VA Department of Veterans Affairs	VA RESEARCH CONSENT FORM
Version Date [Date of submission]: April 2019	**Page: 1 of 12**
Subject Name:	**Informed Consent Date:**
Protocol #: HAR-18-47 **Principal Investigator: Noam Y. Harel, MD, PhD**	**VAMC: James J Peters**

Title of Study:

Effects of Remote Ischemic Conditioning on Hand Use in Individual with Spinal Cord Injury: A Preliminary Study

INTRODUCTION

You are being invited to take part in a research study. Before you decide to take part, it is important for you to know why the research is being done and what it will involve. This includes any potential risks to you, as well as any potential benefits you might receive.

Read the information below closely, and discuss it with family and friends if you wish. Ask one of the study staff if there is anything that is not clear or if you would like more details. Take your time to decide. If you do decide to take part, your signature on this consent form will show that you received all of the information below, and that you were able to discuss any questions and concerns you had with a member of the study team.

1. Purpose of study and how long it will last:

You are being asked to participate in a research study. The purpose of this study is to test whether a transient episode of blood flow blockage on your upper arm, called Remote Ischemic Conditioning (RIC), can improve the ability of your brain to transmit nerve impulses to your hand muscles and the genetic expression of the inflammation mediator. We will also monitor your responses of heart rate, blood pressure and oxygen saturation during the RIC. You are being asked to participate in this research study because you are between the ages of 18 and 75 and you either have an incomplete cervical spinal cord injury (SCI) that happened more than 12 months ago, or you are an able-bodied volunteer.

You will undergo a series of research tests that are not part of usual medical care. There is no drug treatment given as part of this research study. There is investigational use of magnetic and electrical stimulation given as part of this study. All procedures will take place at James J. Peters Veterans Affairs Medical Center (JJPVAMC). If you have spinal cord injury, your participation in this research study is expected to last 3 visits. If you are a non-disabled volunteer, your participation in this study is expected to last 2 visits. Each visit will last roughly 3-3.5 hours.

This study is being sponsored by the National Health Institute (NIH). We plan to enroll 8 participants with spinal cord injury and 8 able-bodied volunteers over the next two years for this study.

2. Description of the Study Including Procedures to be Used:

General: You will come to our research center in Suite 7A-13 of the JJPVAMC main hospital building for all your visits and testing. You will be seated in an adjustable upholstered reclining chair in our testing room within the research center.

SCREENING VISIT (subjects with SCI only; approximately three hours)

Clinical Interview: A clinical interview will be conducted to learn the details of your initial spinal cord injury, how it was treated, and other clinical events that have happened since the injury. It will also determine your other neurological and medical issues.Clinical Examination: A routine physical and neurological exam will be performed. This examination should take about 30-40 minutes to complete. A test of your sensory function and strength at key levels above and below your spinal injury. This test is called the International Standards for Neurological Classification of Spinal Cord Injury. If we are unable to detect some ability to partially move your fingers voluntarily during this screening visit, you will not be eligible for further participation in the study.

Peripheral nerve electrical testing: This test will measure how well the median and ulnar nerves in each of your arms conduct electricity. You will have several surface electrodes attached to muscles on your hands and arms. The electrodes are similar to the ones used if you have ever had an electrocardiogram (EKG) in the past. They are attached with adhesive, not by needles. A computer will record any signals generated during the test procedure. A series of small test currents will be applied to the skin over the soft side of each wrist. They will cause your muscles to twitch – this is normal. If we are unable to detect peripheral nerve responses during this screening visit, you will not be eligible for further participation in the study.

Brain magnetic testing: This test will detect your muscle responses to magnetic stimulation applied to your brain. You will have several surface electrodes attached to muscles on your hands and arms. Then, a device called a Transcranial Magnetic Stimulator (TMS) will be held over your head at the area where your brain sends signals to your hands. The magnetic pulses cause an electric current in your brain. Sometimes, your scalp, forehead, or neck muscles might twitch under the magnet. Also, muscles in your hands and even your feet might twitch from the magnetic signal. We will record any electric

signals detected by the electrodes on your muscles. If we are unable to detect muscle responses to TMS during this screening visit, you will not be eligible for further participation in the study.

Motor tasks: You will be instructed to perform a pinching task using a gauge between your thumb and third finger. We will record your muscle activity at the same time. We will measure the best force you can apply with 100% effort. The maximum force level that we measure will be used to calculate different effort targets for you to aim for during the following visits described below. If we are unable to detect sufficient muscle electrical activity and muscle force during the pinch task, you will not be eligible for further participation in the study.

