

Principal Investigators:

Professor Dirk De Ridder, Neurosurgeon and Professor of Neurosurgery
Professor John Reynolds, Dept of Anatomy

Professor Leigh Hale, Dean of School of Physiotherapy,
Dr Jon Shemmell, Senior Lecturer, School of Physical Education, Sport and Exercise Sciences
Dr Nick Cutfield, Neurologist, Dept of Medicine

PARTICIPANT INFORMATION SHEET

Implanted (brain) Stimulators To Augment stroke Rehabilitation Therapy (iSTART)

Locality:	Dunedin	Ethics committee ref.:	15/STH/171
Lead investigator:	Prof Dirk de Ridder	Contact phone number:	Dept. of Surgical Sciences 03 470 9337; or via Dunedin Public Hospital (03 474 0999)

Thank you for showing an interest in this project. Please read this information sheet carefully before deciding whether or not it is appropriate for you to take part. Your participation is entirely voluntary. If you decide not to take part, you don't have to give a reason, and it will not affect any future care or treatment. If you do agree to take part in the study, you are free to withdraw at any time without having to give a reason and this will in no way affect any future health care.

This Patient Information Sheet explains what the study will involve and will help you decide if you'd like to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. You do not have to decide today whether or not you will participate in this study. Before you decide you may want to talk about the study with other people, such as your legal representative, family, whānau, friends, or healthcare providers. Feel free to do this.

If you agree to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

This document is 10 pages long, including the Consent Form. Please make sure you have read the rest of this information sheet carefully and understood all the pages.

What is the Aim of the Project?

The aim of this study is to improve movement recovery in the arm and hand affected by your stroke by stimulating a part of the brain called the 'motor cortex' using electrical current. The current will be administered by a brain stimulator which, with your consent, will be fitted under the wall of your chest and the electrodes and wires from the stimulator fitted inside the skull above the motor cortex, during a surgical procedure performed under general anaesthetic.

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A stroke is caused by the interruption of normal blood flow within the brain. This results in death of brain cells normally supplied by those blood vessels. Recovery from a stroke requires nerve cells in adjacent brain areas to take over some of the lost function. However, this is resisted by other parts of the brain that tend to 'turn off' or 'inhibit' this change in function. One of the likely offending areas is the motor cortex on the side of the brain opposite to that affected by your stroke. We plan in this study to alter the activity of this area using a brain stimulator. When applied in conjunction with a physiotherapy programme, we hope that neurostimulation applied to the motor cortex will lead to greater recovery than can be obtained by physiotherapy alone.

During surgery, we will fit the electrodes directly onto the layer of tissue that covers your motor cortex on the opposite side of the brain to your stroke, and will apply electrical pulses to this area after you have recovered from the operation. We have studied this idea in models of stroke and found that our approach improves function. We now wish to determine if this approach will be feasible in humans who have arm and hand movement difficulties after stroke. First, we will be using a non-surgical form of brain stimulation to identify people who may respond to this treatment. Unfortunately, this non-surgical form of treatment, called transcranial magnetic stimulation (TMS) only works for a short period of time and is therefore unsuitable as an ongoing treatment for stroke. This is why we believe that a better effect will be achieved by using a stimulator surgically placed directly onto the covering above the motor cortex.

We don't intend in the long term that this neurostimulation will replace physiotherapy, which is the standard approach to improve your movement and function after stroke. Instead, we hope to find a method that will maximise and maintain the gains that can be obtained from these therapies.

What will Participants be Asked to Do?

Potential participants will have a visit scheduled with a neurosurgeon, neurologist or physician who is one of the investigators in this study to determine if you are a suitable candidate for the study. You will be fully informed about the study and given an opportunity to ask questions and time to consider whether you wish to participate. If you agree to participate you will be asked to sign a consent form.

The following procedures will be performed:

- A full medical consultation and physical examination will take place. Particular attention will be given to the degree of disability you experience from the stroke, any history of seizures, other medical disorders, and medication usage.
- Routine blood tests and a heart rhythm trace (ECG) will be performed to make sure there are no unexpected abnormalities and to make sure it is safe for you to be in the study.
- Brain wave tests (EEG) will be performed during screening, and 6 months after the neurostimulation therapy, to allow us to check for signs of changes in connections in the brain.

