Official Title: Project Relief: Developing Brain Stimulation as a Treatment for Chronic Pain
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School of Medicine

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Department of Cancer Biology

PROJECT RELIEF: DEVELOPING BRAIN STIMULATION AS A TREATMENT FOR CHRONIC PAIN

Informed Consent Form to Participate in Research
Dr. Colleen Hanlon, PhD, Principal Investigator

SUMMARY

You are invited to participate in a research study. The purpose of this research is to develop transcranial magnetic stimulation (TMS) as a potential treatment for pain. You are invited to be in this study because you have current chronic pain and may or may not be currently using prescription opiates for your pain. Your participation in this research will involve 24 visits and last about 4 and one-half months.

Participation in this study will involve the following: a screening visit, 16 sessions of TMS (real or placebo TMS, 2x/visit, 3 days/week for 4 weeks followed by 1 day/week for 4 weeks), 3 functional magnetic resonance imaging (MRI) scans of your brain, and 4 follow-up visits every other week for 8 weeks. All research studies involve some risks. A risk to this study that you should be aware of is TMS and MRI risks. For TMS, there are potential risks of seizure, headache, scalp discomfort, hearing loss, and fainting. For the MRI, there is potential risk to individuals with metallic implants or medical devices. Additionally, participants may feel restless or uncomfortable lying in the MRI scanner. The treatment you receive may prove to be less effective or to have more side effects than the other study treatment(s) or other available treatments. There is the possibility that you may benefit from participation in this study.

Your participation in this study is voluntary. You do not have to participate in this study if you do not want to. There may be other choices available to you. Some other choices may include other forms of treatment for pain including counseling and medication. You will not lose any services, benefits, or rights you would normally have if you choose not to participate.

The remainder of this form contains a more complete description of this study. Please read this description carefully. You can ask any questions if you need help deciding whether to join the study. The person in charge of this study is Dr. Colleen Hanlon. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study his/her contact information is: chanlon@wakehealth.edu.

If you have any questions, suggestions or concerns about your rights as a volunteer in this research, contact the Institutional Review Board at [redacted] or the Research Subject Advocate at Wake Forest at [redacted].

INTRODUCTION

You are invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. You are being asked to take part in this study because you have current chronic pain and may or may not be using prescription opiates for your pain. Your participation is voluntary. Please take your time in making your decision as to whether or not you wish to participate. Ask your study doctor or the study staff to explain any words or information contained in this informed consent document that you do not understand. You may also discuss the study with your friends and family.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to develop repetitive transcranial magnetic stimulation (rTMS) as a potential treatment for pain. TMS is a technique that uses magnetic pulses to temporarily stimulate specific brain areas in awake people (without the need for surgery, anesthetic, or other invasive procedures). This study will test whether TMS can be used as an alternative tool to reduce your pain. TMS has not been proven to help with pain, but this study is intended to determine whether it might be an effective treatment in the future. TMS has been approved by the FDA as an investigational tool, as well a therapy for depression. However, TMS is not approved by the Food and Drug Administration as a treatment for pain and opiate use.

In this study real TMS will be compared to placebo. A placebo is made to feel like the real treatment, however it is not thought to have any effect on your disease or condition. In this study you will either receive the active study treatment, TMS or placebo which is not active. Placebos are used in research studies to see if the drug being studied really does have an effect.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

48 people at Wake Forest Baptist Health will be enrolled at this research site. In order to identify the 48 subjects needed, we may need to screen as many as 58 because some people will not qualify to be included in the study.

WHAT IS INVOLVED IN THE STUDY?

You will be randomized to receive either the real TMS treatment or the placebo TMS treatment at one of two possible locations. Randomization means that you are put into a group by chance. It is like flipping a coin. You will have an equal chance of being placed in any group.

Neither you nor the investigator will know which study treatment you are receiving. This is done so that a fair evaluation of results can be made. This information is available to the researchers if needed in an emergency.

If you take part in this study, you will have the following tests and procedures:

1. (Baseline Screening Visit/Consent): You will complete self-report screening measures

(on the computer) designed to assess your chronic pain, your opioid dependence (if applicable), your psychiatric history, and your mood. You will also be asked to track your daily pain medication consumption during the course of the study. You will be asked about your current height and weight, past medical history focusing on chronic (and current) medical problems, seizure history, medications, psychiatric disorders, and substance use. The research procedures, risks, and benefits will be explained.