If there are any major problems, such as significant change in blood pressure, or shortness of breath, or other significant discomfort during the screening visit, the procedure will be immediately halted, appropriate medical care will be provided, and for your own safety, you will not be eligible for further participation in the study.

STUDY VISITS 2 THROUGH 6 (approximately 3-3.5 hours each)

At each of these visits, we will set up brain magnetic stimulation (TMS) and peripheral nerve stimulation (PNS) electrodes and perform TMS and PNS measurements using similar technique as described above in the Screening visit. We will also measure your maximum effort during motor tasks as described in screening visit. You will then receive an episode of blood-flow restriction called remote ischemic conditioning (RIC) on one arm. The RIC involves 5 cycles of 5-min inflation and 5-min deflation and the inflation pressure will be adjusted in each visit. During the RIC, your heart will be monitored using 3 electrodes (small sticky pads) placed on your chest and abdomen. Your blood pressure will be monitored on a beat-to-beat basis using a small finger cuff on your middle or ring finger of the opposite arm. A brachial cuff will be placed on the upper arm to calibrate the finger blood pressure cuff. After the RIC, you will be asked to perform a series of pinching tasks. One computer program will guide you regarding the intensity and the duration of each pinching task.

We will repeat several of the tests described above (response to TMS, response to PNS, and maximum pinch strength) after the RIC, after pinching tasks and again 15 minutes after pinching tasks. By measuring your responses at these time points, we will determine the temporary effects of the RIC on your nerve transmission and hand function.

Blood samples (10 ml = 2.03 teaspoons) will be collected before the RIC cycle and 15 minutes after the end of RIC. The analyses will be to determine blood levels of inflammatory markers by Dr. Ona Bloom, at The Feinstein Institute for Medical Research, Manhasset, NY. The samples of your blood will be sent to her laboratory in transfer tubes that will be labeled only with a participant ID number and study time point.

NOTE: If during your visit we see something wrong that requires you to be checked by your primary care doctor, we will let you know at that time. The tests performed in this study are for specific research purposes and are not set up to find medical abnormalities. These tests are not the same as regular medical care. However, on occasion we may notice a finding that should be followed up by your primary care doctor. If you are a veteran, we will arrange for a visit with your VA primary doctor. If you are a veteran and you do not have a primary care doctor, we will refer you to one within the VA system. If you are not a veteran, we will advise you to follow up with your primary care doctor. You can decide at any time not to continue participating in the Study. Your future care or privacy at the VA will not be affected by dropping out of the Study.

3. Description of any Procedures that may Result in Discomfort or Inconvenience:

You are being asked to participate in a Study that requires a time commitment to make 2 or 3 study visits. This may be an inconvenience.

The remote ischemic conditioning (RIC) has been shown safe in individuals with cardiac diseases and critical ill patients with subarachnoid hemorrhage stroke. However, you could feel pain, discomfort or numbness during the inflation period and possibly have a bruise at the site of skin after a session.

The electrical recording and stimulating electrodes have adhesive backing. Therefore, skin irritation at the sites of electrode application may occur. Areas with too much hair will be shaved prior to adhesive application. Any open skin wounds will be avoided and may prevent you from participating in the study.

We will also frequently check your blood pressure, heart rate, and oxygen levels throughout the procedure.

The applied currents could cause brief irritation or pain in the skin around the stimulation sites. They will also cause your muscles to twitch – this is normal. The amount of stimulation is similar to that used in Functional Electrical Stimulation (FES), which you may have experience with. If you feel discomfort, it should not last more than a few seconds, and you can decide to stop the procedure at any time.

The magnetic pulses could cause brief irritation or pain in your scalp, forehead, or neck area. Sometimes, a muscle in your scalp, forehead, or neck might twitch from the stimulation. If you do feel discomfort, it should not last more than a few seconds, and you can decide to stop the procedure at any time.

If you have a cervical spinal cord injury, there is still a small chance that you could have an episode of "autonomic dysreflexia" while participating in this study. These episodes usually include headache, goose bumps, flushing (red face), and potentially dangerous increase in blood pressure. The investigators will be monitoring your blood pressure and other vital signs the entire time, and if there are significant symptoms or changes in your vital signs, they will halt the procedure immediately and provide appropriate medical care. The investigators are very experienced in treating episodes of autonomic dysreflexia.

A routine blood sample will be drawn from a vein inside your elbow and this can be associated with mild discomfort due to the blood draw. Discomfort and inconvenience associated with blood draw include the possibility of a bruise, or infection at the site of skin puncture, temporary faintness and rarely, temporary loss of consciousness due to vasomotor instability (i.e., the blood vessels reflexively swell resulting in a fall in blood pressure which is commonly called "vasovagal episode").