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- Pre-surgery magnetic stimulation (TMS) will be performed by one of the investigators in the study at the School of Physical Education to determine the strength of the circuits between the motor cortex on the side of your stroke and your affected muscles. This involves placing a special coil on the scalp, which will stimulate the motor cortex with a single magnetic pulse. The size of the pulse will be turned up to a level that might produce a visible muscular twitch. Electrodes will be placed over a number of muscles in your affected arm and hand to enable us to record the effect of the pulse on muscle activity.
- An assessment will be undertaken at the School of Physiotherapy by a physiotherapist who is one of the investigators in the study. This will measure the baseline level of function in your shoulders, arms, and hands. Questionnaires will be administered to determine your own assessment of your general wellbeing after stroke and the level of impairment you experience with the affected limb.
- A brain scan (MRI) will be performed to check the position and size of the stroke and to help us determine where best to place the stimulator during surgery. This will involve you lying still in the scanner for between 30 minutes and an hour and moving your hands one at a time when asked.
- If the assessments performed above indicate that you are likely to gain additional benefit from the neurostimulation procedures, and if you are still willing to have the surgery to implant the stimulator, you will proceed to have routine pre-operative evaluations by a consultant anaesthetist. If it is considered unlikely to be of additional benefit for you to receive the stimulator or physiotherapy rehabilitation procedures, or if you decline either procedure, one of the investigators will meet with you to discuss the next step, which could be to undergo the physiotherapy procedures alone or to finish the study at this point.

Surgery

The operation will take place in one of the main operating theatres in Dunedin Hospital by Professor De Ridder, consultant neurosurgeon. You will have a general anaesthetic for this procedure. The procedure will take approximately 2-3 hours.

The operation involves making an incision into your scalp (within the hairline). A small hole (4x4 cm) is made through the skull bone and two stimulator electrodes are inserted and placed on the covering on the outside of the brain so that they are above the motor cortex on the opposite side of the brain to where the stroke is located. Wires from the electrodes are tunnelled under the skin for later connection to an internal pulse generator, which is a kind of pacemaker to stimulate the brain. The internal pulse generator, a small oblong device, will be implanted under the skin in the upper chest or the abdomen and is noticeable by a small bump only. For the first 10 days after surgery, however, the wires will exit the skin, to be connected to a temporary external pulse generator.

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After the operation you will be monitored overnight in the high dependency unit of the neurosurgical ward at Dunedin Hospital (Ward 3 Surg). It is anticipated that you will be discharged home the following day after a CT of the brain is performed.

After the surgery

Three days later you will revisit the research unit in the School of Physical Education. The wires from the electrodes will be connected to an external pulse generator and the parameters of the electrical pulses will be set, up to intensities that would produce a visible muscular twitch. This will be repeated in conjunction with single pulses applied to the magnetic coil placed over the scalp. Since the electrical pulses and the magnetic pulses will be applied to opposite sides of the brain, electrodes will be placed over a number of muscles in both of your arms and both hands, as well as EEG electrodes over the scalp and the ear on the side of the stroke. This will enable us to determine the effect of the electrical pulses applied to the implanted electrodes on muscle activity, and to set the pulse generator to the correct settings ready for activation during the rehabilitation sessions.

You will then immediately begin to attend daily rehabilitation sessions at the School of Physiotherapy. Each session will be approximately one hour and will involve a circuit of exercises individualised around your level of arm and hand abilities. Up to 30 minutes prior to beginning the exercises and at the end of the session, the physiotherapist will pass a 'wand' over the external pulse generator. This will either ensure that the stimulation is switched on throughout the session or the stimulation will remain off. You will not be informed which of these options will occur and cannot feel whether or not the stimulator is on or off. This is to eliminate a placebo effect of treatment and to enable us to determine whether any improvements you are experiencing in your movements are due to the neurostimulation in conjunction with the rehabilitation or due to the rehabilitation alone. If the stimulator was not switched on at day 3 it will be activated from day 45 of the study. It is very important to attend the rehabilitation sessions, in order to obtain the benefits from the stimulation procedures. You will also be given a home exercise programme to do in the weekends and at other times recommended by the physiotherapist.

Approximately 10 days after the surgery, you will return to the operating theatre for the wires to be connected to an internal pulse generator and then placed under your skin so that nothing is external. This will be performed under local anaesthetic in a procedure that takes approximately 15 minutes. The internal pulse generator will be programmed with the same parameters as the external pulse generator.

The physiotherapy assessment of level of function will be repeated at 6 and 12 weeks after surgery, to monitor the effect of the stimulator on your hand and arm movements and level of function. In the same week, the recordings of muscle activity in response to the pulse generator and magnetic pulses will be repeated. Fine-tuning of the stimulator activity might be made at the 6-week point. At the 12-week point, the neurostimulation and rehabilitation sessions will be completed.

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After 26 weeks we will schedule appointments for you for a repeat EEG and a physiotherapy assessment, and to be evaluated using the same questionnaires you completed at the start of the study. This will determine if the stimulation and rehabilitation has had lasting effects. If it appears that you have been gaining benefit from the neurostimulation, you can continue to use it on an on-going basis in conjunction with your home exercise programme. The study team will provide on-going support to you to manage the stimulator if you choose to continue to use it. Whether the stimulator is effective or not it will not be removed. Although based on relatively small numbers of patients and only over modest duration (e.g. 5 years in Parkinson's disease) it is believed that there is minimal risk in leaving the stimulator in place. Indeed, we believe the risk from a second operation to remove the stimulator is significantly greater than leaving it in place.

