure that it is working properly. You will be taught how to observe your incisions for signs of infection. After discharge from the hospital, you will have to check your skin and your incisions; and observe your patterns of spasticity for significant increase or decrease as well as changes in the pattern of spasticity (flexion/extension) for up to 6 weeks. You should avoid all activities that might put stress on the incisions and implanted components. You will need to communicate any changes immediately to the research team. If a medical problem is suspected after surgery, your hospital stay may be extended or you may need to be readmitted to the hospital for diagnosis and treatment, which may include removal, replacement or relocation of some of the implanted components.

Information for Women of Childbearing Potential:
If you are a woman of childbearing potential, you must have a negative pregnancy test before any x-rays or surgeries are performed. Since the developing embryo-fetus is very sensitive to the harmful effects of radiation and anesthesia, your x-rays and implant surgery will be cancelled if the test shows that you are pregnant. You will not be able to enter the study while you are pregnant, although you may be re-evaluated for participation at a later time. The requirement for a pregnancy test can be waived if you can provide medical evidence to show that you are unable to conceive a child.

Quality of Life Questionnaire
Before your system is activated, you will be asked to complete a multiple-choice questionnaire called the Spinal Cord Injury-Quality of Life (SCI-QOL). Questions will ask you to rate your overall physical and medical health, emotional health, social participation, and physical functioning. You will be asked to complete the questionnaire again after implantation once you complete the rehabilitation and training phase, to compare against your baseline ratings. The questionnaire may take about one hour to complete each time, but items can be completed over multiple visits.

Rehabilitation and Training:
You will need to return to the Motion Study Laboratory at the LSCDVAMC to begin a supervised period of exercise with the implanted system. You will be given an external controller and instructed about how to safely exercise with stimulation at home. You are expected to follow the prescribed home exercise program which may include contracting the muscles against loads using weights or resistive bands and commercially available exercise equipment. You will not modify it without consulting with the research staff. Based on your pre-implant testing, exercises may need to be done for four to eight weeks prior to further training with the system. Braces may also be fitted to your legs to protect your ankles during this time. Casts of your legs may be necessary to assure proper fitting of the braces.

You will then receive training in the use of the implanted system for functional activities such as standing and pivot transfers starting at about week 14 after implantation. During the training period (weeks 14 - 26 after surgery) you will come to the laboratory several times per week to work with a physical therapist. This may include use of a tilt table, standing frame or support harness. Rehabilitation and training with the implanted system typically requires two to three visits per week during this period. The actual number of visits required varies from individual to individual and could total up to 50 sessions. Progress through the rehabilitation and training program is also highly variable. Your personal progress may be faster or slower than most implant recipients. Training and rehabilitation can range from the usual 12 weeks to as long as 26 weeks in volunteers with weaker responses to stimulation or who do not attend the therapy sessions regularly.

The strength and endurance of your stimulated muscle contractions will be measured on a special machine called a dynamometer made by Biodex Medical Systems, Inc., NY, USA. Your leg will be held in the machine either in one position or your joints will be allowed to move at a constant speed while measuring the strength of the contractions. This will be repeated without much rest time in between contractions to measure how quickly the muscles get tired (fatigue). The electrical activity of your muscles may also be monitored during these tests with surface electrodes or wires inserted under your skin to see how well the implanted system is working.

The functions you will actually be able to perform with the implanted system (exercise, standing, etc.) will depend on how your system is customized to meet your specific needs. Progression through the rehabilitation program may vary depending on many personal factors including your health, social situation, stimulated responses and ability to comply with the exercise and training schedule. If you have strong, fatigue resistant responses to stimulation and tolerate tilt-table training, you should be able to stand with the implanted system in the parallel bars with the assistance of the research staff during the first week of rehabilitation. Balance training in the parallel bars will continue over the next 4 weeks as you progress to standing in a walker. By week 18 most implant recipients are able to stand independently with a walker and ankle braces. Based on the performance and safety with the system demonstrated in the laboratory, you should be able to stand independently in a walker at home at this time.

By week 22, you should be able to use the system to perform standing transfers at home with a walker and personal assistance. By the time you are discharged from the rehabilitation phase of the project (ranging from 26 weeks to almost one year post surgery), you should be able to stand and transfer and/or step by swinging both legs forward at the same time using only a walker and the system. Prior to discharge, the research team will work with you on activities specific to your home environment.

Once you have started training with the implant as described above, you will be asked to participate in additional experiments designed to develop new ways to control and modulate your stimulation patterns to optimize the stability of your posture while standing (Phase III). Before participating in these experiments you will be asked to sign a separate consent form (Phase III - Testing) that describes the laboratory procedures in detail.

Follow-Up Visits

System performance will be checked periodically at least every 6 months after completing the rehabilitation and training program for a period of at least one year. The same testing will be repeated for long-term safety at 3 years post implant. A physical examination will be performed by a qualified clinical study staff, including a full ASIA exam (American Spinal Injury Association Impairment Scale Sensory and Motor Evaluation as defined in the International Standards for Neurological and Functioning Classification of Spinal Cord Injury) to measure motor and sensory impairment. A DEXA scan will also be completed. The ASIA and DEXA will be completed approximately 1 year after discharge from post-implant rehabilitation for a comparison against baseline information. If any incidental findings which affect your general health are discovered during the physical examination, the study clinical staff or designee will discuss them with you and communicate with a physician of your choice for follow-up with your permission. Annual follow-up exams will be conducted thereafter, if you are willing. These routine follow-up examinations include stimulated muscle strength and endurance tests and standing times. In addition, all the assessments described above in Pre-Operative Evaluation will be repeated.

Additional visits may be necessary and will be scheduled if either you or the research team identifies a problem that requires evaluation in the laboratory to diagnose and correct. There will also be videotaped analyses of your ability to stand and transfer with and without electrical stimulation. Your face may appear in the video recordings of these sessions. In this case the videos will remain confidential as part of the record of your participation and will not be reproduced or released to anyone else without your permission. You will be requested to answer

questions related to the performance of your system and your personal impressions of it. You may also be requested to keep a daily log of system use and respond to phone inquiries by the research staff.

Additional Testing

Additional evaluations of the stimulation system will involve tests of how your heart and lungs are working (cardiopulmonary status), the amount of oxygen you consume and the calories you burn during an activity (metabolic energy), and how well you are able to stand, walk or balance (motion analysis). Cardiopulmonary testing involves recording your heart rate, blood pressure and amount of air you breathe while you exercise. Metabolic energy testing will require that you breathe through a mask connected to a respiratory gas analyzer. Information about how you move with the FES system will also be collected with a laboratory motion analysis system. During such a test, lightweight markers or other sensors will be taped to your skin and clothing and you will be asked to sit, stand, reach, balance, step or perform other motions while a computer controls stimulation. You will be asked to move objects with your hands while standing, or to keep your balance while you are gently pushed or pulled in different directions. The markers and other sensors will be removed at the end of the test, which will last no more than two hours.

Some subjects may be asked to participate in separate evaluations of other system functions. If you are selected for such an evaluation, and if you agree to participate, you will sign a separate informed consent form and receive additional training and testing.

Discontinuation Visit

If you withdraw from the study prior to implantation, you will not be invited to participate in Phase III Modulation of Stimulation Patterns & Evaluation. This will not preclude you from re-entering screening and evaluation for participation in this study or future studies.