For female participants, since this research may have unknown effects on an unborn child and should not be done during pregnancy, it is necessary for a pregnancy test to be done first. To your knowledge you are not pregnant at the present time. You also agree to avoid becoming pregnant (use contraceptives or take other precautions against becoming pregnant) during this study.

4. Expected Risks of Study:

There is a small risk of falling during transfers between different chairs and stretchers; with the risk of falling is the risk of bone fracture.

- The Study team members are trained and experienced in the care and rehabilitation of participants with limited mobility, including extensive safety experience in preventing falls. You will never be left unattended during a test session.

Remote ischemic conditioning (RIC) has been shown safe in individuals with cardiac diseases and critically ill patients with subarachnoid hemorrhage stroke. However, it has not been tested in individuals with SCI. Therefore, one major purpose in this study is to document pain and/or any adverse effects during RIC.

- We will continuously check your blood pressure, heart rate, and oxygen levels throughout the RIC cycle. If there is any adverse effect or you can not tolerate the pain/discomfort, the study and your participation will be terminated. Dr. Noam Y. Harel, a board-certified neurologist and the principal investigator in this study, will serve as the study physician

There is a possible risk that you may feel discomfort, pain, lightheadedness, dizziness, blurred vision, nausea, and in rare cases, temporary loss of consciousness (syncope) during the needle insertion. There is also the potential risk of developing a bruise or infection at the site of skin puncture.

There is a small risk of seizure from the magnetic stimulation.

- This risk is small, and has only been reported for participants undergoing repetitive magnetic stimulation – you will only be receiving one magnetic pulse at a time, so the risk is even smaller.
- Before you begin participation in the Study, we will screen you for seizure risk, such as history of prior brain injury, or taking certain medications that raise the risk of seizure. If your seizure risk is too high, you will not be able to participate in the Study.
- The principal investigator, Dr. Noam Harel, is neurologist trained in treating seizures and will supervise the procedure of performing the magnetic stimulation.

There is a possible but unlikely risk of TMS triggering psychotic symptoms in participants with bipolar depression.

- This is a very small risk – it is not clearly above the natural rate for these types of symptoms to occur in participants with depression.

- You will not be able to participate in the Study if you have a history of bipolar disease, active psychotic symptoms, or history of suicide attempt.

There is a small risk of having an episode of autonomic dysreflexia. These episodes involve a potentially dangerous increase in blood pressure that rarely can lead to a heart attack or stroke. Usually, there are symptoms such as headache, goose bumps, or flushing (red face).

- The investigators will be monitoring your blood pressure and other vital signs the entire time, and if there are significant symptoms or changes in vital signs, they will halt the procedure immediately and take steps to end the autonomic dysreflexia. This includes sitting you upright, and checking your bladder and bowel to make sure they are empty and not irritated.

There is a possible but unlikely risk that electrical stimulation could cause a heart rhythm problem. However, the electrode configuration used in this study will not cause current to cross over the heart muscle. Nevertheless, to provide further caution against cardiac damage or rhythm problems, potential participants who have significant coronary artery disease, cardiac conduction disease, or implanted pacemaker/defibrillators, will be excluded from participation. To provide further caution, the procedure will be conducted with monitoring of blood pressure, oxygen levels, and other vital signs. Any significant change in blood pressure or oxygen level, associated with symptoms such as sudden shortness of breath, chest pain, or sudden sweating, will lead to immediately stopping the procedure and further medical evaluation and treatment. A medical doctor will be on hand at all times.

There always exists the potential for loss of private information; there are procedures in place to minimize this risk.

There may also be potential risks that are unknown.

5. Expected Benefits of the Study:

It is important for you to know that you may not get any benefit from taking part in this research. Others may not benefit either. However, any information we get from this study can help others with SCI (including you if you have SCI) in future studies.

6. Other Treatments Available:

This study is being done for research purposes. No routine clinical care or medications that you are scheduled for will be withheld from you.

7. Use of Research Results:

Only study team members will have access to the Research materials obtained from you during this Study. These materials will be secured in a locked file cabinet in the Center of Excellence (7A-13) as well as on a password-protected file on the VA server. Your identifiable and personal health information (PHI) will be protected by coding your identity. Only the Study team members will have access to the code. The code is kept in locked files and secure electronic servers. The code will not be used to link the information back to you without your permission, unless the law requires it.

An important part of this research is to save your data in a secure data repository for other research studies in the future. The repository would be held to the same privacy protection standards as described above. Only approved research personnel and approved investigators would be able to access data from the repository.