2. (Urine screening: Screening, Visits 1, 4, 7, 10, 13-20): If you are a woman of childbearing age, you will undergo a pregnancy test by providing a urine sample. The pregnancy test is important because the effects of TMS on the developing fetus in the first trimester of pregnancy are unknown. As such, if you are a pregnant female or lactating, you cannot participate and will be excluded from the study. Birth control methods that are acceptable include abstinence, oral contraceptive pills, or other types of hormones (like Depot-Vera or Norplant) and use of condoms.

   If you are not pregnant, you will have a urine drug screen to detect the presence of drugs in your urine. If you are a man, TMS is not known to affect the sperm and you are not required to use contraceptive measures. Magnetic stimulation is not allowed in people who have a pacemaker, an implanted medication pump, a metal plate in the skull, or metal objects inside the skull (for example, after brain surgery). You will complete a urinalysis drug screen and carbon monoxide (CO) breathalyzer test in order to determine how much alcohol, nicotine, opiates, and other drugs that are in your system.

3. (Pain assessment – Visits 1, 7, 12, 13-20): If you qualify for the study and agree to continue, you will undergo a brief quantitative pain sensitivity task to assess your baseline threshold for pain. A pressure algometer will be used for this assessment. The algometer has a rubber tip which will be pressed into your right forearm. You will be asked to indicate when you first detect a pressure change (sensory threshold), when the stimulus becomes painful (pain threshold), and when you want the threshold testing to end (tolerance threshold). At this time, the algometer will be released immediately.

4. (MRI scanning): Before visit 1 and after visits 12 and 16, you will have a Magnetic Resonance Imaging (MRI) exam of your brain. This test will provide us with an image of your brain and brain activity during various tasks. You will lie still in the MRI machine for about 45 minutes while this image is being made. The MRI does not use radiation, but it can be difficult for persons who have fear of being closed in small spaces because it can feel somewhat confining in the MRI scanner. The MRI utilizes magnetism so you will need to remove loose metal objects such as earrings and key chains prior to the procedure for your safety. If you have pieces of metal in your body, such as a pacemaker or aneurysm clip, you cannot have a MRI. Since you will undergo a regular MRI brain scan procedure, you may benefit from knowing that there are no obvious structural abnormalities of your brain. These research MRI techniques are different from a MRI obtained for medical reasons. However, this is not a study for diagnostic purposes and will not be read by a radiologist. If, by chance, something abnormal is observed, you will

be informed of this and counseled as to what clinical referral would be appropriate.

5. (rTMS overall – Visits 1-16): If you qualify for the study and agree to continue, you will be randomized to receive either placebo-like TMS treatment or one of two real TMS treatments. The randomization process works like flipping a coin, and is pre- determined by a computer program and not by the researchers. A placebo is an inactive treatment that is designed to mimic the sounds, feelings and appearance of the real thing. You will not be told which type of stimulation you are receiving during the treatment session. This improves our ability to determine how effective the treatment is. Previous studies have indicated that the perception of these two types of stimulation is not discernible. This is done so that we can be sure our active treatment is really having an effect. For each of these visits you will arrive at the research laboratory and will be greeted by a member of the Study Personnel. On each of these visits, you will fill out several questionnaires related to pain, mood, and craving. These questionnaires will track your current pain and discomfort levels and assess your urge to use any medications to relieve your pain. You will complete these assessments at each visit before your rTMS session. We will also ask you to track your pain medication consumption daily. We will try to schedule treatments at the same time of day for all of your treatments. You will be asked to do your best to abstain from using any pain medication for 2 hours prior to the rTMS treatment session. You may miss up to 3 sessions of TMS, but all sessions must take place within the 2 month period of TMS.

6. (rTMS motor threshold – Visits 1, 7, 13, 15): Regardless of which treatment you receive, during your visits (real or placebo rTMS), the researchers will first determine your individual level of thumb muscle response to TMS pulses (called the resting motor threshold, rMT). This is done because everyone's response to TMS is a little different, and we want to make sure that we give you the right "dose" of TMS. The researcher will ask you to hold out your hand and fingers. He/she will then slowly and carefully move a magnetic coil over your head. The coil will send a single magnetic pulse every 1-2 seconds. The researcher will continue to move the coil until he/she finds the specific brain area that results in slight movement of your thumb. Once the researcher has your rMT, the research will measure your individual response level to TMS pulses.

