UNIVERSITY OF MICHIGAN
CONSENT TO BE PART OF A RESEARCH STUDY

INFORMATION ABOUT THIS FORM

You may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of the study, and the risks and possible benefits of participating in the study.

Please take time to review this information carefully. After you have finished, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or other doctors) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

1. GENERAL INFORMATION ABOUT THIS STUDY AND THE RESEARCHERS

1.1 Study title:
Investigation and Modulation of the Mu-Opioid Mechanisms in Migraine (In Vivo)

1.2 Company or agency sponsoring the study:
National Institutes of Health – National Institute of Neurological Disorders and Stroke (NIH-NINDS)
University of Michigan Department of Biologic and Materials Sciences – Principal Investigator's Discretionary Funds

1.3 Name, degree, and affiliation of the researcher conducting the study:
Alexandre DaSilva, DDS, DMedSc – Headache & Orofacial Pain Effort (HOPE), Department of Biologic & Material Sciences, University of Michigan

2. PURPOSE OF THIS STUDY

2.1 Study purpose:
Migraine is a type of severe headache. Migraines affect millions of Americans, but few effective and safe treatments exist. This is partly because there's still a lot that doctors don't know about the brain mechanisms related to migraine.

This study has two purposes. First, we want to learn more about migraine-related brain mechanisms. To do that, we plan to take pictures of people's brains and analyze them. Second, we want to find out what effects a mild electrical stimulation of the brain might have on migraine-related brain mechanisms. To test this, we'll use a procedure called high-definition transcranial direct current stimulation (HD-tDCS). HD-tDCS has been helpful in treating other types of pain, and we want to find out if it's helpful for migraine pain. HD-tDCS has not yet been approved by the Food and Drug Administration.

3. INFORMATION ABOUT STUDY PARTICIPANTS (SUBJECTS)

Taking part in this study is completely **voluntary**. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

3.1 Who can take part in this study?
We are looking for two kinds of people to take part in this study:

- people who have between 1 and 14 migraine attacks per month, over the course of at least a year
- healthy people who don't suffer from migraine

All subjects in this study must be between 18 and 65 years old. We will select healthy subjects who match the migraine patients in both age and gender.

You cannot take part in this study if you

- have used opioids any time in the past 6 months; common opioids include
  - Vicodin
  - OxyContin
  - codeine
  - others
- are pregnant
- have at any time suffered from any other
  - chronic pain disorder
  - neurological disorder
  - psychiatric disorder
- plan to start any new headache treatments while taking part in the study

It is very important to provide complete and accurate information about your health condition, health history, and medications you are taking so that we can make sure you are a safe and a good candidate for participation in brain stimulation and brain imaging MRI/PET scans.

3.2 How many people (subjects) are expected to take part in this study?
We expect up to 90 subjects to participate: 60 migraine patients and up to 30 healthy people. Of those 30 healthy people, we may use data from up to 10 subjects from an earlier study.

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?

Screening Visit – If you would like to take part in this study, we will first make sure you qualify. We will first ask you some questions, then ask you to complete several questionnaires:

- All subjects (both migraine patients and healthy people) will complete questionnaires about personal information (such as age, race, education, and occupation) and about their moods and sleep.
- Migraine patients will complete additional questionnaires about their migraines and headache pain.

If we determine that you qualify for the study, we will schedule additional study visits:

- Healthy people who don't suffer from migraine will come back for up to 2 more study visits.
- Migraine patients will come back for up to 17 more study visits.

The details of each visit are as follows:

MRI #1 Visit — *both migraine patients and healthy subjects — Must be migraine-free for 48 hours prior to scan*

Magnetic Resonance Imaging (MRI): MRI is a type of body scanning that involves magnetic energy, but no radiation. Because it involves magnetic energy, it will interfere with the functioning of any electric or mechanical devices that may be inside your body. If you believe that you have any metallic devices, pacemakers, metallic implants, or metallic objects in your body, such as pellets, metal fragments, or surgical clips or implants, let us know prior to agreeing to participate in the study. We will also ask you to read and sign a form describing in further detail the devices that are contraindicated for MRI scanning. The MRI allows us to see the brain at work

inside your head. We will take a special kind of picture of the inside of your brain while your body is in the MRI scanner. This appointment should take 70 minutes. The scan itself will last 60 minutes.

If a problem occurs during the MRI scan, you may be asked to come in for an additional scan.

