Subject's Name: **Date:**

Principal Investigator: Dr. McRae-Clark

Study Title:
An Exploratory Investigation Utilizing Repetitive Transcranial Magnetic Stimulation (rTMS) as a Tool to Decrease Pain and Improve Functioning in Veterans with Opioid Use Disorder

SUMMARY:

This is a research study and is voluntary. The purpose of this study is to determine if repetitive transcranial magnetic stimulation (rTMS) reduces opiate craving, and pain, when given to people who are undergoing treatment for opiate use disorder. The study takes 7 visits over approximately three months. There will be a screening visit, 3 treatment visits and 3 follow-up visits.

During rTMS, focused magnetic waves are directed at a part of the brain that is important in pain and craving to increase its activity. If you participate, you will receive six sessions of either active rTMS, or placebo rTMS, each day for three (18 total sessions). Each session lasts 15 minutes. People typically do not have side effects with rTMS, though they initially may find it mildly painful at the application site. About 1 out of every 20 people who get rTMS have mild headaches after sessions that are typically relieved with over-the-counter medicines. A few people who have had rTMS have had seizures, though the chance of this happening is very small.

People who receive active rTMS may have a reduction in any pain they are experiencing, and may also have fewer opiate cravings, though it is unknown whether or not rTMS helps with either pain or craving. There is also a chance that you will receive the placebo rTMS, and will not have any direct benefit. Regardless of whether you are individually helped during this study, your participation will help the researchers learn if rTMS can help people who are being treated for opiate use disorder.

Since this is an add-on study to your treatment program, the alternative to participating in the study is to simply not participate. You will then receive the typical treatment without rTMS.

A. PURPOSE AND BACKGROUND:

Please read this consent form carefully and take your time making your decision. As your study doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. You are being asked to participate in this study because you are a Veteran being treated for opioid use disorder. The study is sponsored by the Medical University of South Carolina and the Ralph H. Johnson VA Medical Center. The investigator in charge of this study is Aimee McRae-Clark. The study is being done at one site. Approximately 20 people will take part in this study.

The purpose of this study is to determine if repetitive Transcranial Magnetic Stimulation (rTMS) can reduce opiate craving or pain in participants undergoing treatment for opioid use disorder. rTMS is an FDA approved treatment for depression, and is used commonly to treat people if medications are not helpful for their depression. It works by rapidly turning a focused magnetic field on-and-off over your head which passes directly through your hair, scalp, and skull and on to your brain, and can temporarily increase or decrease brain activity under the magnetic field. rTMS is not currently FDA approved to

treat any addictions, however previous studies using rTMS have shown that it can reduce drug use and craving in other addictions. We are hoping to find out if it can reduce opiate craving and pain. In order to see if it works, we will do a study where half of the participants receive active rTMS, and half will receive a placebo rTMS which looks and sounds like active rTMS, but does not have any effect. There is a 50:50 chance you will receive the active rTMS (like a coin flip), and neither you nor the investigators will know if you got active rTMS.

B. **PROCEDURES:**

If you agree to be in this study, the following will happen:

For this study, you will receive either active or placebo rTMS. Placebo rTMS sounds and feels just like active rTMS, but has no effect on brain function. You have a 50% chance of receiving the active rTMS, and a 50% chance of receiving the Placebo rTMS.

On your first visit:

You will meet with the study team and undergo a standardized interview. You will be asked about psychiatric, substance use and medical history. If you are eligible, you will be asked to fill out several questionnaires about your substance use, mental health, pain and medical history. If you are a woman of childbearing age, you will have a urine pregnancy test. If the pregnancy test is positive, you will not be allowed to continue in the study. If you are male or your pregnancy test is negative your urine will be tested for drugs of abuse.

Treatment phase:

Prior to each session of rTMS, you will provide a urine sample that will be tested for drugs of abuse and you will have a breathalyzer test performed. You will fill out questionnaires about your mood, pain, and recent drug use.

You will receive six rTMS sessions each day for three days (a total of 18 sessions). Each session will take about 15 minutes, and you will have a break that lasts about thirty minutes in between sessions. We will provide you and require that you wear a special hat, similar to a swimmer's cap, during each of the rTMS sessions, which will allow us to place the TMS coil in the same spot each time. During each session, you will be awake in a reclined chair. The sessions feel like there is a mild tapping on your head that comes and goes. Some people find these sessions uncomfortable at first, but usually adjust to the tapping feeling. You will be presented with

pictures of opiates during rTMS. Before and after each session, we will ask you about your opiate craving, and how painful the rTMS is.

Pain threshold:

At your first and third TMS visits, we will test your response to pain by using a blunt probe that will be pressed into one of your forearms while recording your response to the pressure (when you feel pain). The pain test will then be repeated while your opposite hand is submerged in cold water (4° Celsius, or 40° Fahrenheit). Finally, you will leave your hand in the cold water until it becomes painful to you, and you will then remove it. There is no chance that either the probe or the cold water can cause you any injuries, and both of these procedures will be stopped when they become painful to you. Your pain response will tested again at the one-week follow-up.

