UF | Institutional Review Board
UNIVERSITY of FLORIDA

INFORMED CONSENT FORM
to Participate in Research, and

AUTHORIZATION
to Collect, Use, and Disclose Protected Health Information (PHI)

INTRODUCTION

Name of person seeking your consent:_____

Place of employment & position: _____

GENERAL INFORMATION ABOUT THIS STUDY

1. Name of Participant ("Study Subject")

_____

2. What is the Title of this research study?

Pain Relief for OsteoArthritis through Combined Treatment (PROACT)

3. Who is paying for this research study?

The sponsor of this study is the National Institute on Aging

4. In general, what do you need to know about this Research Study

Agreeing to become involved in any research is always voluntary. By signing this form, you are not waiving any of your legal rights. If you decide not to participate in this research, you will not be penalized in any way and you will not lose any benefits to which you are entitled. If you have questions about your rights as a research subject, please call the University of Florida Institutional Review Board (IRB) office at (352) 273-9600.

a) **In general, what is the purpose of the research, how long will you be involved?** The purpose of this research study is to see if two different treatments can be combined to improve pain and disability in people who have knee osteoarthritis (OA). Everyone with knee OA has a condition in

their knee joint that can cause pain and disability, but people with knee OA have very different amounts of pain. While this is partly because some people have worse arthritis in their knee than others, many other things affect how much pain and disability people have due to their knee OA. A lot of research shows that brain activity affects pain in OA, and other studies also show that stress can increase pain. So, we are combining two treatments, one that may improve brain function (Transcranial Direct Current Stimulation, tDCS) and another that can lower stress (Breathing and Attention Training, BAT), to see how they affect pain in people with OA. For the brain stimulation treatment, you will be randomly assigned (like the flip of a coin) to receive either real or sham stimulation. Sham stimulation is not expected to have any benefit. For the breathing treatment, you will be randomly assigned to either standard or focused BAT. The focused BAT includes more instructions to help you focus on your breathing. Your participation in this study will be about 2 weeks of clinic visits, plus once a month follow-up questionnaires for three months.

b) What is involved with your participation, and what are the procedures to be followed in the research? Participation in this study will consist of a total of 6 to 8 visits over a 2-3 week period, plus monthly follow-up questions for three months. The first two visits are for assessments, which include questions about your health and pain, a test of sitting standing and walking, questions about how you think and feel, some sensory and pain tests to measure how you feel pressure, poking, and cold sensations. Also, for most participants we will do some brain scans to see how your brain responses relate to your pain. In the next five visits, you will have the brain stimulation and breathing and attention training treatments. These treatments will happen at the same time and will last 20-30 minutes each time. In the last visit, after the treatment, we will repeat some of the same tests as in the first two sessions to see if things have changed. It is possible that the last visit may be split into two separate visits.

- There will be some questionnaires to complete between visits and monthly for three months after the treatment is complete.

c) What are the likely risks or discomforts to you?

a. The pain testing procedures may be uncomfortable or unpleasant
b. The physical exam procedures and activity tests may produce discomfort
c. The MRI may be unsafe if you have metal implanted in your body. It also creates a loud noise that has caused hearing loss.
d. Claustrophobia in the MRI scanner
e. The MRI may be unsafe for a woman of childbearing potential
f. The questionnaires may make you feel upset
g. The brain stimulation may cause some side effects (itching, tingling, dizziness, nausea, headaches)

h. The breathing training could make you feel uncomfortable

d) What are the likely benefits to you or to others from the research?

We don't know if these treatments will be helpful, but there is a chance that the treatments might improve your pain.

e) What are the appropriate alternative procedures or courses of treatment, if any, that might be helpful to you?

The other option to taking part in this study is not participating.

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.

Additional and more detailed information is provided within the remainder of this Informed Consent form, please read before deciding if you wish to participate in this study.

WHAT CAN YOU EXPECT IF YOU PARTICIPATE IN THIS STUDY?

5. What will be done as part of your normal clinical care (even if you did not participate in this research study)?

Regular medical care for your arthritis and other medical conditions will continue to be given by your regular doctors, nurses, and other providers. This study does not offer any additional medical care.

6. What will be done only because you are in this research study?

You have already completed a brief telephone or in-person screening to find out if you are eligible for the study. You are now here to complete up to 7 in-person visits. At the first two visits we will do some tests to find out more about your pain and function, and we will do MRI (Magnetic Resonance Imaging) testing to see how your brain activity is related to your pain. At the first visit, we will collect more health information from you in order to make sure that you are still eligible for the study. Also, we may ask you to sign a form giving us permission to get medical information from your primary healthcare provider, so that we can make sure it is OK for you to be in the study. Then, if you are still eligible for the study, the next five visits (Visits 3-7) will involve two different treatments that may help with pain (tDCS, BAT).