III. INCONVENIENCES:

Participation in this research is demanding. You will be expected to come to the Motion Study Laboratory at the LSCDVAMC as often as two to three times per week for certain phases of the investigation. While most procedures and tests are shorter, some sessions may take several hours. The implantation procedure requires you to be hospitalized for several days and after discharge to home your activity is limited for six weeks. You will be responsible for monitoring the condition of the incisions and take adequate precautions to insure your safety while using the IMPLANTED system. It is also your responsibility to communicate any problems to the research team in a timely manner. You need to be available for routine checks of your system, and you must keep the research team up to date on how to contact you with accurate and current phone numbers and addresses.

IV. DISCOMFORTS / RISKS / SIDE EFFECTS:

Your participation in this study may involve the following risks:

Discomfort and unpleasant sensations: A qualified clinical study staff will perform the ASIA exam to measure your level of intact movement and sensation. A rectal exam is included to test for sensation and contraction. The clinical study staff will insert a gloved finger into the rectum. This portion of the exam will only take seconds to complete. You may feel a slight momentary discomfort during the test. The exam is not expected to cause any significant pain or damage.

If you have sensation in the areas with paralysis, you may experience discomfort or pain during electrical stimulation while the proper levels of current are being determined. To minimize this discomfort we will slowly increase the stimulation to remain within your comfort level.

Surgery: At the time of implantation the usual risks associated with surgery and the use of anesthesia are present. These include puncture of a vessel and blood loss, irritation of a nerve, pain and bruising, or an adverse reaction to the anesthesia agents. Although it is possible to injure a nerve during implantation, there have been no instances of permanent nerve damage from the implant procedure or from the electrodes themselves. Some muscle tissue is destroyed during surgery. The increases in muscle strength with exercise using electrical stimulation usually compensate for any loss of muscle tissue during implantation. During surgery, monitoring will be accomplished by a qualified anesthesiologist to assure safety. There is a possibility of nerve injury while installing nerve cuff and other electrodes. Nerve damage can lead to pain, burning sensations, sweating, extreme sensitivity to temperature or touch, local heating or cooling, or other changes in the skin, nails, or hair of the affected area. These symptoms can usually be treated effectively with drugs, exercise or other therapies. Squeezing the nerve too tightly can cause a compression injury that can result in numbness, tingling, aches and/or muscle weakness that may last for days or weeks after the surgery. This could also trigger muscle spasms and reflexes that cause stomach upset, dizziness, sweating or other unusual symptoms. This situation can usually be detected during implantation or the first several days after surgery. Removing the pressure usually corrects the condition, such as in carpal tunnel syndrome, and these symptoms usually resolve over time. Accidental damage to a nerve from a scalpel or surgical instrument may also result in permanent loss of sensory or motor function.

Infection: There is the risk that the implanted device(s) could become infected. To reduce the likelihood of infection, special steps (including extensive cleaning of the skin prior to surgery, taking antibiotic medication before and after the operation, and performing the procedure in an operating room) will be taken. As with any other implanted material, there is the risk that the blood can carry bacteria or other infectious agents to the location of the stimulator(s) or electrodes where they can collect and multiply long after the time of surgery. An infection of this type is a known complication for artificial joints and other implants and has occurred once in this study. To reduce the risk of such systemic infections, it is important to seek medical treatment quickly for any cold, flu, or respiratory or viral infection. An aggressive antibiotic treatment would be prescribed to treat the infection and if unsuccessful, the device would be removed in a second surgical procedure. Open wounds, burns or dental cavities should also be treated rapidly since they can be sources of infection. You should also continue to monitor yourself diligently for urinary tract infections or pressure sores, and take the other reasonable precautions required for someone with a spinal cord injury to remain in good health.

Device malfunction: There is a risk that the implant(s), electrodes, connectors or leads could fail to operate properly. If a failure should occur, the investigators will analyze the malfunction and help you decide whether to replace the failed component, leave it in place, or have the entire system removed. There is a potential for interference when using the wireless finger switch; therefore, the user can always employ the buttons on the main controller enclosure as a backup or default alternative if needed.

Tissue erosion: Pressure over the implant(s) or leads could erode the skin and expose the internal components of the system. The implant size is kept as small as possible and edges are tapered to reduce possible mechanical abrasion. The surgical placement of the device(s) and leads is designed to reduce the possibility of erosion by locating them in deeper tissue layers for additional protection. If the tissue were to erode, you will be counseled regarding the nature of the problem and the device or lead would be removed or replaced. The entire device could be removed if deemed appropriate by the surgeon.

If any part of the device is too close to the skin surface, you may notice redness, swelling, or a break in your skin with fluid drainage. If this occurs, it is your responsibility to contact the laboratory staff immediately for counseling and treatment. Treatment may include oral antibiotics, diagnostic X-rays, or surgical removal or replacement of the component.

Burns and electrical hazards
There is a possibility of electrical shock, including electrical burn, whenever electricity is used to stimulate or to power the instruments necessary to record test results. There has been one instance of an electrical burn from a component failure early in the research program. Stimulators and measurement instruments are designed to prevent any current flow at levels that could produce tissue damage. To further minimize these risks, the electrical safety officer associated with the research group will check and certify all experimental set-ups and custom laboratory instrumentation, including stimulation systems for electrical safety before they are applied to you.

Risks to the heart and nervous system
There is a risk of heart or nervous system problems such as abnormal rhythms or autonomic dysreflexia (sudden increases in blood pressure) with electrical stimulation. The electrical stimulation used in this study is similar to that routinely used on a therapeutic basis in the general medical practice. If you have had a history of cardiac problems, you should not be a candidate for FES without consulting your cardiologist and informing the research team.

Nerve or vessel injury
The usual dangers of any hypodermic injection are present at the time the electrodes are inserted. These include puncture of a blood vessel, irritation of a nerve or breaking of the needle in the body. In more than 15 years of experience, there have been no instances of permanent nerve damage from implanted procedure or from electrodes themselves. These risks are extremely small and have not been encountered in the previous applications of this technology.

Nerve cuff electrodes have been associated with nerve compression injuries. There can be several causes for nerve compression: incorrectly sizing the cuff, and external pressure applied by the surrounding tissues to the nerve through the cuff. Nerve compression may not develop for days or weeks after implantation and can change the patterns of spasms, eliminate tendon tap reflexes and diminish the responses of the muscles to stimulation. Compression can also trigger autonomic dysreflexia or other reflexes that cause stomach upset, dizziness, sweating, blood pressure changes, pain, muscle weakness, burning sensations and other unusual symptoms. The nerve can recover from compression with removal of the applied pressure, and symptoms usually resolve over time as in carpal tunnel syndrome. However, high pressure applied for prolonged periods of time can result in permanent nerve damage. At the recommendation of the research team, the device may need to be removed.

Skin irritation
The conductive gels and adhesives used with surface electrodes or body-mounted sensors can irritate your skin. You may experience a temporary redness of your skin from either the tapes used to secure surface electrodes or sensors to your body or the heat generated by electrical stimulation. This redness should fade within a few hours of testing and there should be no long-term effects of the heating. There is also a risk of abrasion or pressure from the surface electrodes, sensors, or the straps and pads used to secure your limbs in measurement devices. The research staff will check your skin at regular intervals and discontinue testing if there is any evidence of irritation or potential skin breakdown.

Pressure sores are a common complication of paralysis, especially spinal cord injury. Almost one-third (33%) of all persons with spinal cord injury can expect to develop pressure sores. Therefore, you are already at risk for developing a pressure ulcer based on your spinal cord injury. There is no evidence that the implanted material increases the risk for pressure sores, and stimulation has been shown to reduce the risks of developing such sores.

