# Use of Repetitive Transcranial Magnetic Stimulation (rTMS) to Augment Hypnotic Analgesia

Informed Consent Form

NCT02969707

May 28, 2019

# SCREENING CONSENT FORM

**********

Are you participating in any other research studies? _____ Yes _____No

Please read this form carefully. It tells you important information about a research study. A member of our research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called "subjects." This term will be used throughout this consent form.

If you have any questions about the research or about this form, please ask us. Taking part in this research study is up to you. If you decide to take part in this research study, you must sign this form to show that you want to take part. We will give you a signed copy of this form to keep.

## PURPOSE OF RESEARCH

We are doing this research study to find out if a new treatment for pain is effective for treating pain in people who have a diagnosis of Fibromyalgia. This new treatment called repetitive Transcranial Magnetic Stimulation (rTMS) involves stimulating the brain with an electromagnet placed on the scalp that rapidly turns on and off. As the magnet rapidly turns on and off, the electrical currents in the brain tend to synchronize with the magnet. This treatment does not involve any form of anesthesia or mild sedation. You will be able to drive immediately after the treatment and there are no limitations on activity after the treatment. Brief treatments with rTMS appear to help patients with pain.

rTMS is approved by the U.S. Food and Drug Administration (FDA) for the treatment of depression. However, rTMS is **not** approved by the FDA for the treatment of pain.

We are asking you to take part in this study looking at a new way of combining TMS with hypnosis to treat pain because you have a diagnosis of fibromyalgia. We hope to learn if the combination of transcranial magnetic stimulation and hypnosis is effective in treating pain. The name of this new treatment is "rTMS-augmented hypnotic analgesia." You were selected as a possible participant in this study because you have a history of pain related to fibromyalgia.

This research study will compare active rTMS versus sham (or pretend) rTMS in combination with hypnosis. You will have a 50% chance of receiving either active or sham rTMS. Every subject will receive hypnotic analgesia in addition to either active or sham rTMS.

If you decide to terminate your participation in this study, you should notify Dr. Nolan Williams (Co-PI) at [redacted].

This research study is looking for 100 subjects with Fibromyalgia for the study. Stanford University expects to enroll 100 research study participants.

## VOLUNTARY PARTICIPATION

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

## DURATION OF STUDY INVOLVEMENT

This research study is expected to take approximately 3 years to complete. Active involvement for individual participants will require 2 screening visits and 2 study visits. The duration of total time will be dependent on your availability as well as the study team's scheduling availability.

## PROCEDURES

If you choose to participate, the Protocol Director and his research study staff will ask you to sign two consent forms. In this first consent form, you will be asked to give your consent for the research staff to evaluate your eligibility to participate in this research study. Based on the results of the screening assessments, if you are identified as an eligible participant, the Protocol Director will then consent you to the study procedures, which will include the MRI scans, rTMS treatments, hypnotic procedures and assessments.

### Screening Visit

The screening visit will take about 3 hours and will be broken up into 2 separate visits. During the screening, we will do some tests and procedures to see if you qualify to take part in this research study. The study doctor or research staff will review the results of these tests and procedures.
At this visit will we will:

- Ask about your medical history
- Complete some questionnaires to confirm a diagnosis of Fibromyalgia

- Draw a blood sample if you have not had blood work done in the past year. If you have, we will request a copy of this blood work from your doctor.
- Give you some questionnaires to fill out about your general health and well-being, pain, mental health, emotional health, and mood.
- Complete a questionnaire to carefully screen for TMS safety. The purpose of this form is to assess if you are at an increased risk for adverse effects from TMS based on safety considerations.
- Complete a screening MRI scan.

Urine Drug Screen
During this study, we will test your urine for certain drugs, including illegal drugs such as cocaine and other opiates. If your urine shows you have taken any of these drugs, you can't be in this study. The results of the urine drug test will not become part of your permanent medical record. These test results will, however, remain part of your study record. If the drug screen was positive for an illicit drug and was subpoenaed or somehow disclosed, an unlikely event, it could be incriminating. The responses to questions concerning illegal drug use could be self-incriminating and harmful to you if they became known outside the study. As explained in the confidentiality statement of the consent, we do not intend to disclose this information.

Stopping Your Current Medications ("The Washout Period")
If you qualify for the study, we may ask you to stop taking some of your current medications during the study. This allows your regular medications to leave your body, and is called the washout period. The study doctor will help you come up with a plan to stop these medications safely, and monitor your condition throughout the washout period. This plan will be created in consultation with you and your physician. Without your regular medications, some of your symptoms may get worse. If this happens, please call your physician AND the study doctor at the phone number provided in this consent form.

The study doctors will tell you how to slowly stop taking some of your medications. This will help your body adjust to the change and may prevent your pain from getting worse. Additionally, the research staff will contact you during the washout period to make sure that your symptoms are not getting worse.