Procedures for Visit 1: We will do the following things at the first visit (~2-3 hours)

1) a review of the Informed Consent form with you to make sure that you understand everything that is involved in the study

2) a medical history and brief physical exam
3) a urine pregnancy test in women of childbearing potential
4) we will do a test of your knowledge of some medical words
5) we will ask you to complete several questionnaires about your health, your thoughts about pain, previous life experiences, and how you think and feel about things. We will ask some personal questions, because this will help us know about all of the things that might be affecting your symptoms of OA.
6) Pressure Sensations. We will use a handheld device with a small (less than ½ inch wide) rubber tip to apply pressure to the knee that hurts you the most, and to your thigh, and shoulder. The pressure will be slowly increased, and you will be asked to tell the examiner when you begin to feel discomfort or mild pain. As soon as you tell us you feel pain, the pressure will be removed.
7) Mechanical Sensation Tests. We will use a handheld probe that has a small nylon tip to tap your knee and your hand. We will ask you how painful this feels.
8) Combined Pressure and Cold Test. We will do the pressure test where you push a button when you first feel pain. Then, we will ask you to do a cold test, by putting your hand in cold water and telling us how painful it feels. While your hand is in the water and after you take your hand out of the cold water, we will repeat the pressure pain test.

This first visit will last around 2 to 3 hours. We may find out that you have health issues (e.g. high blood pressure) or things that make it unsafe for you to do an MRI (e.g. metal implants) that could mean you are not eligible for the rest of the study. If you are eligible for the rest of the study, we will schedule some more visits to our testing center. Also, if you are eligible, we will ask you to do some activities for us, including standing still, walking a short distance, and getting out of a chair.

Procedures for Visit 2: In participants who are able to undergo an MRI, we will do several brain imaging tests in the MRI machine to measure how your brain activity is related to your pain. This will take around 1.5 hours.

We will ask you to complete some questionnaires between visits as well. These questionnaires will ask about your pain, general health, and your thoughts and feelings. While there are several different questionnaires, we ask you to complete only a few at a time so that each time you complete the questionnaires should take no more than 30 minutes.

Procedures for Visits 3 – 6 (~60-90 minutes each). In each of the treatment visits, we will do the following things.

1) Questionnaires: You will be asked to complete some brief questionnaires about your pain and how you are thinking and feeling.
2) Brain Stimulation: You will receive 20 minutes of either real or sham brain stimulation (explained further below), using tDCS.
3) Breathing Attention Training (BAT): While you are receiving tDCS, you will receive instructions on breathing, including paying attention to certain ways of breathing.

Procedures for Visit 7 (~ 3 - 4 hours). Visit 7 is the final treatment visit, but also includes the post-treatment assessments. Thus, in addition to the doing all of the things that occur in every treatment visit (as described for Visits 3-6), at Visit 7 we will repeat several of the tests that you did before the treatment, to see if the treatment caused any changes in your pain or function or in your brain activity. If it works better for your schedule or for our clinic schedule, we may split the last visit into two visits on separate days.

1) Questionnaires: We will ask you to fill out questionnaires about your arthritis pain and your thoughts and feelings. Also, we will ask you to complete a questionnaire about the treatment you received, including any side effects you experienced and how well the treatment worked for you.
2) Standing, walking and sitting tests. We will repeat the tests of standing, walking and sitting that we did during the first visit.
3) Pressure and Mechanical Tests. We will repeat the pressure and mechanical tests as in the first visit.
4) Combined Pressure and Cold Test. We will repeat the combined pressure and cold test as we did in Visit 1.
5) Brain MRI: We will repeat the same brain imaging tests in the MRI machine.

Occasionally, study visits last longer than expected. If this happens you may receive extra compensation based on how much extra time you spent at the visit.

- **Monthly Follow-Up Assessments**. After you complete your final clinic visit, we will ask you to complete a questionnaire every month for 3 months to let us know how you are doing. This questionnaire will ask you questions about your pain, your sleep, your mood, and your activities. Each questionnaire will take around 5-10 minutes, and you will be able to do this on paper, on the computer or over the phone.