Electrode movement and/or breakage: Another risk is that the electrodes could move or break internally. The chance of this occurring depends on the design of the electrode, how it is anchored in the tissue, and the length of time in the body. When an electrode moves away from the nerve it activates, it can stimulate a different muscle, produce an unwanted reflex, cause pain, or result in a weaker contraction. When an electrode breaks, it can no longer conduct electricity and is not effective in producing contraction. The amount of material left behind upon removal will vary, but is usually benign and well tolerated. The body may try to expel a fragment of retained electrode. This is a foreign body rejection reaction and does not indicate the presence of an infection. After migrating to the skin surface, the fragment can be removed and the open sore treated to prevent infection. If a failed electrode significantly compromises standing performance, it can be removed and replaced in a separate surgical procedure.

Scarring: Tissue around the implanted components could become excessively scarred from the surgical procedure or the presence of the implanted material. It is also possible that the application of electrical currents for long periods of time might result in scarring of the tissue. If such scarring interfered with the function of the device(s) or presented a safety problem, you would be informed as soon as possible after the investigators identify the situation. The problem component could then be removed or replaced with your approval. In our experience with human and animal studies involving implanted devices leading up to this study, such tissue changes have never been encountered.

Device rejection: The implanted components are made from materials that have been used in other medical devices and are not toxic or dangerous to the body tissues. They include stainless steel, titanium, platinum and other substances accepted by the FDA for human use. There have been no instances of allergic reactions or toxicity due to the implanted materials in this study to date. It is still possible that your body may reject the device through some yet unknown process. If this were to happen, you will be counseled regarding the nature of the problem and the device would be removed.

Blood pressure changes and muscle fatigue: Dizziness associated with lower blood pressure to your brain can occur while standing or exercising with STIMULATION. You will be instructed to sit down immediately if you begin to feel dizzy. Further attempts to use FES will be made with your consent only after resting and drinking fluids. There have been two instances of fainting reported by subjects in the past for this research program, neither of which was directly related to use of STIMULATION. Neither instance resulted in injury. Fatigue and shortness of breath can result from prolonged walking or strenuous exercise with electrical stimulation. The standing and walking required for these studies has been shown to be well below the threshold for such a response.

Your body can fatigue from prolonged strenuous exercise with electrical stimulation and you might experience shortness of breath. The muscles in your hands, arms and shoulders may tire when standing with stimulation because of the weight placed on your walker, support frame or parallel bars. Any soreness of the muscles in your upper extremities should go away with rest.

Bone or joint injury
Individuals with paralysis generally have weaker bones than able-bodied individuals. Because of this, up to one-quarter (25%) of all persons with SCI may experience a bone fracture at some time after their injury. Therefore, you are already at risk for a bone fracture based on your paralysis. Exercise, weight bearing, and the muscle testing involved in this study may place stresses on your bones that can lead to fractures. Tendons and soft-tissues can also be ruptured by the mechanical stresses produced by FES. To minimize the risk of fracture to your bones or injury to your tendons, it is important for you to follow the exercise program prescribed by the research staff and observe the precautions for safe FES use.

In addition, there is a risk of falling and mechanical injury while exercising, standing, or walking with stimulation. Sprains, joint damage, or other injury from overuse is also possible if you lack sensation in your joints and lower extremities. In similar studies, about 20% of the patients fall during the program. Although falls are common, injuries related to falls are more rare (about 10%).

Metabolic testing
Metabolic testing involves using a nose clip and mouthpiece that might cause claustrophobia or discomfort in some individuals. The metabolic tests will be short and they will be stopped if you find them to be intolerable.

Pregnancy risks
The effects of electrical stimulation on an unborn child or a pregnant woman are unknown. It is possible that the electrical currents used to stimulate the nerves and muscles of a pregnant woman could induce premature labor contractions or a miscarriage, cause a birth defect in the unborn child, or result in other unknown or

unanticipated side effects in the unborn child and/or mother. For these reasons, female subjects under the age of 61 years will be screened for pregnancy as explained above under the "DESCRIPTION OF STUDY" section. If you know or suspect you are pregnant, notify a member of the research team immediately."

Reproductive Health
Pregnancy: The effects of using functional electrical stimulation during pregnancy and on the developing fetus are not known at this time. It is recommended that women of child-bearing potential should not become pregnant during the course of the study. If you do become pregnant you must stop using your stimulation system and notify study personnel as soon as possible.

Radiation exposure
Subjects will undergo procedures involving ionizing radiation exposure in excess of what they would if not enrolled in the study. The various procedures will occur just prior to, and after surgery. Procedures and the number for each are as follows – prior to surgery, 4 X-rays of both hips, knees, and ankles, 2 bone densitometry (DEXA) scans of either the femoral neck, distal femur, or proximal tibia and one chest X-ray (for medical clearance if indicated). During surgery one session of fluoroscopic visualization of the spine will be taken. After surgery, one X-ray of the region of the body from the chest to the mid-thigh will be taken. This radiation exposure is not necessary for your medical care and is for research purposes only. The total amount of radiation each patient will receive in this study is about 5.2 mSv or 520 mrem, and is approximately equivalent to a whole body exposure of 630 days (1.7 years) of exposure to natural background radiation. This use involves minimal risk and is necessary to obtain the research information desired.

Magnetic Resonance Imaging (MRI): You should not have an MRI performed on any part of your body. The implant stimulator and electrodes have not been tested for safety within an MRI machine. You should not have ultrasound imaging or a sonogram applied directly over the implant stimulator. Contact one of the study investigators before scheduling nuclear imaging procedures.

Do not use surface stimulation such as Transcutaneous Electrical Nerve Stimulation (TENS) or Neuromuscular Electrical Stimulation (NMES) without first contacting one of the investigators in this study. There is a risk of inducing current flow through the implanted stimulator that could result in damage to the device. Diathermy, which is a deep tissue heat treatment, should not be performed in the area of the stimulator or electrodes. Contact one of the study investigators before undergoing any surgery near the implant or before undergoing implantation of orthopedic or cardiovascular devices (such as artificial hips or pacemakers). All other surgical procedures that will not take place near implanted devices must be reported.

Blood Draws
The insertion of the needle to draw blood is painful; however, this discomfort is brief. For most people, needle punctures to get blood samples do not cause any serious problems; however, they may cause bleeding, bruising, discomfort, infections, dizziness, or fainting.

Other potential discomforts or risks: Metabolic testing involves using a nose clip and mouthpiece that might cause claustrophobia or discomfort in some individuals. The duration of the metabolic tests will be short (typically less than one hour) and the testing will be discontinued if you find them to be intolerable.

Compartment syndrome describes the death of muscle tissue due to the buildup of large pressures within a limb that prevent blood from flowing. Other studies have shown that exercise with stimulation produces pressures that are within safe ranges and therefore you should not have a greater risk of developing compartment syndrome. Four complaints of lower limb swelling after stimulation have been reported, all of which went away with rest. Another potential risk is that you could develop unreasonable high expectations of the implanted system that may lead to depression if the expectations are not met. As part of the screening process for admission into the project, we repeatedly stress that there is no guaranty that the system will provide any improvement in function. If you should get depressed as a result of this project, you will be referred for counseling.

You may notice that the strength of your spasms increases after using FES to exercise. This is most likely due to an increase in strength and general health of the muscles involved in the spasms. Several users have reported experiencing fewer, but stronger spasms, although no data exist to support this observation. Similar subjective reports suggest that exercise and standing with stimulation does not adversely affect the number or severity of urinary tract infections (UTIs).