**Pain Assessments**
Baseline pain intensities and maximum heat tolerance temperature will be determined for you using an MRI-safe thermode stimulator during the study visit assessing pain. Pain threshold will be determined using a steadily increasing sensation to establish the pain threshold. Decreased pain ratings will indicate

that the intervention is having an effect. You will be asked to rate your thermode-evoked pain following each block of stimulus during each scan. You will separately be asked to rate your fibromyalgia-related pain during each scan using the same scale.

**Related Studies**
Data collected during participation in the current study will be used for data analyses in other studies within our research group. No additional disclosure of PHI will occur. Data will not be shared outside of the research group except as otherwise described in this consent form.

## PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

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

## WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

If you decide to withdraw your consent to participate in this study, you should notify Dr. Nolan Williams at [redacted]. At that time, your care will be transferred back to your primary physician for further assessment and treatment.

If you withdraw from the study,

- You will no longer be eligible for this experimental treatment and will be referred back to the primary physician providing psychiatric care prior to starting the study.

The Protocol Director may also withdraw you from the study and the study experimental treatment may be stopped without your consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and study staff.
- The Protocol Director decides that continuing your participation could be harmful to you.
- Pregnancy
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

## POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director if you have any questions.

Risks of rTMS
The most important risk associated with the TMS procedure is a risk of a seizure during the procedure. There is no known risk of seizure with the stimulation parameters selected for this study. TMS has been shown to cause seizures with other parameters that use more energy than this study is using. There is no known risk of seizure after the procedure. Ear plugs will be provided for this research study.

Risks of MRI
During this time, you will not be exposed to X-rays but rather a magnetic field and a radio frequency magnetic field. You will not feel either. However, there is a possibility that you will experience a localized twitching sensation due to the magnetic field changes during the scan. This is not unexpected and should not be painful. Dizziness or nausea may occur if you move your head rapidly within the magnet. If you feel discomfort at any time, notify the operator and you can stop the exam at any time.

The scanner uses a very strong magnet that will attract some metals and affect some electronic devices. As such, the researchers will follow the CNI safety protocols to check that you do not have medical devises or conditions that can

cause a strong attraction to the magnet. These devices include cardiac pacemakers, surgical clips and implants that are in or on your body.

These devices must be removed (if possible) before entering the magnet room. In some cases, having those devices means you should not have an MRI scan performed.

We will also check for additional items that may be attracted to the magnetic field of the scanner or impacted it. These include watches, credit cards (in your pockets, etc.), removable or irremovable jewelry, and tattoos. To establish safety, the researchers might need to ask you about the specifics of these items (e.g., for tattoos, how big they are, how old they are, where on the body, what colors they have, etc.). You will be provided a way to secure these items, such as watches and credit cards.

In addition, we will check for medical histories relevant to establishing safety in the MRI. These include any history of head or eye injury involving metal fragments, if you have ever worked in a metal shop, and any kidney problems.

Some of the radio frequency imaging coils, the imaging software and other devices being used to perform scans are not approved by the FDA, thus are considered experimental in nature.

Incidental MRI Findings: The scans performed in this study are for specific research purposes and are not optimized to find medical abnormalities. Our research scans do not qualify as a clinical diagnostic scan. The investigators for this project may not be trained to perform medical diagnosis. The investigators are not responsible for failure to find existing abnormalities with these MRI scans. However, on occasion the investigator may notice a finding on an MRI scan that seems abnormal. If this occurs, we will follow CNI's protocol for incidental findings. In this case the research scans are referred to an approximately qualified individual (neuroradiologist) designated by the CNI Board for further review, the reviewer will determine if the potential abnormality merits further investigation and will inform the Principal Investigator of the action to be taken. The CNI operations team promptly provides a DVD with the scans in question or in another way that makes the images available to the reviewer to be read "as is". The reviewer, a doctor specializing in MRI, will be asked to look at the images to see if any medical follow-up is needed. If follow-up is recommended, the investigator will contact you with the appropriate information. Because the images are taken using research settings, they will not be made available for clinical purposes.

An exception will be for participants recruited from a residential treatment program in a facility in which all medical record updates (including any record of an incidental finding that occurs because a doctor at Stanford looks at the research scan) are shared with the treatment providers as part of the inpatient program.

Finding out that you may have a medical abnormality that you had not been aware of before could cause psychological stress to you or your family and possibly affect your health insurance coverage in the future.

Risks of thermode stimulation
The main risk of thermode stimulation is a remote risk of skin injury or burning by the overheating of the skin. However, there will be a safety stop in place that will not allow the thermode to heat up to a temperature sufficiently high to cause damage to the skin.

Risks of hypnotic analgesia
There have been no identified risks involved with hypnotic analgesia.

Risks of Stopping your Current Medications
During the washout period, when you may stop taking some of your current medications, your condition might get worse; the research team and study doctor will monitor during the washout period to make sure that your symptoms are not getting worse. If this happens, contact the study doctor.