At the 26-week point, you will also be invited to take part in some research to evaluate your experiences with the neurostimulation and rehabilitation study, to help us design similar future studies. This will consist of a series of interviews conducted by the physiotherapy team. These interviews will use an open-ended question technique. You will be able to talk freely. The interviewers will record these interviews by audio-recorders. The recordings will be transcribed word for word. You will have the opportunity to comment on your transcribed interview if you so wish. The open-ended technique of questioning means that the precise nature of the questions that will be asked has not been determined in advance. Consequently, the Human Ethics Committee is aware of the general areas to be explored in the interview but has not reviewed the precise questions to be used. You are reminded of your right to decline to answer any particular question(s) if you wish.

What Type of Participants are we looking for?

- Men and women, aged at least 18 years of age, who have had a stroke affecting their hand or arm function at least 4 months earlier, which was confirmed by a previous head scan result (either CT or MRI).
- Participants must have a supportive social network (minimum 1 person) that they will provide contact details for, who will be willing to sign the consent form and to support the participant to attend pre-/post-surgery appointments.

Please make sure that you inform the study staff if any of the following criteria apply to you. This would make you ineligible for participation in this study and could lead to dangerous side effects:

- A history of epileptic seizures
- Presence of a pacemaker or defibrillator
- A reason why you cannot undergo an MRI e.g. metallic implants, severe claustrophobia
- Females who are or intend to become pregnant
- The presence of pain or significant movement restrictions or chronic disease (other than stroke) that would independently cause significant disability or weakness of your affected upper limb.

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What Are The Side Effects And Risks?

The risks of participation are:

1. Those associated with surgery and general anaesthesia. These risks include bleeding in the brain, stroke, infection, brain swelling, coma, memory and concentration problems, impaired speech, weakness, bowel and bladder problems. These complications are considered very rare because the surgery is performed without opening the layer of tissue above the brain (i.e. the surgery is 'extradural'). If complications were to occur, they could be devastating: for example, the risk of having a permanent complication of a bleed are about 1%, of an infection 4% and of a seizure 3%. These risks will be minimised by careful pre and post-operative care as well as meticulous care during the operation. All general anaesthetics carry risk although they are very low. These include allergic reaction, damage to your vocal cords, tongue or teeth, lung infection, heart attack, memory problems or confusion. You will have an opportunity to carefully discuss these risks preoperatively with both the surgeon and anaesthetist. You will be carefully monitored overnight after the operation in the neurosurgical high dependency unit, with hourly neuro-observations. You will be given antibiotic prophylaxis to reduce the chance of infection and you will also receive postoperative pain management as necessary.
2. Unexpected consequences of the neurostimulation itself, such as the onset of seizures or movement twitches. Stopping the stimulation or changing to another stimulation pattern can treat these side effects.
3. That the stimulation may not improve the movements or function in your stroke-affected limb. It is possible that you may never have any benefit, or, after an initial successful effect, that the benefit wears off. It is important that you are aware that regardless of your response to stimulation, the electrodes will remain inside your head. There do not appear to be any significant long-term risks from leaving these electrodes in place and, as noted above, the risks of removing them outweighs any small risk from leaving them where they are. A further advantage of leaving the electrodes where they are is that as scientific knowledge increases, new ways of stimulation may be discovered that can then be proposed to you as a way to try and still obtain a beneficial effect, without having to implant the electrodes again.
4. That the stimulation could possibly cause your arm and or hand function to worsen. However, this is highly likely to be only temporary and will reverse after the stimulation procedures are stopped.
5. Another possible complication is that the electrode moves, breaks or does not work properly. If this occurs the electrode can be repositioned or replaced.

Will I be paid for my participation on this project?

No, you will not be paid to participate in this study. However, we will reimburse any out-of-pocket expenses that you or your support person incur from participating in the assessment appointments e.g. travel expenses to attend appointments at baseline, 6 weeks, 12 weeks and 26 weeks.

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Will there be any costs for my participation on this project?

No. There will be no costs for you regarding this project.

Can Participants Change their Mind and Withdraw from the Project?

You may withdraw from this project at any time and without any disadvantage of any kind. In addition, the study staff may decide to withdraw you from the study if you have any unexpected side effects from the treatment or if they have any other concerns. As noted above, however, we do not plan to remove the electrodes from your brain if you withdraw from the study. The reasons being that the risk of surgery to remove the electrodes would be greater than leaving them where they are and, as new stimulation designs are identified in the future, you may be eligible for further treatments which could be of benefit to you if the electrodes are still in place.