Unsupervised use of the system can pose additional risks, especially if you choose to ignore the exercise prescription and general precautions explained to you by the research staff. It is possible to injure yourself by over-using your stimulated muscles. Alternatively, not exercising enough can compromise your strength, endurance, and performance with the implanted system. This may ultimately risk the safety of your heart, bones, joints, and skin. It is your responsibility to follow the guidelines for responsible system use as communicated to you by the research staff and listed in this document.

Some of the SCI-QOL questions focus on personal or difficult topics. You may experience mild discomfort answering these questions, but no significant risks to your health or well-being are anticipated.

Unanticipated risks: There may be as yet unknown, delayed risks that may occur months or years after participating in this research. The investigators will tell you of any new information learned during the course of the study that might cause you to change your mind about continuing your participation.

To better analyze your standing pattern and to collect baseline information about how you stand, you could be videotaped during screening and evaluation visits. Only the research staff will have access to the video(s). Your face may appear in the video recordings of these sessions. You will be asked to sign a VA audiotape/videotape consent form (VA Form 10-3203).

V. BENEFITS:

You will not directly benefit from participating in this study. This program is only in the research stage. Your participation will help the investigators develop newer technologies that may help paralyzed people to move and exercise in the future.

Subject Name: _____ Date:

Title of Study: A Neuroprosthesis For Prolonged Standing After SCI Using Multi-Contact Peripheral Nerve Electrodes-Implant Phase II

Principal Investigator: Ronald J. Triolo, Ph.D. VAMC: Cleveland (541)

Consent Version Date: December, 2017

VI. ALTERNATIVE PROCEDURE(S) / TREATMENT(S):
You have the alternative to not participate in these screening procedures. This will in no way effect your current treatment, the possibility of future research participation or the availability of FES technology to you as it is further developed.

VII. PRIVACY, CONFIDENTIALITY, AND USE OF RESEARCH RESULTS:
Any information obtained about you in this study will be treated as confidential and will be safeguarded in accordance with the Privacy Act of 1974.

Participation in this study will involve a loss of privacy, but information about you will be handled as confidentially as possible. Your research records will be labeled with a code number. The list that matches your name with the code number will be kept in a locked file in the research team's office. The research records will be kept in a password-protected computer file that only the study team has access to. The paper research records will be kept in a locked filing cabinet in a locked office. Your information will be combined with information from other people taking part in the study. We will write about the combined information we have gathered. Any presentations or publications from this information will not identify you.

VA policy requires us to keep study records indefinitely. However, protections will be put in place to be sure that this information is kept confidential.

By joining this study, you give the investigators your permission for them to collect data from your medical records to determine if you are eligible to participate in the study. In order to comply with federal regulations, research records identifying you may be reviewed by the following:

- Representatives of the sponsor of this study, Louis Stokes Cleveland VA Medical Center
- Authorized representatives of the LSCDVAMC Institutional Review Board and VA
- Federal Agencies such as the Government Accounting Office (GAO), the Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP)

Because this research involves articles regulated by the FDA, the FDA may choose to inspect and copy medical or research records that identify individual research participants.

If any incidental findings which affect your general health are discovered during medical record review or physical exam, the clinical study staff will discuss them with you and communicate with a physician of your choice for follow-up with your permission.

VIII. SPECIAL CIRCUMSTANCES:

New Findings:
You will be told by the study doctor or Principal Investigator of any significant new findings during the course of the study, which may affect your willingness to continue to participate

Financial Considerations

Your participation in this research study will be done at no cost to you, nor will you receive any payment for your participation. Some veterans are required to pay co-payments for medical care and services provided by VA. These co-payment requirements will continue to apply to medical care and services provided by VA that are not part of this study.

If you are selected to participate in this study and you agree to participation in the regularly scheduled aspects of this research project, you will receive no special compensation. You will receive no special compensation for participating in the regularly scheduled aspects of this research project required to install, maintain or monitor the performance of the system. You will only be reimbursed for legitimate travel expenses up to a maximum of $2,000.

When you participate in follow-up testing, experiments, teaching sessions or demonstrations other than what is required to install, maintain or monitor the performance of the system, you will receive either $50.00 per session or reimbursement for legitimate travel expenses. You can expect this to be less than $1,000 per year.

Total annual reimbursement received greater than $600.00 will be reported to the IRS.

Ending Participation

The investigators may stop your participation in this study without your consent, for example, if they think that it will be in your best interest, if you do not follow the study plan, if you experience a study-related injury, or for any other reason.

Participation in this research project is designed to last for up to three years or longer until study closure (dependent on available funding), with optional yearly exams for your safety. If you know now that you may not be able to participate for this length of time, you should discuss your situation with the investigators. You have the right to refuse to participate in this or any other research study without any negative consequences and you can withdraw from the study at any time. If your muscle strength and fatigue resistance do not increase as expected from the treatment, you may be asked to withdraw from the study. If you are unable to continue following the prescribed exercise program, including regular visits to the LSCDVAMC, you may be asked to withdraw from the study. If your participation is no longer mutually beneficial to you and the investigators, you may be asked to withdraw from the study.

The implanted system is for your private use only. You should not attempt to demonstrate the system to the media, for payment, or in any official capacity representing the VA, MetroHealth, or Case Western Reserve University without the knowledge or assistance of the investigators and program staff.

If you successfully complete the study, you can retain and continue to use your implanted system as long as the research staff is able to provide continued support and you can comply with routine follow-up and maintenance procedures. If you do not or cannot comply with the laboratory schedule but also do not wish to withdraw from the study, you will be placed on inactive status. This means that you will not stimulate and you must have your implanted system, electrodes and incisions examined regularly by a doctor or research study staff associated with

the research project. All equipment (which are not implanted) you receive during the course of participation are on loan to you and must be returned if you withdraw from the study or are placed on inactive status. You will be required to sign a separate document to that effect.

Stimulation requires a clear mind, normal reaction time, and unimpaired judgment. Use of FES while under the influence of any mind-altering drug, including alcohol, heightens the potential risks. In the interest of the welfare of study participants, random drug screening may be performed. Participants testing positive for controlled substances may be retested on a regular basis. Continued positive screening or refusing to be tested is grounds for dismissal from the research project.

Compensation for Research-Related Injury

If you sustain an injury as a direct result of your study participation, medical care will be provided by the LSCDVAMC at no cost to you. Financial compensation for such things as lost wages, disability, or discomfort due to an injury is not available.

Financial Conflict of Interest

This study is being sponsored by grants and awards from the US Department of Veterans Affairs and other agencies. Portions of the salaries of Dr. Triolo and his research team are being paid by these grants. The research team has no financial conflicts of interest with these studies.