7. (rTMS treatment – Visits 1-12): You will receive either two real TMS session over the left side frontal head or two sham TMS session during your treatment sessions (2 sessions/visit, 3 visits per week, for 4 weeks). You will receive only one pattern of stimulation, either two sessions of continuous stimulation for 39 seconds, or two sessions of discontinuous stimulation, where you will have stimulation for 2 seconds followed by 8 seconds of rest for a total duration of 3 minutes. During the TMS sessions, we will ask you to think about your current chronic pain.

8. (rTMS tapering sessions – Visits 13-16): You will receive the same type of rTMS treatment that you received previously, but will come in for your two rTMS sessions once per week. We will try to schedule you to come in on the same day each week around the

same time.

9. (rTMS assessments and self-report questionnaires: All Visits): During each rTMS session, you will complete the same set of computer based visual analog ratings for discomfort, stress, and desire to use a pain reliever. You will also be asked about how much money you would spend on a pain reliever of your choice. You will be asked these short questions between the two rTMS sessions at each visit.

10. (Follow-up visits – Visits 17-20): You will have four in person follow-up visits every other week for two months after the last rTMS session. At these follow-ups, you will be asked to complete the assessments rating your current pain, mood, and desire to use a pain reliever on a computer. You will also undergo a urine screen as well as the pain assessments at these visits.

Table 1. Summary of Events During Each Study Visit

Visit	Visit Procedures	Payment to Participant
Screening	-Questionnaires on Medical History -Self-reported Screening Measures -Urine screen -Questionnaires on pain, mood, and craving	$20
MRI V1	-Functional MRI	$30
1 (Week 1)	-Urine screen -rTMS Treatment Session #1 -Questionnaires on pain, mood, and craving -Quantitative Pain Assessment	$20 for TMS
2	-rTMS Treatment Session #2 -Questionnaires on pain, mood, and craving	$20
3	-rTMS Treatment Session #3 -Questionnaires on pain, mood, and craving	$20
4 (Week 2)	-Urine screen -rTMS Treatment Session #4 -Questionnaires on pain, mood, and craving	$20
5	-rTMS Treatment Session #5 -Questionnaires on pain, mood, and craving	$20
6	-rTMS Treatment Session #6 -Questionnaires on pain, mood, and craving	$20

7 (Week 3)	-Urine screen -rTMS Treatment Session #7 -Quantitative Pain Assessment -Questionnaires on pain, mood, and craving	$20
8	-rTMS Treatment Session #8 -Questionnaires on pain, mood, and craving	$20
9	-rTMS Treatment Session #9 -Questionnaires on pain, mood, and craving	$20
10 (Week 4)	-Urine screen -rTMS Treatment Session #10 -Questionnaires on pain, mood, and craving	$20
11	-rTMS Treatment Session #11 -Questionnaires on pain, mood, and craving	$20
12	-rTMS Treatment Session #12 -Quantitative Pain Assessment -Questionnaires on pain, mood, and craving	$20 for TMS
MRI V2	-Functional MRI	$30
13 (Week 5)	-Urine screen -rTMS Maintenance Session #13 -Quantitative Pain Assessment -Questionnaires on pain, mood, and craving	$20
14 (Week 6)	-Urine screen -rTMS Maintenance Session #14 -Quantitative Pain Assessment -Questionnaires on pain, mood, and craving	$20
15 (Week 7)	-Urine screen -rTMS Maintenance Session #15 -Quantitative Pain Assessment -Questionnaires on pain, mood, and craving	$20
16 (Week 8)	-Urine screen -rTMS Maintenance Session #16 -Quantitative Pain Assessment -Questionnaires on pain, mood, and craving	$20 for TMS
MRI V3	-Functional MRI	$30
17 (Week 10)	-Urine screen -Quantitative Pain Assessment -Questionnaires on pain, mood, and craving	$20

18 (Week 12)	-Urine screen -Quantitative Pain Assessment -Questionnaires on pain, mood, and craving	$20
19 (Week 14)	-Urine screen -Quantitative Pain Assessment -Questionnaires on pain, mood, and craving	$20
20 (Week 16)	-Urine screen -Quantitative Pain Assessment -Questionnaires on pain, mood, and craving	$20 + $20 completion bonus

Due to several COVID related factors, including challenges with scheduling and hesitation some participants may have wearing a mask in the MRI scanner, some participants may not receive the MRI portion of this study. You will not be compensated for an MRI scan that is not completed (i.e., unable to be scheduled or you do not attend). If you complete the entire study but are unable to complete the MRI portion, you will still receive the study completion bonus. As such, you may receive up to $530 total for completing the study.