What Information will be Collected and What Use will be Made of it?

We will be collecting and storing information from you regarding your relevant medical history along with information gathered during your physical examination. Prior to surgery you will have blood/urine tests taken to ensure you are safe to proceed to surgery. You will also have an MRI scan and EEG testing. As outlined above you will have various measures of your ability to move, your level of function and the strength of your movement circuits recorded by way of questionnaires, muscle recordings and physiotherapy assessments. The information from all of these tests will also be stored and analysed. If you decide to participate in this study we will inform your GP and other medical professionals currently involved in your medical care of your decision.

The results of this study will be published in an international scientific journal. The data included in this publication will in no way be linked to any specific person and your identity will not be recorded with the data. If you want access to your personal data later you will need to record the identification number used for your particular tests. You are most welcome to request a copy of the results of the project should you wish. These will be available once all the data is analysed, two years following the commencement of the study, nominally in early 2018.

The data collected will be securely stored in such a way that only those involved in the research program will be able to gain access to it. At the end of the project any personal information will be destroyed immediately except that, as required by the University's research policy, any raw data on which the results of the project depend will be retained in secure storage for ten years, after which it will be destroyed.

Support Person

The researchers believe that it is important for your safe participation in this study that you have a person available to provide support to you during this study. It is important that you identify a suitable person who is willing to provide this role.

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The support person:

1. Will be fully informed about the study in the same way that you are.
2. Will be required to sign a consent form indicating that they understand the study and are willing to provide you with support over the 6-month study duration.
3. Should be someone that you are happy to confide in and is aware of your current impairments due to the stroke.
4. Will contact the study team or other suitable medical professional if they have concerns for your health or welfare

The support person is someone who should be able to assist you to attend study appointments, is willing to advocate for you if necessary, can be a point of contact for the study team if you are not available, and will provide general support for you if necessary.

What if you have any Questions?

If you have any questions about our project, either now or in the future, please feel free to contact us via:

Dr Joyce Lim, Dept. of Surgical Sciences, 03 470 9337; or leave a message with the Dept of Anatomy, 03 479 7362.

Professor Dirk De Ridder, Dept. of Surgical Sciences, 03 470 9337.

If after hours and/or urgent please contact the above via Dunedin Public Hospital (03 474 0999).

ACC statement

In the unlikely event of a physical injury as a result of your participation in this study, you would be eligible to apply for compensation from ACC just as you would be if you were injured in an accident at work or at home. This does not mean that your claim will automatically be accepted. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery.

If you have any questions about ACC please feel free to ask the researcher for more information before you agree to take part in this trial. If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

Health and Disability Statement

If you have any queries or concerns about your rights as a participant in this study you may wish to contact a Health and Disability Services Consumer Advocate, telephone: (03) 479 0265 or freephone 0800 37 77 66 or freefax 0800 2787 7678 (0800 2 SUPPORT) or email advocacy@hdc.org.nz. If there is a specific Maori issue/concern please contact Linda Grennell at 0800 377 766.

This project has been reviewed and approved by the Southern Health and Disability Ethics Committee (Ref: 15/STH/171).

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CONSENT FORM FOR PARTICIPANTS AND SUPPORT PERSON(S)

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I have read the Participant Information Sheet concerning this project. All my questions have been answered to my satisfaction. I understand that I am free to request further information at any stage.

Interpreters may be available on request. Please make the study staff aware if you would like an interpreter to be available.

1. I have read and I understand the information sheet dated 24/07/17 for volunteers taking part in the study designed to assess the effect of motor cortex neurostimulation on recovery after stroke. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.
2. I have had the opportunity to use whānau support or a friend and/or legal representative to help me ask questions and understand the study.
3. I understand that taking part in this study is voluntary (my choice), and that I may withdraw from the study at any time, and this will in no way affect my future health care.
4. I understand that my participation in this study is confidential and that no material that could identify me will be used in any reports on this study.
5. I understand that the treatment will be stopped if it should appear harmful to me.
6. I understand the compensation provisions for this study.
7. I have had time to consider whether to take part in the study.
8. I know who to contact if I have any side effects from the study.
9. I know who to contact if I have any questions about the treatment used in this study or about the study in general.
10. I consent to blood samples being destroyed at the end of the study Y N
11. I wish to receive a copy of the results. Y N
12. If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be used. Y N
13. I agree to my GP or other current provider being informed of my participation in this study. Y N

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I _____ hereby consent to take part in this study.

Participant Signature:

Date:

The involvement of a support person is
recommended by the researchers.

I _____ hereby consent to supporting the above participant
during this study.

Support Person Signature:

Date:

Full name of researcher obtaining
consent:

Project role:

Signature:

Date:

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