Subject Name: _____ Date:

Title of Study: A Neuroprosthesis For Prolonged Standing After SCI Using Multi-Contact Peripheral Nerve Electrodes-Implant Phase II

Principal Investigator: Ronald J. Triolo, Ph.D. VAMC: Cleveland (541)

Consent Version Date: December, 2017

IX.CONTACT INFORMATION

To answer questions about the research or if you sustain a research related injury contact the following:

- During the Day: Ronald J. Triolo, Ph.D.at (216) 791-3800 ext. 4138,
  Lisa Lombardo, PT at (216-791-3800 ext. 4909 or
  Dr. Stephen Selkirk at (216) 791-3800 ext. 6076

- After Hours: Lisa Lombardo, PT at (216) 402-0190or
  page Dr. Stephen Selkirk at (440) 562-0243

For answers to questions about rights as a research participant or to voice a concern or complaint contact the following:

- The Research Administrative Officer at (216) 791-3800 ext. 4657
- The LSCDVAMC Patient Representative at (216) 791-3800 ext. 4026

If you wish to speak with someone other than study staff to provide input concerning the research process, check whether a study is being conducted at the LSCDVAMC ,and if study staff are permitted to represent the study contact :

- The LSCDVAMC Institutional Review Board Office at (216) 791-3800 ext. 4658

Subject Name: _____ Date:

Title of Study: A Neuroprosthesis For Prolonged Standing After SCI Using Multi-Contact Peripheral Nerve Electrodes-Implant Phase II

Principal Investigator: Ronald J. Triolo, Ph.D. VAMC: Cleveland (541)

Consent Version Date: December, 2017

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

Dr./Mr./Ms. _____has explained the study to me and answered all of my questions. I have been told of the risks or discomforts and possible benefits of the study. I have been told of other choices of treatment available to me.

I understand that I do not have to take part in this study, and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw from this study at any time without penalty or loss of VA or other benefits to which I am entitled.

The results of this study may be published, but I will not be identified in publications by name, photograph, or other identifiers. My records, including my name and results of my participation, may be revealed as required by laws and regulations of state and federal agencies.

I understand my rights as a subject, and I voluntarily consent to participate in this study. I understand what the study is about and how and why it is being done. I will receive a signed consent form or a photocopy of it. I understand that in signing this consent form I do not waive my legal rights nor release the LSCDVAMC from liability for negligence.

Subject's Signature_____ Date __ / __ /__

Signature of Subject's Representative _____ Date __ / __ /__
(if subject not competent)

Printed name_____

Signature of Person Obtaining Consent_____ Date __ / __ /__

VA Department of Veterans Affairs	VA RESEARCH CONSENT FORM

Subject Name: _____ Date: _____

Title of Study: A Neuroprosthesis For Prolonged Standing After SCI Using Multi-Contact Peripheral Nerve Electrodes-Modulation of Stimulation Patterns- Phase III Testing

Principal Investigator: Ronald J. Triolo, Ph.D. VAMC: Cleveland (541)

Consent Version Date: December, 2017

DESCRIPTION OF RESEARCH BY INVESTIGATOR

TO POTENTIAL PARTICIPANTS: Federal regulations require written informed consent before participation in a research study. This is to be certain that research volunteers know the nature and risks of the study, so they can make an informed decision about participation. You are asked to read the following information and discuss it with the investigator, so that you understand this research study and how it may affect you. Your signature on this form means that you have been fully informed and that you freely give your consent to participate. It is also important that you read and understand these principles that apply to all individuals who agree to participate in the research project below:

1. Taking part in the research is entirely voluntary.

2. You may not personally benefit from taking part in the research but the knowledge obtained may help the health care professionals caring for you to better understand the disease/condition and how to treat it.

3. You may withdraw from the study at any time without anyone objecting and without penalty or loss of any benefits to which you are otherwise entitled.

4. If, during your participation in the research project, new information becomes available concerning your condition (disease) or concerning better therapies, which may affect your willingness to continue in the research project, your doctor will discuss the new information with you and will help you make a decision about continuing in the research.

5. The purpose of the research, how it will be done, and what your part in the research will be, is described below. Also described are the risks, inconveniences, discomforts, and other important information, which you need to make a decision about whether or not you wish to participate. You are urged to discuss any questions, concerns, or complaints you have about this research with the research staff members.

Cleveland VAMC IRB approved the use of this version on 2/13/18

Subject Name: _____ Date:

Title of Study: A Neuroprosthesis For Prolonged Standing After SCI Using Multi-Contact Peripheral Nerve Electrodes- Modulation of Stimulation Patterns- Phase III Testing

Principal Investigator: Ronald J. Triolo, Ph.D. VAMC: Cleveland (541)

Consent Version Date: December, 2017

A description of this study will be available on http://www.ClinicalTrials.gov. 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.

I. PURPOSE OF THE STUDY:

The primary objective of this study is to improve the performance of neuroprostheses for standing by developing a method for advanced stimulation that use multi-contact peripheral nerve electrodes to delay fatigue and prolong standing duration. The Specific aims of this study are:

1) Establish the clinical feasibility of new stimulation patterns for prolonged muscle force production in subjects with spinal cord injury (SCI).
2) Develop methods to tune stimulation patterns to maximize performance.
3) Demonstrate improved functional outcomes including standing duration, body weight distribution, subjective and objective measures of stability.

You have been invited to participate in Phase III of this study because:

- You have successfully completed the preliminary screening phase of the research study.
- You have an implanted neuroprosthesis to assist in your standing.

Neuroprostheses for standing after SCI currently rely on continuous activation of the hip and knee extensor muscles, which results in rapid fatigue and ultimately compromises elapsed standing time. The primary objective of this study is to improve the performance of neuroprostheses for standing by developing and implementing advanced stimulation patterns that use multi-contact peripheral nerve electrodes to delay fatigue onset and prolong standing duration. The new stimulation patterns will take advantage of the ability of multi-contact nerve cuff electrodes to selectively activate independent portions of a muscle, or independent muscles that perform the same action. Stimulation waveforms that alternate activation to multiple muscles (or parts of the same muscle), rather than continuously activate the entire muscle group constantly, should allow muscles to rest and recover from fatiguing contractions. This should allow users to remain upright for longer periods of time to perform activities of daily living, reduce the risk of falls due to fatigue, and increase the potential of receiving the health benefits of standing.

II. DESCRIPTION OF STUDY:

Your participation in this study will last approximately 3 years or longer until study closure (dependent on available funding).

As a participant in this study, you will be asked to come to the LSCDVAMC. You will be asked to participate in a number of different tests during the course of this investigation. These will be combined with your participation in Phase II of this study when you are training with the system unless you have already completed your training. You may not need to participate in each test. The investigators will describe in detail the time commitment required for each test for which you volunteer. Some tests can be performed in one session lasting several hours,

while others will be distributed over several weeks. Your sessions will last for several hours and there will not be more than 3 sessions per week. These sessions will overlap with your participation in Phase II of the study. The specific tests that are completed are described below which you may or may not be asked to complete during study participation. Each test that may apply to you will be explained prior to testing.

Motor and Sensory Evaluation:
A doctor or other members of the research team will examine you to assess your current, or "baseline," motor and sensory status. This involves putting your arms and legs in different positions, and asking you to make voluntary movements. If you have sufficient control of your muscles, their strength and endurance will be measured by a special machine called a dynamometer. Similarly, the natural electrical activity of your muscles (the electromyogram, or EMG) will be recorded. EMG recording will be done either with surface or intramuscular electrodes, both of which are commonly used in general medical practice. Surface electrodes are small patches of conductive material that stick to the skin over each muscle to be monitored. Wire electrodes are used when more specific recording of your muscle activity is required. They are thin, sterile wires that are inserted with a hypodermic needle after the skin has been properly cleaned. They are left in place for the duration of testing and then removed. Test objects will be pressed or brushed against your skin to determine the extent of your sensation. Your reflexes and spasticity will also be evaluated by standard methods such as tendon tapping, moving your joints or EMG recording.

Electrical Stimulation:
Since you have already participated in a lower extremity FES research project, you may have had stimulating electrodes implanted in some of your lower extremity muscles. Your existing electrodes will be tested in this new series of studies. If the investigators need information on muscles that are not already implanted, surface stimulation will used. In this case you will be given a surface stimulator and all necessary supplies and instructed in their use. You will be taught the proper procedures for positioning and attaching stimulating electrodes to the surface of the skin, as well as the proper precautions for monitoring the condition of the skin under the electrodes.