	Baseline		Treatment					Monthly Follow-Up		
Study Activities	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	1-Mo	2-Mo	3-Mo
Informed Consent	X									
Baseline Questionnaires	X	X					X			
Activity Tests	X						X			
Sensory & Pain Tests	X						X			
Brain Imaging		X					X			
Tx Questionnaires			X	X	X	X	X			
Treatment Session			X	X	X	X	X			
Pain Assessment			X	X	X	X	X			
Follow-Up Questionnaire								X	X	X

More Information About the Treatments

1. **Brain Stimulation**: You will receive either the full-length session of brain stimulation (active stimulation) or a shorter session of brain stimulation (sham stimulation). The sham stimulation feels like and is performed in the same way as

the active stimulation session, but stimulation is stopped before it can have much of an effect on the brain. This type of stimulation is called *transcranial direct current stimulation (tDCS*), which involves placing two sponge-like electrodes on your head and delivering a very tiny, weak electrical current to your scalp, which is generated by a 9V battery. We will take a brief set of pictures of your head after the electrodes are placed on your head to make sure that the electrodes are in the correct location. These photos will be used to create a 3D model of your head that will give us accurate information about where the electrodes were placed. You will be asked to wear a small wristband during stimulation sessions. This wristband provides non-invasive physiological recording such as pulse.

You will be randomly assigned (much like the flip of a coin) to receive either active stimulation or sham stimulation. The sham stimulation is like a placebo. A placebo is a substance that looks like and is given in the same way as an actual treatment but contains no medicine, for example [a sugar pill, an injection of saline (salt water)]. A placebo is used in research studies to show what effect a treatment has compared with taking nothing at all. If you are assigned to receive placebo, you will not receive the benefits of the active stimulation if there are any, nor will you be exposed to its risks, which are described below under "What are the possible discomforts and risks?" Studies have shown, however, that about 1 in 3 persons who take a placebo do improve, if only for a short time. You and the physician and other persons doing the study will not know whether you are receiving placebo or active stimulation but that information is available if it is needed. Also, you will have a 50% chance of receiving active stimulation and a 50% chance of receiving placebo.

Both versions of the stimulation may cause an effect in some people, improving pain or helping the breathing training to be more helpful. It's possible the stimulation will have no positive benefit in some individuals. Some people may notice a slight tingling or itching at the sight of the electrodes, but it should not be painful at all, and stops immediately when the current is stopped. If this bothers you, the stimulation level can be turned off. Remember, you can stop the research study at any time if you no longer want to participate. You will not know which group you have been assigned to while participating in the research, but you may find out at the completion of the research study.

2. **<u>Breathing Attention Training (BAT)</u>**: While you are receiving tDCS, you will also be asked to focus on your breathing and on the thoughts that go along with breathing. This type of training can help lower feelings of stress in some people. You will get specific BAT instructions at each visit, and each session lasts about 20 minutes. The BAT treatment will include instructions on deep breathing and focusing on different parts of your breathing. You will be randomly assigned (like the flip of a coin) to receive either standard-BAT or focused-BAT. Both of these treatments include breathing and attention training, but the focused version includes some more specific instructions to increase your ability to focus on certain parts of your breathing and to lower any distracting thoughts or feelings that might happen during the breathing training. The training will include instructions to help you practice during the brain scanning that we will do at the

last session. This training may or may not help your arthritis pain.

Video Recording: We would like permission to take video or photos of your assessment and intervention sessions. These videos or photos will be reviewed by the study team to assess the quality of our treatment visits. These videos will not be released and will only be accessible by study investigators. Do you give permission to have quality control videos or photos taken during your intervention visits?

YES _____

NO _____

Tests done only for research purposes will not be evaluated or used to diagnose or treat any of your medical problems. These tests may need to be repeated if required for your medical care in the future.

Once this research study is completed, any information that could identify you **might** be removed from any identifiable private information collected and that, after such removal, the information could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you or your legally authorized representative

If you have any questions now or at any time during this Research Study, please contact one of the Research Team members listed in question 1 of the Addendum to this form.

7. What identifiable health information will be collected about you and how will it be used?

The Research Team will collect the following identifiable health information:

- Medical and mental health history
- Physical examination findings
- Results of functional and sensory tests
- Results of MRIs, including brain imaging findings
- Responses to questionnaires
- Telephone interviews
- Your Social Security number for compensation purposes

The Research Team may collect this information from other healthcare providers, such as laboratories, which are a part of this research, as well as healthcare providers that are not part of this research (other doctors, hospitals or clinics). Other professionals at the University of Florida or Shands Hospital or the University of Alabama at Birmingham who provide study-related care, and the University of Florida Institutional Review Board (IRB), may also collect your health information.