How Long Will I Be in the Study?

You will be in the study for about 4 and one-half months.

You can stop participating at any time. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. If you choose not to participate, it 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.

What Are the Risks of the Study?

Being in this study involves some risk to you. You should discuss the risk of being in this study with the study staff. Risks and side effects related to the TMS device we are studying include:

1. Potential risk of a seizure: In designing this experiment, we have followed the latest safety guidelines for TMS. Despite these precautions, there is a chance of a seizure as a result of TMS. Eight seizures have been noted in previous studies, with six of them occurring in healthy volunteers without any history of seizures, brain tumors or traumatic brain injuries. All of these seizures have occurred during TMS with the participant in the treatment chair and a trained operator on hand. All seizures have stopped by themselves without any medication. No participants have had any problems after the seizures. Additionally, if a participant has a seizure an emergency response team will be called. Most seizures, including those caused by TMS, last less than 60 seconds and do not require any medication. Participants will be evaluated by a physician associated with the Research Laboratory following recovery from the seizure. Any participant who has a seizure cannot continue with the study.

Following the adoption and widespread use of safety guidelines, 1 seizure has been reported since 1997 and it involved parameters of higher settings than the safe range. The TMS used in this study follows the published TMS safety guidelines.

To further reduce this risk, we will ask a series of screening questions prior to TMS administration. You will be asked if you have ever had a seizure or if any member of your family has ever had a seizure. You will be asked if you have any known tumors or lesions or if you have ever had an abnormal MRI or CI scan. We will ask if you have ever had a severe head injury and/or have ever been unconscious for more than a few minutes. A positive response to any of these screening questions will warrant follow-up questions and may mean you are ineligible to participate.

2. Potential for scalp discomfort and headaches: You may report some mild discomfort when the magnetic pulses are applied over your scalp, and a small number of people (~1 in 20 people) report headache following TMS. However, the headaches are temporary, go away on their own within 60 minutes, and are manageable with common over-the-counter pain remedies.

3. Potential worsening of mood with TMS: Several studies have so far demonstrated the feasibility of TMS as a treatment for depression. However, there is a chance you may feel that your mood is worsened, though there is no evidence that this will occur.

4. Potential Worsening of Pain with TMS: To date, we have not seen any evidence that TMS is associated with increases in pain perception or worsening of pain conditions. Most of the available evidence of the effects of TMS on pain perception suggests that TMS provides temporary relief from pain, a temporary decrease in sensitivity to pain, or no effect at all.

5. Potential hearing loss: The discharge of the TMS coil generates a high-energy click that may cause hearing damage. Foam earplugs can protect against these changes and will be given to you to wear during TMS sessions.

6. Potential changes in cognitive function: There have been no reports of long-term changes (more than a minute) in cognitive function (memory, attention, etc.) in TMS studies.

7. Safety in case of pregnancy: If you are pregnant, you will be excluded from this study. The risks of using TMS with pregnant women are currently largely unknown. All female participants will be required to be using an acceptable form of birth control (including abstinence) during the TMS visits in order to continue participation. If there is a chance you may be pregnant, a urine pregnancy test will be done. Further, while the risks of using TMS with pregnant women are unknown, there is no available evidence to date suggesting that TMS is harmful during pregnancy. Of note, South Carolina state law requires that the South Carolina Department of Social Services (DSS) be notified if a

pregnant woman tests positive for illegal drugs. You will be at risk of going to jail or losing custody of your children.

8. Potential for fainting event: Fainting or "passing out" is defined as a temporary loss of conscious. Although fainting episodes are very rare with TMS (less than 1 in 100 people), they typically occur before the TMS treatment, when the study members are finding your "dose" of TMS, known as the motor threshold. Individuals that are sleep deprived and have low or unstable blood pressure are at greater risk.