You will be placed on an electrical stimulation exercise program and the strength of your muscles will be evaluated on a regular basis. You will be instructed about FES exercise at home and will follow the prescribed home exercise program, which may include resistive exercises using weights or resistive bands and commercially available exercise equipment. You should not modify the exercise program without consulting the research staff.

Development of Advanced Stimulation Patterns:
Once training is completed, we will begin to develop advanced stimulation patterns to delay fatigue of the knee extensor muscles. This will be a three step process. First stimulation parameters will be chosen to produce a strong muscle contraction with little or no overlap between contacts in the electrodes. Next patterns must be tuned to develop the desired joint torque. The final step will be to record the joint torque during each stimulation pattern. To accomplish the above steps you will be asked to sit on a special machine called a dynamometer that is routinely used during physical rehabilitation to measure the position, speed and strength of muscle contractions.

A computer program will set up the best stimulation to each contact. These three steps can be completed in five-two hour long sessions.

Muscle Strength and Endurance Testing

Several measurements will be taken to describe the status of your electrodes, muscles, and joints before testing begins. These include passively moving the joint to determine its range of motion (ROM), testing of reflexes by tapping the tendon, and collection of pertinent information regarding your history of medical treatment for bone, joint or muscle problems. The strength and endurance of your stimulated muscle contractions will be measured on a special machine called a dynamometer that is routinely used during physical rehabilitation to measure the position, speed and strength of muscle contractions. Your limbs will be secured in the dynamometer by pads and straps that will be adjusted to be comfortable while maintaining close contact with the testing machine. Active (stimulated) strength and endurance will be measured with your legs or trunk fixed at various angles or while moving at constant speeds similar to those produced by standing up and sitting down. Strength tests will involve a small number of repetitions at maximal effort with ample rest in between (typically three sets of 10 repetitions or less). Endurance testing involves repeated contractions for several minutes with little time for rest. In addition to these active measurements, your joints may also be moved passively (without stimulation) by the testing machine to determine their natural stiffness and flexibility. These tests will be done with each of the advanced stimulation patterns and compared with continuous stimulation.

Standing Duration and Body Weight Distribution

Each or the advanced stimulation patterns will be evaluated for function and compared to continuous stimulation. Functional ability will be tested during the Standing Duration and Body Weight distribution test. You will be asked to use your FES system to rise from the seated position and stand in a special set of parallel bars or using an instrumented walker. You will remain standing with your feet on the force plates and one hand on each parallel bar or walker handle until one of your knees fatigues or you decide to sit because your arms are uncomfortable as your hip muscles fatigue and increased weight is placed on your arms.

We will evaluate changes in your posture and stability while you are standing using the VICON motion capture system in the Motion Study Laboratory. We will place reflective markers on various sites of your body (shoulders, elbows, wrists, back, chest, hips, knees and ankles). We will ask you remain standing while we evaluate your posture in standing with each of the advanced stimulation patterns and with continuous stimulation.

We will ask you to rate your perception of stability after each stand to determine your perception of effort and preference.

Effects of stimulation on quality of life

You may be asked to complete a multiple-choice questionnaire called the Spinal Cord Injury-Quality of Life (SCI-QOL) at follow-up intervals. Questions will ask you to rate your overall physical and medical health, emotional health, social participation, and physical functioning. The questionnaire may take about one hour to complete, but items can be completed over multiple visits. You can decline to answer any questions you do not want to answer.

III. INCONVENIENCES:

Participation in this research is demanding. The number of visits can range from 1 to 4 with each visit lasting from 2 to 3 hours depending on your functional abilities. Visits can be scheduled on consecutive days or spread out over a few weeks depending on your preference. While most procedures and tests are short in duration, some sessions may take several hours. It is your responsibility to communicate any problems to the research team in a timely manner.

IV. DISCOMFORTS / RISKS / SIDE EFFECTS:

In addition to all risks listed in the implant consent, your participation in Phase III Testing of this study may involve the following additional risks:

Discomfort and unpleasant sensations: If you have sensation below the level of your spinal cord injury, you may experience discomfort or pain during electrical stimulation while the proper levels of current are being determined. To minimize this discomfort we will slowly increase the stimulation to remain within your comfort level.

Device malfunction: There is a risk that the implant(s), electrodes, connectors or leads could fail to operate properly. If a failure should occur, the investigators will analyze the malfunction and help you decide whether to replace the failed component, leave it in place, or have the entire system removed. There is a potential for interference when using the wireless finger switch; therefore, the user can always employ the buttons on the main controller enclosure as a backup or default alternative if needed.

Skin irritation, abrasions and pressure sores: The conductive gels used with surface electrodes, the adhesives on bandages, or the tapes used to secure surface electrodes or sensors to your body may irritate your skin. You may experience a temporary redness under surface electrodes or other dressings in contact with your skin. Occasionally, braces may need to be used in portions of this study. With the use of braces, there is a risk of scrapes and blisters. Similar risks are associated with the straps and pads to stabilize your limbs in the machines that are necessary to test the strength and endurance of your stimulated muscles. Braces will then be modified to minimize undue pressure on the skin, and the muscle testing apparatus will be adjusted or padded to alleviate the pressure points. Muscle testing devices used in this study have built in safety limits and emergency shut-off switches that minimize the possibility of injury.

Pressure sores are a common complication of paralysis, especially spinal cord injury. Almost one-third (33%) of all persons with spinal cord injury can expect to develop pressure sores. Therefore, you are already at risk for developing a pressure ulcer based on your spinal cord injury. There is no evidence that the implanted material increases the risk for pressure sores and stimulation has actually been shown to reduce the risks of developing such sores.

Electrode movement and/or breakage: Another risk is that the electrodes could move or break internally. The chance of this occurring depends on the design of the electrode, how it is anchored in the tissue, and the length of time in the body. When an electrode moves away from the nerve it activates, it can stimulate a different muscle, produce an unwanted reflex, cause pain, or result in a weaker contraction. When an electrode breaks, it can no

longer conduct electricity and is not effective in producing contraction. The amount of material left behind upon removal will vary, but is usually benign and well tolerated. The body may try to expel a fragment of retained electrode. This is a foreign body rejection reaction and does not indicate the presence of an infection. After migrating to the skin surface, the fragment can be removed and the open sore treated to prevent infection. If a failed electrode significantly compromises standing performance, it can be removed and replaced in a separate surgical procedure.

Scarring: Tissue around the implanted components could become excessively scarred from the surgical procedure or the presence of the implanted material. It is also possible that the application of electrical currents for long periods of time might result in scarring of the tissue. If such scarring interfered with the function of the device(s) or presented a safety problem, you would be informed as soon as possible after the investigators identify the situation. The problem component could then be removed or replaced with your approval. In our experience with human and animal studies involving implanted devices leading up to this study, such tissue changes have never been encountered.

Burns and electrical hazards: There is a possibility of electrical shock, including electrical burn, whenever electricity is used to stimulate or to power the instruments necessary to record test results. Stimulators and measurement instruments are designed to prevent any current flow at levels that could produce tissue damage. A safety officer associated with the research group will check all experimental set-ups and custom laboratory instrumentation, including stimulation systems before they are applied. The risk of electrical burns is low.

It is also possible to receive a chemical burn if the material inside the stimulator batteries comes in contact with your skin. The batteries are sealed inside the cases of the external stimulators, and all batteries are located outside of the body. The implanted components of the systems being tested are passive and do not contain batteries.