Follow- up:

You will be scheduled to come in one-week, four-weeks and three months after your final rTMS session. During those visits, you will provide urine samples to be tested for drugs of abuse and you will be asked to repeat questionnaires about mood, opioid withdrawal and craving, pain, and recent drug use. Additionally, we will check your VA electronic medical record to check things such as how many appointments you have attended, and which medications you have been prescribed.

You may be withdrawn from the study without your consent if the researchers believe it is in your best interest of if you fail to follow study procedures.

While participating in this research study, do not take part in any other research project without approval from the investigators. This is to protect you from possible injury from things such as extra blood drawing, extra X-rays, or potential drug interactions. Taking part in other research studies without first discussing it with the investigators of this study may invalidate the results of this study, as well as that of the other studies.

C. **DURATION:**
Participation in this study will involve a total of 7 visits over approximately three months. The screening visit may take up to 3 hours. Treatment visits will take approximately five hours spread out over the day, and follow-up visits will take approximately 30 minutes each.

D. **RISKS/DISCOMFORTS:**
Potential Risk of Randomization: Since there is a 50% chance you will not get the active treatment, the

treatment you receive may prove to be less effective, or to have more side effects than the other study treatment, or other available treatments.

Potential Risk of the Drug Cue Task:
Exposure to opiate cues may produce some craving for opiates or other discomfort. However, this discomfort is usually brief and you will be in the opiate-free safety of the hospital.

Potential Risk of the Pain Testing: The pain testing may be uncomfortable for you, however the study staff will stop the pain testing when it becomes uncomfortable, and there is no risk of permanent injury.

Potential Risks of rTMS:

Potential risk of a seizure: rTMS acts in the brain at below the level that would cause a seizure, although eight seizures have been reported. Six seizures were in healthy volunteers without any history of seizures or brain issues. The risk of seizure is related to how long and intense the TMS treatments are. One seizure has been reported since 1997 when new safety guidelines were put in place, and the TMS in that case was at a very high intensity. To our knowledge, the settings we use will not cause seizures, and we will adjust treatments based on your individual needs. If you have a seizure, you will lay down with your legs up and an emergency response team will be called. Most seizures, including those caused by rTMS, last less than 60 seconds and do not require any medication. Once you recover from the seizure, you will be seen by a neurologist. Any participant who has a seizure cannot continue with the study.

Potential for scalp discomfort and headaches: Some people have some mild discomfort when the rTMS is administered, and a small number of people (~5%) report headache following rTMS. However, the headaches are temporary and manageable with common over-the-counter pain remedies such as acetaminophen.

Potential hearing loss: When in use, the TMS machine makes a clicking sound that may cause hearing loss. People have had temporary decreases in hearing sensitivity (especially at high frequencies) lasting at least 5 minutes and less than 4 hours. Earplugs protect hearing and will be worn during rTMS sessions.

Safety in case of pregnancy: The risks of using rTMS with pregnant women are currently unknown. Pregnant women will not be allowed to participate.

Unknown Risks: rTMS is an experimental procedure that has not been approved by the FDA as a treatment for addiction and it may have unknown side effects. It is approved for the treatment of depression, and there are now several thousand patients who have experienced rTMS much like you will receive it in this study. You will receive 18 sessions. For the treatment of depression patients return for anywhere from 20-36 sessions over several weeks. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

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Risks regarding Confidentiality:
If you are pregnant and test positive for illegal drugs, SC state law requires that the SC Department of Social Services (DSS) be notified if your drug use is endangering your developing fetus if you are 24 weeks or greater of gestation. You will be at risk of going to jail or losing custody of your children. If you are pregnant however, you will not be eligible to participate in the study, and we will not test your urine.

Despite efforts to maintain participants' anonymity and confidentiality, there is always some minimal risk of people other than the study investigators gaining access to your health information. The information we collect will contain your initials and/or code number and not your name to protect your confidentiality. Codes linking numbers and names will be kept in a locked secure location and will not be accessible to anyone outside the research team, You should also know that if you threaten to harm yourself or others or give information about child or elder abuse, this information will be reported to appropriate clinical staff and other persons outside the research program as necessary to protect yourself and others as mandated by law.

Your urine will be screened for the use of opiates and other potentially abused or illegal drugs. The results will not be part of your medical record but will be kept in research records maintained by the investigator. Every effort will be made to protect the confidential nature of this information. There may however be circumstances under which the investigator would be legally required to release this information.

There is always a chance that any procedure can harm you. The procedures in this study are no different. In addition to the risks described above, you may experience a previously unknown risk or side effect.