9. Unknown Risks: TMS is an experimental procedure that has not been approved by the FDA as a treatment for chronic pain and it may have unknown side effects. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

In addition to TMS risks, there may also be risks related to the MRI device we are using. This includes:

1. The risk from magnetic resonance imaging (MRI) is low. No radiation or x-rays are used in making pictures of your brain during the MRI's. You cannot have an MRI scan if you have metal in the skull, metal implants, a cardiac or brain pacemaker, or old metal fragments in the eye or retina. If you have a question about metal in your body, you should inform the researchers and they will determine whether it is safe in a MRI scan.

2. Some discomfort may occur from having to remain still for the 45 minutes you that will be in the scanner.

3. The MRI scanner is noisy, and there is a risk of hearing damage if you do not wear earplugs. To eliminate this risk, you will be given earplugs to wear during each scan.

4. Although the MRI scanner is open on both ends, some people become anxious when entering the MRI scanner due to the feeling of being enclosed. If this has happened to you in the past, you should inform the study personnel, as you may be ineligible for the study. The researchers will work with you to keep this from happening by allowing you to view relaxing pictures on a screen above your head prior to the start of the research procedure (until any anxiety has passed). Also, the researchers can talk with you during the procedure through a microphone in the scanner to reduce your concern.

5. If you are female and of child-bearing potential, you must have a pregnancy test performed prior to the scanning procedures. This test must be negative for you to participate in the study. You must also practice an acceptable method of birth control during the course of the study. If you are pregnant, you will be excused from the study.

Further risks include the following:

1. Randomization risk: In addition, there is a randomization risk involved in this study. The treatment you receive may prove to be less effective or to have more side effects than the other study treatment(s) or other available treatments.

2. Security of confidentiality and privacy risk: Taking part in this research study may involve providing information that you consider confidential or private. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe.

3. Potential Risk of Psychiatric Interviewing (minimal risk): As part of this study, you will be asked questions about sensitive personal information. You may feel anxiety about disclosing your substance use history and reporting some aspects of your demographics. The Beck Depression Inventory (BDI) scale includes a question on suicidal ideation. In the event that you endorse suicidal ideation on the BDI, the staff present with you will be authorized to contact the PI or one of the Co-I's on the study who will then assess the situation to see whether further intervention is required. Based upon the answers to these questions the study personnel will provide the participant with means to help them receive treatment. This may include providing the patient with information on contacting a physician or therapist to discuss their thoughts or to work with them on a plan to get them to the Wake Forest Baptist Health emergency room for safety if they indicate that they are in danger of harming themselves within the next 24-48 hours.

4. Potential risks of mechanical stimulation procedures: Mechanical stimulation will be delivered with the Medoc Pathway system which is specifically designed for safe pain assessments. It has built-in safety mechanisms (e.g., real-time visual and auditory feedback, threshold selection, and an easy to reach shut-off button). Participants may experience redness or irritation of the skin in the area stimulated, and vitamin E cream will be provided after the trial to reduce this potential. If redness occurs, it tends to go away on its own within about 60 minutes. The application of vitamin E cream may speed this up (i.e., redness goes away within about 20 minutes). Participants may also experience bruising in the area stimulated; bruising typically resolves itself within a few days.

A Data Safety and Monitoring Committee, an independent group of experts, will be reviewing the data from this research throughout the study.

In addition, there is a slight risk of a breach of confidentiality. We will do our best to protect your confidential information. There also may be other risks that we cannot predict. You should tell the research staff about all the medications, vitamins and supplements you take and any medical conditions you have. This may help avoid side effects, interactions and other risks.

REPRODUCTIVE RISKS AND OTHER ISSUES TO PARTICIPATING IN RESEARCH

Due to unknown risks and potential harm to the unborn fetus, sexually active women of childbearing potential must use a reliable method of birth control while participating in this study. Reliable methods of birth control are: abstinence (not having sex), oral contraceptives, OrthoEvra patch, NuvaRing, intrauterine devices (IUD), Nexplanon implant, DepoProvera, tubal ligation, or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable, although less reliable, method involves the careful use of condoms and spermicidal foam or gel and/or a diaphragm with spermicide with Plan B used for any noticed condom or diaphragm failures. We encourage you to discuss this issue further with your physicians if you have any questions.