PET #1 Visit — *both migraine patients and healthy subjects — Must be migraine-free for 48 hours prior to scan*

Positron Emission Tomography (PET): PET is a type of body scanning that involves radiation. The radiation is in the form of a "tracer" substance containing very small amounts of radioactivity, which is injected into your body. The PET machine will detect the tracer throughout your body, allowing us to evaluate the functioning of your brain. The PET scan will be 90 minutes long and will use a radioactive tracer (called [^{11}C]carfentanil) that clings to parts of your brain that help control pain. Right before the scanning begins, we will inject a small amount of this radioactive tracer into your vein. Then we will use the PET scan machine to create images of your brain.

When you arrive to the PET appointment, the following will occur prior to the scan:

1. Drug and Pregnancy Testing: You will be asked to provide a small amount of urine for both pregnancy (females only) and drug testing. If either test is positive, we will privately show you the result; you may be ineligible for the study for safety reasons and because recent drug use can alter the study results. If you're pregnant, we will take you out of the study.
2. Thermal Quantitative Sensory Testing (QST): Thermal QST will be performed in four areas of the skin (face and hands) to test your sensitivity to cold and warm temperatures. We'll produce both warm and cold sensations on your skin using a small probe. The probe will slowly get hotter or colder, and you will be able to control the temperature with a computer mouse. You will click the mouse as soon as it gets too hot or too cold and starts to hurt. Each hot and cold sensation will be delivered 3 times in each location. The QST procedure will not damage your skin.

The procedures involved during the PET scan are outlined below.

1. We'll show you how to use a pain rating system, which will come up again in step 5 (below).
2. You'll lie quietly and still on a cot with your head inside the PET scanner.
3. One catheter (tubes for introducing fluids) will be inserted into a vein of your arm.
4. We'll inject the radioactive tracer (10 to 15 milliCurie of [^{11}C]carfentanil) into your IV. All of the supplies that we use are sterile, disposable, and have not been in contact with any other person.
5. The thermal challenge will begin 40 minutes after we inject the tracer. Each scan will consist of multiple thermal challenges. In a thermal challenge, we'll administer a warm sensation on your skin and then ask you to click a computer mouse when a warm sensation becomes almost painful. The temperature will start at just below 90 degrees Fahrenheit (32 degrees Celcius) and will increase until you click the mouse. As soon as you click, the temperature will quickly go back to the starting point. There's also a safety feature in the software that prevents the temperature from reaching an unsafe level.

If a problem occurs during the PET scan, you may be asked to come in for an additional scan.

Upon completion of the PET scan, healthy subjects' participation in the study will be complete. Migraine patients will continue to come to our clinic for further study visits.

HD-tDCS Visits #1-10 — *migraine patients only — 10 daily brain stimulation sessions*

Transcranial Direct Current Stimulation (tDCS): tDCS is a method of non-invasive brain stimulation that involves sending a mild electrical current into a person's head. The current flows between electrodes in a special cloth cap.

You will participate in daily sessions (Monday through Friday) tDCS for 2 weeks in a row, for a total of 10 sessions. If you miss a tDCS session, two tDCS sessions will occur the next day.

At the beginning of the study, we will use a random method (like flipping a coin) to decide whether you'll be in the Active tDCS Subject Group or the Sham tDCS Subject Group. A sham is a fake procedure.

- If you're in the Active tDCS Subject Group, your tDCS sessions will involve a real electrical current going into your brain.
- If you're in the Sham tDCS Subject Group, we will attach the tDCS device to your head, but it will only send electricity into your brain at the very beginning and very end of the session.

Neither you nor the doctors in charge of the research will know whether your tDCS procedure is real or a sham. The staff performing the tDCS will know whether you are in the active or sham group.

Each tDCS appointment will last approximately 45-60 minutes. Procedures will include

- an examination
- device set-up
- clean-up
- pain/mood questionnaires for you to complete
- a tDCS side effects form to fill out

During each session, we will place a cloth cap containing electrodes over your head. First, in a small area your hair will be parted and your scalp will be wiped with alcohol, followed by aloe vera gel. After placing the cap, conducting gel will be inserted into the electrode casings (holes in the cap). You will be given supplies and time to clean up after the session is over.

If you are in the active tDCS subject group, the device will send a mild electrical current (≤2 milliamperes) into your head for 20 minutes. If you are in the sham tDCS subject group, the device will send the electrical current for only the first and last 30 seconds of the 20-minute session; the rest of the time, no electrical current will enter your brain.