Answering questions on some of the questionnaires and interviews used in this study may provoke mild feelings of frustration, fatigue, sadness or anxiety. You have the right to refuse to answer any question that makes you feel uncomfortable on any of the questionnaires or interviews. Information you provide will remain anonymous and will be used only for the purposes of the research study. However, it is possible that, based on information gained from this study, the researchers may be required to report information (e.g., information relating to suicide, physical or sexual abuse or other conditions reflecting imminent risk) to the appropriate authorities.

There may be other risks associated with participating in this study that are unknown.

## POTENTIAL BENEFITS

You may or may not benefit from taking part to the study. If you receive Active rTMS, it is possible that your pain symptoms may improve. However, if the rTMS treatment is helpful for you, it is still unlikely that you will be able to

continue to receive rTMS treatment upon completion of the study.

The study may also benefit other people with Fibromyalgia by furthering our understanding of the effectiveness and safety of rTMS for the treatment of pain. We cannot and do not guarantee or promise that you will receive any benefits from this study.

## ALTERNATIVES

The alternative is to not receive the experimental therapy, and simply continue with the existing therapy for pain.

## PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, tell the Protocol Director.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

## ClinicalTrials.gov

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

## CONFIDENTIALITY

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed except as authorized by you or as required by law**.** However, there is always some risk that even de-identified information might be re-identified.

Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

The purpose of this research study is to obtain data or information on the safety and effectiveness of transcranial magnetic stimulation in participants with pain. The results will be provided to the sponsor, the Food and Drug Administration and other federal and regulatory agencies as required.

We will keep your study data as confidential as possible, with the exception of certain information that we must report for legal or ethical reasons to the proper authorities, such as suspected child, elder or dependent abuse or neglect, or potentially dangerous future behavior to others or yourself.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by NIH which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law of abuse, neglect or harm to self or others.

# Authorization To Use Your Health Information For Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

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

The purpose of this study is to determine if a type of rTMS is effective as an augmentation strategy to hypnotic analgesia. There will be two groups, active or sham rTMS. If you are eligible for this study, you will have two MRI scan sessions with one week apart. The information gathered in this study will be submitted to the sponsor and the FDA.

## Do I have to sign this authorization form?

You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study including receiving any research-related treatment. Signing the form is not a condition for receiving any medical care outside the study.

## If I sign, can I revoke it or withdraw from the research later?

If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your health

information in this study, you must write to: (Dr. David Spiegel, 401 Quarry Road, Palo Alto, CA 94304).

## What Personal Information Will Be Obtained, Used or Disclosed?

Your health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to,

- Your name
- Your address
- Your telephone number
- Your date of birth
- Your social security number
- Other details about you, such as your race/ethnicity or gender
- The PHI obtained in this study will include trial records, information about general health, mental health history, physical examinations, side effects experienced and the result of any tests done during the study. This may include information in medical records and information created or collected during the study.

## Who May Use or Disclose the Information?

The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Directors, David Spiegel, MD and Nolan Williams, MD.
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Research Staff

## Who May Receive or Use the Information?

The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S.

- Department of Health and Human Services
- National Institute of Health (NIH)
- Food and Drug Administration (FDA)
- Research group Protocols IRB numbers 33797 and 39234

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

**When will my authorization expire?**
Your authorization for the use and/or disclosure of your health information will end on January 01, 2030 or when the research project ends, whichever is earlier.

**Will access to my medical record be limited during the study?**
To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make a medical or billing decision about you (e.g., if included in your official medical record).

_____
Print Name of Adult Participant

_____ _____
Signature of Adult Participant Date

## FINANCIAL CONSIDERATIONS

Payment
You will be paid a total of $300 when you complete the study. If you do not meet the criteria for the study, you will be paid $50 for the screening visit. Payments may only be made to U.S. citizens, legal resident aliens, and those who have a work eligible visa. You may need to provide your social security number to receive payment.

Costs
There is no cost to you for participating in this study, other than basic expenses like transportation and the personal time it will take to come to all of the study visits.

Sponsor
The sponsor for this study is the National Institutes of Health (NIH).

## COMPENSATION for Research-Related Injury

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.**

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

You do not waive any liability rights for personal injury by signing this form.

## CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the Co-Protocol Director, Nolan

Williams, MD at [redacted]. You should also contact him at any time if you feel you have been hurt by being a part of this study.

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at [redacted] or toll free at [redacted]. You can also write to the Stanford IRB, Stanford University, 3000 El Camino Real, Five Palo Alto Square, 4th Floor, Palo Alto, CA 94306.

## EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

May we contact you about future studies that may be of interest to you?

____ Yes ____ No

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

_____
Print Name of Adult Participant

_____ _____
Signature of Adult Participant Date

_____
Print Name of Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date