Pregnant women are excluded from participation in this study. Because NO method of birth control is 100% reliable, a pregnancy test is required at least 10 days from your last normal menstrual period, if you are a sexually active woman of childbearing potential.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct benefit to you. We hope the information learned from this study will benefit other people in the future. The benefits of participating in this study may be the following: the treatment you receive may prove to be more effective than the other study treatment or than other available treatments, although this cannot be guaranteed. From a biological perspective, you may benefit from the positive effects of real TMS if you are randomized to the active groups. Your pain may be reduced from your participation in this study although this cannot be guaranteed. From a psychological perspective you will likely benefit from the additional time you will spend in contact with the study team when you will be surrounded by educational materials on pain management and an environment that is generally supportive and encouraging despite your struggle with chronic pain.

WHAT OTHER CHOICES ARE THERE?

You do not have to be in this study to receive treatment. You should talk to your doctor about all the choices you have. Instead of being in this study, you have a number of options. Most types of treatment for pain involve some form of counseling and medication. If you would like to receive additional information on alternative treatments for pain, you will be referred clinically from the PI.

WHAT ARE THE COSTS?

All study costs, including any study medications and procedures related directly to the study, will be paid for by the study. Costs for your regular medical care, which are not related to this study, will be your own responsibility.

WILL YOUR RESEARCH RECORDS BE CONFIDENTIAL?

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 unless it is authorized by you, required by law, or necessary to protect the safety of yourself or

others. There is always some risk that even de-identified information might be re-identified.

WILL YOU BE PAID FOR PARTICIPATING?

You will be paid up to $530 if you complete all the scheduled study visits, including all 3 MRI scans. If you withdraw for any reason from the study before completion, you will be compensated for each complete study visit.

Payment will be made using a pre-paid debit card called Greenphire ClinCard. It works like a bank debit card. We will give you a debit card and each time you receive a payment for participation in this study, the money will be added to the card after each completed visit. You may use this card at any store that accepts MasterCard or you can use a bank machine to remove cash. However, there may be fees drawn against the balance of the card for cash withdrawals (ATM use) and inactivity (no use for 3 months). We will give you the ClinCard Frequently Asked Questions information sheet that answers common questions about the debit card. You will also receive letters with additional information on how you can use this card and who to call if you have any questions. Be sure to read these letters, including the cardholder agreement, for details about fees.

The debit card system is administered by an outside company, Greenphire. Greenphire will receive neither your personal information nor any information about your health status or the study in which you are participating.

On the day of the Screening Visit, you will receive $20 for completing baseline assessments to see if you meet study requirements. If you remain eligible, you will be scheduled to attend the MRI scanning visits in which you will be paid $30 for completion of each of the three visits. You will receive $20 for completion of each of the 16 TMS visits, along with $20 for each of the four follow-up visits. If you complete all aspects of the study visits within the specified time frame, you will also receive an additional $20 study completion bonus at your last follow-up. If participation discontinues before the end of the study, you will not receive a completion bonus. If you do not show up to your scheduled appointment time, or your urine screens are not consistent with the information you reported on the screening day, you will be given two opportunities to reschedule before you are no longer eligible to participate.

WHO IS SPONSORING THIS STUDY?

This study is being sponsored by Wake Forest University of Health Sciences. The sponsor is providing money or other support to Wake Forest University Health Sciences to help conduct this study. The researchers do not, however, hold a direct financial interest in the sponsor or the product being studied.

WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THIS STUDY?

Should you experience a physical injury or illness as a direct result of your participation in this

study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim and is limited to a total of $250,000 for all claims in any one year. The Wake Forest University School of Medicine, and the North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance Management, at [redacted].

If you are injured, the insurer may require information such as your name, social security number, and date of birth in order to pay for your care. This is because the insurer is required by law to report any payments made to cover the care of any persons who are members of a government insurance plan to the Department of Health and Human Services.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call Dr. Colleen Hanlon at [redacted].

WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any new information we collect from you and/or information we get from your medical records or other facilities about your health or behaviors is considered Protected Health Information. The information we will collect for this research study includes**:** Names, all elements of date (except year) for dates directly related to an individual (DOB, admission date, discharge date), telephone numbers, electronic mail addresses, medical records/physician notes/hospital discharge records, and medical test results.

If this research study involves the diagnosis or treatment of a medical condition, then Protected Health Information collected from you during this study may be placed in your medical record, and may be used to help treat you, arrange payment for your care, or assist with Medical Center operations.

We will make every effort to keep your Protected Health Information private. We will store records of your Protected Health Information in a cabinet in a locked office or on a password protected computer.