Risks of the usual care you receive are not risks of this study. Those risks are not included in this consent form. You should talk with you healthcare providers if you have any questions about the risks of usual care

E. **MEDICAL RECORDS:**
If you are a Ralph H. Johnson VA Medical Center patient, you have a VA medical record. Results of research tests or procedures will be included in your VA medical record. All information within your medical record can be viewed by individuals authorized to access the record. We will make every effort to keep confidential all research information in the medical record that identify you to the extent allowed by law.

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F. **BENEFITS:**
There is a 50% chance that you will receive a course of rTMS. It is possible rTMS may help reduce opiate craving and/or pain. It is also possible that rTMS may not be helpful, so there may be no direct benefit to you from participating in this study. It is hoped that the information gained from this study will help the investigators learn more about how rTMS affects opiate use, opiate craving, and pain.

G. **COSTS:** You will not be charged for any treatments or procedures that are part of this study. If you usually pay co-payments for VA care and medications, you will still pay these copayments for VA care and medications that are not part of this study.

H. **PAYMENT TO PARTICIPANTS:** In return for your time, effort and travel expenses, you will be paid $40 for completing the screening visit, $40 for each rTMS day, and $40 for each follow-up visit, for a possible total of $280. Payments will be made with electronic funds transfer. The IRS requires a tax form be filed if your compensation exceeds $600.00/year. However, if the payment for participation will be made through Austin Financial Services Center, it may generate IRS Form 1099 automatically, regardless of amount.

I. **ALTERNATIVES:**
Your alternative is to not participate in this study. This is a scientific investigation and not part of standard clinical care. This study is voluntary and you may choose to not participate in this study. Whether or not you choose to participate in this study will not affect your relationship with any current treatment provider you may have, or your right to health care or other services to which you are otherwise entitled now or in the future.

J. **DATA SHARING:**

You will not receive a report of the study's findings. If there are significant new findings during the course of the study, you will be notified.

K. **DISCLOSURE OF RESULTS:**

Information about you (including your identifiable private information and/or any identifiable biospecimens) may have all of your identifiers removed and used for future research studies or distributed to other researchers for future research without additional informed consent from you or your legally authorized representative.

L. **CLINICAL TRIAL REGISTRY DATABANK:** 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.

CONSENT

Results of this research will be used for the purposes described in this study. This information may be published, but you will not be identified. Information that is obtained concerning this research that can be identified with you will remain confidential to the extent possible within State and Federal law.

The investigators associated with this study, the sponsor, and the MUSC Institutional Review Board for Human Research will have access to identifying information. There are times when we may have to show your records to other people from Federal agencies that oversee our research such as the Department of Health and Human Service's Office of Human Research Protections, the Food and Drug Administration (for FDA regulated research only), the Government Accountability Office, the Office of the Inspector General, the VA Office of Research Oversight, our local VA Research and Development Committee, and other study monitors may look at or copy portions of records that identify you. Also, all records in South Carolina are subject to subpoena by a court of law.

The VA will provide necessary medical treatment to a research subject injured by participation in a research project. This requirement does not apply to treatment for injuries that result from non-compliance by a research subject with study procedures. If you sustain an injury as a direct result of your study participation, medical care will be provided by the Ralph H. Johnson VA Medical Center. Financial compensation is not available for such things as lost wages, disability or discomfort due to an injury.

Your participation in this study is voluntary. You may refuse to take part in or stop taking part in this study at any time. You should call the investigator in charge of this study if you decide to do this. Your decision not to take part in the study will not affect your current or future medical care or any benefits to which you are entitled.

The investigators and/or the sponsor may stop your participation in this study at any time if they decide it is in your best interest. They may also do this if you do not follow the investigator's instructions.

Department of Veterans Affairs Ralph H. Johnson VA Medical Center	Research Consent Form Version Date: 01.02.20

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Volunteer's Statement

A research study doctor or coordinator has explained the research study to me. 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 have been given the chance to ask questions and obtain answers.

If I have any more questions about my participation in this study or study related injury, or if I have comments, concerns or complaints, I may contact: **Dr. McRae-Clark at (843) 792-5216.**

If I have questions about my rights as a study participant, or I want to make sure this is a valid VA study, I may contact the Medical University of South Carolina's Institutional Review Board (IRB). This is the Board that is responsible for overseeing the safety of human participants in this study. I may call the MUSC IRB (843) 792-4148, or the Ralph H. Johnson VA Medical Center's Research Compliance Officer at (843) 789-7399, if I have questions, complaints or concerns about the study or if I would like to obtain information or offer input.

By signing this document below, I voluntarily consent to participate in this study. I also confirm that I have read this consent, or it has been read to me. I will receive a copy of this consent after I sign it.

I agree to participate in this research study as has been explained in this document.		
_____ Participant's Name	_____ Participant's Signature	_____ Date

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_____ Name of person obtaining consent	_____ Signature of person obtaining consent	_____ Date