☐ _____ By checking and initialing this box, you allow the researchers to store your data to use in future

We will let you and your physician know of any significant new findings made during this Study which may affect your willingness to participate in this Study.

Your medical records will National Archives and Records Administration, in accordance with Records Schedule RCS-10-1.

We may ask to video record you for the purposes of using your video recordings at various presentations. A separate waiver will be presented to you at that time for you to give permission for use of any video recordings of you. If you do not wish to be video recorded we will not do so.

If results of this Study are reported in medical journals or at meetings, you will not be identified by name, by recognizable photograph, or by any other means without your specific consent. No information by which you can be identified will be released or published unless required by law.

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

- Representatives of the sponsor [JJPVAMC, Center of Excellence for the Medical Consequences of SCI and the SCI Service] of this study,
- Authorized representatives of the JJPVAMC (e.g. Institutional Review Board, Research Compliance Officer), including the Office of Research Oversight, and similarly authorized representatives of the Mount Sinai Medical Center,
- Federal Agencies such as the Government Accounting Office (GAO), Food and Drug Administration (FDA), and
- The Office for Human Research Protections (OHRP)
- Office of Inspector General (OIG)

☐ _____ By checking and initialing this box, you agree to be contacted by the Principal Investigator or his investigative team at a future date for additional studies being conducted in the Center of Excellence for the Medical Consequences of SCI.

8. Special Circumstances:

Your participation in this Study will be included in the VHA health record. A copy of the signed informed consent form and signed HIPAA authorization for participation in the study will be in your health record

9. Compensation and/or Treatment in the Event of Injury:

The VA must provide necessary medical treatment to a research Participant injured by participation in a research project approved by a VA R&D Committee and conducted under the supervision of one or

more VA employees. Further information about compensation and medical treatment may be obtained from the medical administration service at this VA medical center.

10. Voluntary Participation:

You are not required to take part in this study; your participation is entirely voluntary. You can refuse to participate now or you can withdraw from the study at any time after giving your consent. This will not interfere with your regular medical treatment if you are a patient.

11. Termination of Participation:

If you decide to withdraw from this Study please notify us. This will not interfere with your regular medical treatment at the VA. Your participation may be terminated by the investigator without regard to your consent under certain conditions, such as if you suffer a seizure at any time during your involvement.

12. Costs and Reimbursements:

As a veteran or non-veteran, you will not be charged for any treatments or procedures that are part of this study. For veterans who are required to pay co-payments for medical care and services provided by the VA, these co-payments will continue to apply for medical care and services provided by the VA that are not part of this study.

You will be reimbursed to offset any travel expenses and inconvenience you may incur due to participation in this study. You will be reimbursed $75 for each visit up to 2 or 3 visits. The total amount for participating in all sessions would add up to $225 if you have SCI or $150 if you are an able-bodied volunteer. You will be reimbursed according to the number of visits that you complete. You will receive payments in approximately 4-6 weeks after completing participation.

13. Contact Person(s):

To obtain answers to questions about the research, report or seek treatment for a research-related injury, or to voice concerns or complaints about the research, contact the following (investigator/research team):

- **During the Day:** **Dr. Yu-Kuang Wu: 718-584-9000, x1738**
- **After Hours:** **Dr. Yu-Kuang Wu can be reached at 412-706-3532**

To voice concerns or complaints about the research to someone outside of the research team, contact the following:

I understand that should I wish to discuss my participation in this study with any other doctor or layperson, I can contact **Mary Sano, Ph.D.** ACOS-R&D Program by requesting an appointment at **(718) 741-4228** hospital extension **4228**, first floor in the research building, room **1F-01** If I have questions, concerns and/or complaints concerning the research study, I can ask one of the researchers listed above or contact **Dr. Sano**. Medical problems during the course of the study should be addressed to the investigator at the phone listed above.

If I have problems, concerns, and questions about the research and research Participant's rights, I can contact Dr. Sano, who is not affiliated with this research study, to obtain information or to offer input.

To obtain answers to questions about your rights as a research Participant, provide input about the research process, or to check whether this study is being conducted at the James J Peters VAMC and whether study staff is permitted to represent the study, contact the following:

Mary Sano, Ph.D. (718) 741-4228, ext. 4228

RESEARCH SUBJECTS' RIGHTS: I have read or have had read to me all of the above. Dr. Harel or his delegate 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 my records will not be revealed unless required by law. This study has been explained to me. I have had a chance to ask questions. I voluntarily consent to participate in this study. I will receive a signed copy of this consent form.

Subject Signature	Date	Time

Person Obtaining Informed Consent (Print Name) (Investigator or Delegate as indicated on Assurance Page)	Signature of Person Obtaining Informed Consent	Date