Your personal health information and information that identifies you ("your health information") may be given to others during and after the study. This is for reasons such as to carry out the study, to determine the results of the study, to make sure the study is being done correctly, to provide required reports and to get approval for new products.

Some of the people, agencies and businesses that may receive and use your health information are the research sponsor; representatives of the sponsor assisting with the research; investigators at other sites who are assisting with the research; central laboratories, reading centers or analysis centers; the Institutional Review Board; representatives of Wake Forest University Health Sciences and North Carolina Baptist Hospital; representatives from government agencies such as the Food and Drug Administration (FDA) or the Office of Human Research Protections (OHRP), the Department of Health and Human Services (DHHS) and similar agencies in other countries.

Some of these people, agencies and businesses may further disclose your health information. If disclosed by them, your health information may no longer be covered by federal or state privacy regulations. Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This information may be used by other researchers. You will not be directly identified in any publication or presentation that may result from this study unless there are photographs or recorded media which are identifiable.

Monitors, auditors, IRB or other regulatory agencies will be granted direct access to the participant's original medical record for verification of clinical trial procedures or data, without violating confidentiality of the participant and to the extent permitted by other applicable laws.

If required by law or court order, we might also have to share your Protected Health Information with a judge, law enforcement officer, government agencies, or others. If your Protected Health Information is shared with any of these groups it may no longer be protected by federal or state privacy rules.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for an indeterminate period of time. This authorization does not expire.

You can tell Dr. Colleen Hanlon that you want to take away your permission to use and share your Protected Health Information at any time by sending a letter to this address:

Dr. Colleen Hanlon
[redacted]

However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study.

By signing this form you give us permission to use your Protected Health Information for this study.

WakeOne, the electronic medical record used by Wake Forest Baptist Health, will not be used during this study.

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

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. The investigators also have the right to stop your participation in the study at any time. This could be because it is in your best medical interest, your condition worsened, new information becomes available, you had an unexpected reaction, you failed to follow instructions, or because the entire study has been stopped. Information that identifies you may be removed from the data or specimens that are collected as part of this study and could be used for future research or shared with others without additional consent.

You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

This study will be enrolling students from the Wake Forest University campus. In addition to your rights as a research participant noted in the previous section, as a student, you are under no obligation to participate in this study. You may refuse to participate or withdraw from the study at any time and for any reason without affecting your grades, performance evaluations, or assignments. You will not be pressured into participating in this research study by any statements or implied statements that your grades, performance evaluations or assignments will be affected by your willingness to enroll in the study. Your medical records/information will not be used by the faculty, administration or study staff to make decisions regarding the status of your medical benefits. If you have questions regarding your enrollment in the study and your status as a medical student, please contact the Office of Student Services for additional information.

FUTURE RESEARCH?

From time to time we have other research studies that you may be eligible to participate in. We are inviting you to allow us to contact you by phone, mail, or both to see if you would be interested in participating in any future studies. By initialing next to the "yes" box below, you are indicating that you would like to give us your phone number, any alternate phone numbers, and address so that we may contact you if another study becomes available that you might qualify for. **To maintain your confidentiality, we will <u>not</u> leave identifiable messages or any identifiable information on letters or envelopes that are mailed to you.** By initialing next to the "no" box below, you are indicating that you do not want study personnel to contact you for

any future studies. You may still participate in the current study if you choose "no" and you will not suffer any adverse consequences in doing so.

☐ Yes. I would like to be re-contacted for future studies. I give permission for study personnel to contact me by phone or by mail to inform me of other available studies I may be eligible for. Please initial here_____.

☐ No. I do not wish to be re-contacted for any future studies. Please initial here_____.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or in the event of a research-related injury, contact the study investigator, Dr. Colleen Hanlon at (336)-716-5180.

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, or you would like to discuss problems or concerns, have questions or want to offer input, or you want to obtain additional information, you should contact the Chairman of the IRB at [redacted] or the Research Subject Advocate at [redacted].

You will be given a copy of this signed consent form.

SIGNATURES

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Addendum: During COVID-19, the study team will use the Wake Forest Baptist Health (WFBH) WebEx videoconference software to remotely interact with study participants as necessary. By signing below, I agree to use WebEx.

Subject Name (Printed):_____

Subject Signature: _____ Date: _____Time:_____ am pm

Person Obtaining Consent (Printed):_____

Person Obtaining Consent:_____ Date:_____ Time:_____ am pm