The Research Team will use or share your health information as described below to carry out this research study.

8. With whom will this health information be shared?

This health information may be shared with:

- the study sponsor (listed in Question 4 of the Core Consent form).
- The Principal Investigator and research team at the other study site (either University of Florida or University of Alabama at Birmingham) who work on this project.
- United States governmental agencies who are responsible for overseeing research, such as the Food and Drug Administration, the Department of Health and Human Services, and the Office of Human Research Protections.
- Government agencies who are responsible for overseeing public health concerns such as the Centers for Disease Control and federal, state and local health departments.
- The IRB that reviewed this Research Study and ensures your rights as a Study Subject are protected

Otherwise, your identifiable health information will not be shared without your permission unless required by law or a court order. Once your health information is shared with those listed above, it is possible that they could share it without your permission because it would no longer be protected by the federal privacy law.

9. How long will you be in this research study?

Your participation in this research project will last about 12-14 weeks and will include seven visits total to our testing center at the University of Florida or the University of Alabama at Birmingham over about a two-week period. The visits last from 45 minutes to 4 hours, depending on which visit it is. Also, we will ask you to do a brief questionnaire every month for three months after the visits. These can be done on the internet, on paper or by phone. Thus, your total time commitment is expected to be 12-18 hours over a 12-14 week period.

This Authorization to use and share your health information expires at the end of the study, unless you revoke it (take it back) sooner.

10. How many people are expected to take part in this research study?

If you decide to participate in this study, you will be one of approximately 360 people in this research study from one of two Universities (University of Florida at Gainesville and University of Alabama at Birmingham). Each site will enroll about 180 participants.

WHAT ARE THE RISKS AND BENEFITS OF THIS STUDY AND WHAT ARE YOUR OPTIONS?

11. What are the possible discomforts and risks from taking part in this research study?

This study might involve the following risks and discomforts to you:

- The pain testing procedures may be uncomfortable or unpleasant. You will experience some temporary discomfort from the pressure and cold pain testing. However, if you feel the pain is greater than you wish to tolerate, you can stop any of the procedures at any time.
- The physical exam procedures and activity tests may produce discomfort, and you can stop these procedures at any time.
- The MRI scanner contains a very strong magnet. Therefore, you may not be able to have the MRI if you have any type of metal implanted in your body, for example, any pacing device (such as a heart pacer), any metal in your eyes, or certain types of heart valves or brain aneurysm clips. Someone will ask you questions about this before you have the MRI.
- There is not much room inside the MRI scanner. You may be uncomfortable if you do not like to be in close spaces ("claustrophobia"). During the procedure, you will be able to talk with the MRI staff through a speaker system, and in the event of an emergency, you can tell them to stop the scan. The MRI scanner produces a loud hammering noise, which has produced hearing loss in a very small number of patients. You will be given earplugs to reduce this risk.
- If you are a woman of childbearing potential, there may be unknown risks to the fetus. Therefore, before you can have the MRI, you must have a pregnancy test in order to rule out that you are pregnant.

Risks of Brain Stimulation: This type of Brain Stimulation is considered safe and has been used in more than 3000 research subjects around the world. This type of stimulation has not caused serious side effects. Our study uses techniques that are considered safe and procedures that have been safely employed by prior research at the University of Florida and in many other universities. The FDA has ruled that the Brain Stimulator used in this study is a "non-significant risk" device. However, a small number of people do experience some side effects.

- The most common side effects are itching and tingling or mild discomfort at the area of stimulation, and headache. Other possible side effects include dizziness and nausea. Whenever an electrical stimulation is applied to the body, it could possibly cause a seizure or abnormal heartbeat, but this has never occurred, or been reported in the research conducted anywhere in the world, while using the brain stimulation levels used in this study.
- To decrease the risks of Brain Stimulation, we will pay close attention to your reactions during stimulation sessions, and we ask you to tell us if you are having any discomfort. If scalp sensation is uncomfortable, stimulation will be stopped. In the event of a headache, stimulation will be stopped. All sessions will be administered and continually supervised by a trained experimenter.
- Brain Stimulation has not been shown to cause seizures nor lower the seizure threshold in animals. There are no reports of seizure induced by Brain Stimulation, in human participants in the literature. However, this may not be true for people

with epilepsy, so if you have any history of seizures, you cannot be in this study for safety reasons.