Blood pressure changes and muscle fatigue: Dizziness associated with lower blood pressure to your brain can occur while standing or exercising with stimulation. You will be instructed to sit down immediately if you begin to feel dizzy. Further attempts to use FES will be made with your consent only after resting and drinking fluids. There have been two instances of fainting reported by subjects in the past for this research program, neither of which was directly related to use of stimulation. Neither instance resulted in injury. Fatigue and shortness of breath can result from prolonged walking or strenuous exercise with electrical stimulation. The standing and walking required for these studies has been shown to be well below the threshold for such a response.

Your body can fatigue from prolonged strenuous exercise with electrical stimulation and you might experience shortness of breath. The muscles in your hands, arms and shoulders may tire when standing with stimulation because of the weight placed on your walker, support frame or parallel bars. Any soreness of the muscles in your upper extremities should go away with rest.

Risks to the heart and nervous system: There is a risk of heart or nervous system problems such as abnormal rhythms or autonomic dysreflexia (sudden increases in blood pressure and heart rate). If you have had a history of cardiac problems, you should not be a candidate for stimulation without consulting your cardiologist. The issue would need to be cleared by the cardiologist prior to further evaluation. Similarly, if you develop heart problems during the course of this investigation, you must notify the investigators immediately and discontinue stimulation.

Fractures and falls: Individuals with paralysis generally have weaker bones than able-bodied individuals. Because of this, up to one-quarter (25%) of all persons with SCI may experience a bone fracture at some time after their injury. Therefore, you are already at risk for a bone fracture based on your paralysis. Exercise, weight bearing, and the muscle testing involved in this study may place stresses on your bones that can lead to fractures. Tendons and soft-tissues can also be ruptured by the mechanical stresses produced by stimulation. Two out of about 50 users (less than 5%) have experienced minor fractures in our laboratory over the past 20 years. Both were unrelated to stimulation and healed without permanent injury. To minimize the risk of fracture to your bones or injury to your tendons, it is important for you to follow the exercise program prescribed by the research staff and observe the precautions for safe system use.

In addition, there is a risk of falling and mechanical injury while exercising, standing, or walking with stimulation. Sprains, joint damage, or other injury from overuse is also possible if you lack sensation in your joints and lower extremities. There have been no injuries resulting from falls in the studies leading to this investigation.

During standing there is a risk of sprain or joint deterioration resulting from overuse, especially when there is an absence of sensation. After daily use of the system for many years no deterioration of joints has been noted. There is also a risk of falling and mechanical injury while exercising and standing with stimulation. The risk of injury is reduced when proper precautions are taken. Subjects will be closely supervised by a member of staff during standing and experimental procedures and will be given detailed instructions and training on safe use of their implanted system. In addition, subjects will be placed in parallel bars or a safety harness for stability during testing. All experimental procedures will use standard clinical equipment and any external electric or mechanical testing devices will be set up and tested in advance so the safety officer associated with our research group can qualify their safety. Able-bodied volunteers also are at risk of a fall if they lose balance when they are perturbed using the laboratory force actuator system.

Do not use surface stimulation such as Transcutaneous Electrical Nerve Stimulation (TENS) or Neuromuscular Electrical Stimulation (NMES) without first contacting one of the investigators in this study. There is a risk of inducing current flow through the implanted stimulator that could result in damage to the device. Diathermy, which is a deep tissue heat treatment, should not be performed in the area of the stimulator or electrodes. Contact one of the study investigators before undergoing any surgery near the implant or before undergoing implantation of orthopedic or cardiovascular devices (such as artificial hips or pacemakers). All other surgical procedures that will not take place near implanted devices must be reported.

Other potential discomforts or risks: Metabolic testing involves using a nose clip and mouthpiece that might cause claustrophobia or discomfort in some individuals. The duration of the metabolic tests will be short and they will be discontinued if you find them to be intolerable. If blood needs to be drawn for testing there may be some temporary discomfort and the usual risk of local bruising, infection, or blockage of the vein. Occasionally fainting can occur. The chances of these things happening are no more than with routine drawing of blood samples in a general medical setting. Suitable precautions will be taken to minimize these risks.

Compartment syndrome describes the death of muscle tissue due to the buildup of large pressures within a limb that prevent blood from flowing. Other studies have shown that exercise with stimulation produces pressures that are within safe ranges and therefore you should not have a greater risk of developing compartment syndrome beyond the risk you already have due to your spinal cord injury.

Unsupervised use of the implanted system can pose additional risks, especially if you choose to ignore the exercise prescription and general precautions explained to you by the research staff. It is possible to injure yourself by over-using your stimulated muscles. Alternatively, not exercising enough can adversely affect your strength, endurance, and performance with the system. This may ultimately risk the safety of your heart, bones, joints, and skin. It is your responsibility to follow the guidelines for responsible system use.

Another potential risk is that you could develop unreasonable high expectations of the system that may lead to depression if the expectations are not met. As part of the screening process for admission into the project, we repeatedly stress that there is no guarantee that the system will provide any improvement in function. If you should get depressed as a result of this project, you will be referred for counseling.

You may notice that the strength of your spasms increases after using stimulation to exercise. This is most likely due to an increase in strength and general health of the muscles involved in the spasms. Several system users have reported experiencing fewer, but stronger spasms, although no data exist to support this observation. Similar subjective reports suggest that exercise and standing with FES does not adversely affect the number or severity of urinary tract infections (UTIs).

Unsupervised use of the system can pose additional risks, especially if you choose to ignore the exercise prescription and general precautions explained to you by the research staff. It is possible to injure yourself by over-using your stimulated muscles. Alternatively, not exercising enough can compromise your strength, endurance, and performance with the system. This may ultimately risk the safety of your heart, bones, joints, and skin. It is your responsibility to follow the guidelines for responsible system use as communicated to you by the research staff and listed in this document.

Some of the SCI-QOL questions focus on personal or difficult topics. You may experience mild discomfort answering these questions, but no significant risks to your health or well-being are anticipated.

Pregnancy and birth defects: The effects of electrical stimulation on an unborn child are not known. It is possible that the electrical currents used to stimulate the nerves and muscles of a pregnant woman could affect the health of her developing child. There may be a risk of birth defect, miscarriage or other unanticipated side effect of electrical stimulation during pregnancy. It is recommended that women of child-bearing potential should not become pregnant during the course of the study. The risks of radiation exposure in an unborn child are known to be greater than those for an adult. There are also risks associated with anesthesia and surgery and the overall impact could affect both mother and unborn fetus and could lead to eventual birth defects. The risks of radiation exposure in an unborn child are known to be greater than those for an adult. There are also risks associated with anesthesia and surgery and the overall impact could affect both mother and unborn fetus and could lead to eventual birth defects. If you become pregnant after receiving the implanted system, you should stop all stimulation and notify the investigators immediately. You should advise your OB/GYN and primary physician of the situation and consult with the research staff about the best course of action. This might involve removing all the implanted electrodes. Although extra lengths of lead wire are placed under the skin when the electrodes are inserted to allow some movement and growth, they may not be long enough to accommodate the changes the body goes through during pregnancy. The implanted electrodes and leads are not designed to stretch as pregnancy progresses, and may put pressure on the skin or internal organs that would not normally exist. It is also possible that the implanted electrodes could be damaged as a result of pregnancy or during a Cesarean delivery.

Unanticipated risks: There may be as yet unknown, delayed risks that may occur months or years after participating in this research. The investigators will tell you of any new information learned during the course of the study that might cause you to change your mind about continuing your participation.

V. BENEFITS:

You will not directly benefit from participating in this study. This program is only in the research stage. The procedures described in this consent form will not improve your condition. Your participation will help the investigators develop newer technologies that may help paralyzed people to move and exercise in the future.

VI. ALTERNATIVE PROCEDURE(S) / TREATMENT(S):

You have the alternative to not participate in these screening procedures. This will in no way effect your current treatment, the possibility of future research participation or the availability of FES technology to you as it is further developed.

VII. PRIVACY, CONFIDENTIALITY, AND USE OF RESEARCH RESULTS:

Any information obtained about you in this study will be treated as confidential and will be safeguarded in accordance with the Privacy Act of 1974.

Participation in this study will involve a loss of privacy, but information about you will be handled as confidentially as possible. Your research records will be labeled with a code number. The list that matches your name with the code number will be kept in a locked file in the research team's office. The research records will be kept in a password-protected computer file that only the study team has access to. The paper

research records will be kept in a locked filing cabinet in a locked office. Your information will be combined with information from other people taking part in the study. We will write about the combined information we have gathered. Any presentations or publications from this information will not identify you.

VA policy requires us to keep study records indefinitely. However, protections will be put in place to be sure that this information is kept confidential.

By joining this study, you give the investigators your permission for them to collect data from your medical records to determine if you are eligible to participate in the study.

In order to comply with federal regulations, research records identifying you may be reviewed by the following:

- Representatives of the sponsor of this study, Louis Stokes Cleveland VA Medical Center
- Authorized representatives of the LSCDVAMC Institutional Review Board and VA
- Federal Agencies such as the Government Accounting Office (GAO), the Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP)

Because this research involves articles regulated by the FDA, the FDA may choose to inspect and copy medical or research records that identify individual research participants.

VIII. SPECIAL CIRCUMSTANCES:

New Findings

You will be told by the study doctor or Principal Investigator of any significant new findings during the course of the study, which may affect your willingness to continue to participate.

Financial Considerations

Your participation in this research study will be done at no cost to you, nor will you receive any payment for your participation. Some veterans are required to pay co-payments for medical care and services provided by VA. These co-payment requirements will continue to apply to medical care and services provided by VA that are not part of this study.

If you are selected to participate in this study and you agree to participation in the regularly scheduled aspects of this research project, you will receive no special compensation. You will receive no special compensation for participating in the regularly scheduled aspects of this research project required to install, maintain or monitor the performance of the system. You will only be reimbursed for legitimate travel expenses up to a maximum of $2,000.

When you participate in follow-up testing, experiments, teaching sessions or demonstrations other than what is required to install, maintain or monitor the performance of the system, you will receive either $50.00 per session or reimbursement for legitimate travel expenses. You can expect this to be less than $1,000 per year.

Total annual reimbursement received greater than $600.00 will be reported to the IRS.

Ending Participation

The investigators may stop your participation in this study without your consent, for example, if they think that it will be in your best interest, if you do not follow the study plan, if you experience a study-related injury, or for any other reason.

Participation in this research project is designed to last for up to three years. If you know now that you may not be able to participate for this length of time, you should discuss your situation with the investigators. You have the right to refuse to participate in this or any other research study without any negative consequences and you can withdraw from the study at any time. If your muscle strength and fatigue resistance do not increase as expected from the treatment, you may be asked to withdraw from the study. If you are unable to continue following the prescribed exercise program, including regular visits to the LSCDVAMC, you may be asked to withdraw from the study. If your participation is no longer mutually beneficial to you and the investigators, you may be asked to withdraw from the study.

The implanted system is for your private use only. You should not attempt to demonstrate the system to the media, for payment, or in any official capacity representing the VA, MetroHealth, or Case Western Reserve University without the knowledge or assistance of the investigators and program staff.

If you successfully complete the study, you can retain and continue to use your system as long as the research staff is able to provide continued support and you can comply with routine follow-up and maintenance procedures. If you do not or cannot comply with the laboratory schedule but also do not wish to withdraw from the study, you will be placed on inactive status. This means that you will not stimulate and you must have your implanted system, electrodes and incisions examined regularly by a doctor or nurse associated with the research project. All equipment (which are not implanted) you receive during the course of participation are on loan to you and must be returned if you withdraw from the study or are placed on inactive status. You will be required to sign an undertaking to that effect.

Stimulation requires a clear mind, normal reaction time, and unimpaired judgment. Use of FES while under the influence of any mind-altering drug, including alcohol, puts the user at potential risk. In the interest of the welfare of study participants, random drug screening may be performed. Participants testing positive for controlled substances may be retested on a regular basis. Continued positive screening or refusing to be tested is grounds for dismissal from the research project.

Compensation for Research-Related Injury

If you sustain an injury as a direct result of your study participation, medical care will be provided by the LSCDVAMC at no cost to you. Financial compensation for such things as lost wages, disability, or discomfort due to an injury is not available.

Financial Conflict of Interest

This study is being sponsored by grants from the Louis Stokes Cleveland Veterans Affairs Medical Center. Portions of the salaries of Dr. Triolo and his research team are being paid by these grants. The research team has no financial conflicts of interest with these studies.

IX.CONTACT INFORMATION

To answer questions about the research or if you sustain a research related injury contact the following:

- During the Day: Ronald J. Triolo, Ph.D.at (216) 791-3800 ext. 4138 or
  Lombardo, PT at (216) 791-3800 ext. 4909 or
  Dr. Stephen Selkirk at (216) 791-3800 ext. 6076

- After Hours: Lombardo, PT at (216) 402-0190 or
  page Dr. Stephen Selkirk at (440) 562-0243

For answers to questions about rights as a research participant or to voice a concern or complaint contact the following:

- The Research Administrative Officer at (216) 791-3800 ext. 4657
- The LSCDVAMC Patient Representative at (216) 791-3800 ext. 4026

If you wish to speak with someone other than study staff to provide input concerning the research process, check whether a study is being conducted at the LSCDVAMC ,and if study staff are permitted to represent the study contact :

- The LSCDVAMC Institutional Review Board Office at (216) 791-3800 ext. 4658

Subject Name: _____ Date:

Title of Study: A Neuroprosthesis For Prolonged Standing After SCI Using Multi-Contact Peripheral Nerve Electrodes- Modulation of Stimulation Patterns- Phase III Testing

Principal Investigator: Ronald J. Triolo, Ph.D. VAMC: Cleveland (541)

Consent Version Date: December, 2017

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

Dr./Mr./Ms. _____has explained the study to me and answered all of my questions. I have been told of the risks or discomforts and possible benefits of the study. I have been told of other choices of treatment available to me.

I understand that I do not have to take part in this study, and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw from this study at any time without penalty or loss of VA or other benefits to which I am entitled.

The results of this study may be published, but I will not be identified in publications by name, photograph, or other identifiers. My records, including my name and results of my participation, may be revealed as required by laws and regulations of state and federal agencies.

I understand my rights as a subject, and I voluntarily consent to participate in this study. I understand what the study is about and how and why it is being done. I will receive a signed consent form or a photocopy of it. I understand that in signing this consent form I do not waive my legal rights nor release the LSCDVAMC from liability for negligence.

Subject's Signature_____ Date _ _ / _ _ /_ _

Signature of Subject's Representative _____ Date _ _ / _ _ /_ _
(if subject not competent)

Printed name_____

Signature of Person Obtaining Consent_____ Date _ _ / _ _ /_ _