Other possible risks to you may include: You may feel uncomfortable, upset or sad about answering some of the questions on the questionnaires. You do not have to answer those questions. Researchers will take appropriate steps to protect any information they collect about you. However, if the researcher believes it is in your medical best interest, they may share information with other health care providers so that they can help you. Also, there is a slight risk that information about you could be revealed inappropriately or accidentally. Depending on the nature of the information, such a release could upset or embarrass you, or possibly affect your insurability or employability. Below in this form we discuss what information about you will be collected, used, protected, and shared.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You have been informed that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information. That is, if you give written consent for the release of information, we cannot withhold that information and we cannot hold responsibility for how that person may use your information. The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project under the following circumstances. If we learn about child abuse, elder abuse, or intent to harm yourself or others, we will report that information to appropriate authorities.

This study may include risks that are unknown at this time.

Please note, participating in more than one research study or project may further increase the risks to you. If you are already enrolled in a research study, please inform one of the Research Team members listed in question 1 of the Addendum to this form or the person reviewing this consent with you before enrolling in this or any other research study or project.

During the study, the Research Team will notify you of new information that may become available and might affect your decision to remain in the study.

The University of Florida and the University of Alabama at Birmingham are required by law to protect your health information. Your health information will be stored in locked filing cabinets or on computer servers with secure passwords, or encrypted electronic storage

devices, as required by University policy. However, there is a slight risk that information about you could be released inappropriately or accidentally. Depending on the type of information, a release could upset or embarrass you, or possibly affect your ability to get insurance or a job.

If you wish to discuss the information above or any discomforts you may experience, please ask questions now or call one of the Research Team members listed in question 1 of the Addendum to this form.

12a. What are the potential benefits to you for taking part in this research study?

You may or may not benefit from participating in this study. A potential benefit is that the brain stimulation and breathing attention training could improve your pain. If the treatment does improve your pain, we do not know how much it will help. It is possible that any improvement in pain could be small and may not last very long. We expect that people in the active brain stimulation treatment and those in the focused-BAT will benefit the most from these treatments.

12b. How could others possibly benefit from this study?

The results of this study may help us to better understand whether treatments like tDCS and BAT can help reduce pain in people with arthritis. We may also learn more about how and why these treatments are helpful, which might help us to create better treatments for pain in the future.

13. What other choices do you have if you do not want to be in this study?

The other option to taking part in this study is not participating. If you do not want to take part in this study, tell the Principal Investigator and do not sign this Informed Consent Form.

You may also refuse to authorize the use of your health information, but if you refuse, you may not be allowed to be in this research study or receive any research-related treatment that is only available in this research study. However, your decision not to sign this Authorization will not affect any other treatment you may be eligible to receive.

14a. Can you withdraw from this study?

You may withdraw your consent and stop participating in this Research Study at any time. If you do withdraw your consent, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

If you decide to withdraw your consent to participate in this Research Study for any reason, please contact the Research Team listed in question 3 of this form. They will tell you how to safely stop your participation.

You can also change your mind and take back this Authorization at any time by sending a written notice to the Research Team listed in question 3 of this form to let them know your

decision. If you take back this Authorization, the Research Team may only use and disclose your health information already collected for this research study. No additional health information about you will be collected or disclosed to the Research Team. However, if you take back this Authorization, you may not be able to continue in this study. Please discuss this with a member of the Research Team listed in question #3.

14b. Can the Principal Investigator withdraw you from this study?

You may be withdrawn from the study without your consent for the following reasons:

a. You do not meet the eligibility criteria for the study
b. You have had too many side effects or an unexpected negative reaction to the study
c. You have failed to follow instructions
d. The entire study has been stopped
e. Also, if the study team believes that your continuing in the study could cause problems for you or for the study, you can be withdrawn.

SIGNATURES

As an investigator or the investigator's representative, I have explained to the participant the purpose, the procedures, the possible benefits, and the risks of this Research Study; the alternative to being in the study; and how the participant's protected health information will be collected, used, and shared with others:

_____ _____

Signature of Person Obtaining Consent and Authorization — Date

You have been informed about this study's purpose, procedures, possible benefits, and risks; the alternatives to being in the study; and how your protected health information will be collected, used and shared with others. You have received a copy of this Form. You have been given the opportunity to ask questions before you sign, and you have been told that you can ask questions at any time.

You voluntarily agree to continue to participate in this study. You hereby authorize the collection, use and sharing of your protected health information as described above. By signing this form, you are not waiving any of your legal rights.

_____ _____

Signature of Person Consenting and Authorizing — Date