You will have a total of 10 brain stimulation sessions over the course of two weeks.

MRI #2 Visit — *migraine patients only — Must be migraine-free for 48 hours prior to scan*

MRI: A second MRI scan will be performed so that we can see if the tDCS treatments resulted in changes in your migraine-related brain functions. The procedures at this visit will be identical to those at visit 2 (above).

PET #2 Visit — *migraine patients only — Must be migraine-free for 48 hours prior to scan*

PET: A second PET scan will be performed so that we can see if the tDCS treatments resulted in changes in your migraine-related brain functions. The procedures at this visit will be identical to those at visit 2 (above).

Follow-Up Visits (1-Week, 1-Month, and 2-Months) — *migraine patients only*

Appointments will be scheduled at MCRU for 1 week, 1 month, and 2 months following the last HD-tDCS day. During these appointments, we will ask about your migraines, and you will complete the same questionnaires provided at the screening appointment. This will provide us with important information regarding the lasting effects of tDCS treatment.

The table below shows which procedures will occur at the study visits. Keep in mind that healthy subjects' participation ends after the first PET scan.

Type of Visit*	**Screening**	**fMRI* #1**	**PET* #1**	**HD-tDCS 10 Daily Sessions**	**fMRI #2**	**PET #2**	**Follow Up Wk #1**	**Follow Up Mo #1**	**Follow Up Mo #2**
Timing	Up to 3 Weeks Prior to HD-tDCS	1 Week Prior to HD-tDCS	1 Week Prior to HD-tDCS	Week 1 (M-F) Week 2 (M-F)	1 Week After HD-tDCS	1 Week After HD-tDCS	1 Week After HD-tDCS	1 Month After HD-tDCS	2 Months After HD-tDCS
Duration	1 hr	1.25 hr	2.5 hr	1 hr ea x 10 visits	1.25 hr	2.5 hr	1 hr	1 hr	1 hr
Compensation	$25	$50	$100	$25/ea x 10	$50	$100	$25	$25	$25
*Healthy Volunteers: Screening, 1st fMRI, 1st PET only									

Optional Sub-Study for Both Healthy Subjects and Migraine Patients:

- **Blood Collection & Genetic Study (optional)**: If you consent to participate in this part of the study, blood samples that do not exceed 70 mL (5 Tbsp) will be collected during each PET scan. Blood will be collected from a separate intravenous line placed into the vein of your arm (opposite the arm used for the tracer injection). The blood samples will be frozen for future testing to look at biological substances in the blood (biomarkers) and potential hereditary traits associated with migraine. The blood for genetic analysis will be collected prior to tracer administration and will not exceed 24 mL (2 Tbsp) per scan. Approximately 6 mL (<1 Tbsp) of blood will be drawn at 20 minute intervals during each PET scan starting at time 0 s for analysis of biomarkers.

  The genetic study may help to identify genes that we suspect to be associated with the function of the chemical signals between nerve cells, affecting the responses to pain in patients with migraine. Your blood samples will be processed down to DNA, the part of your blood that holds genetic information, and stored at a secure laboratory. No "pathological" markers in the DNA will be analyzed but only those possibly related to inter-individual variations in response to painful and other stimuli. Once we have analyzed all markers of interest the study will be considered complete. In order to decide whether you should join this part of the study, here is some information about DNA testing that you should know:

  a. Your blood will be stored at the University of Michigan under a unique identifying code for this study and it will become anonymous, i.e. not linkable to a person, after completion of the study.
  b. Your confidentiality will be protected to the extent permitted by law. Samples will be coded and the code will be stored at a locked location. The University of Michigan collaborates with many other organizations, and data are generally shared. However, no data shared with other investigators will include your name or other information that would allow anyone to know who you are.
  c. In the future your blood may be used at any time for more studies of migraine. It is possible that new tests might be available in the future, which could be useful in understanding migraine. Stored blood may be used later for identification of new risk factors for migraine. These studies will not be about your genetic makeup or in any way describe your genes or DNA.
  d. You have the right to refuse to allow your blood to be studied or saved for the future study (i.e. not to participate in the genetic study or to withdraw from it). You may withdraw from this part of the study at any time, and withdraw your sample from research use. However once your sample has

become anonymous, even if you choose to withdraw your sample the researchers will not be able to identify which sample is yours.

e. Information about your race, ethnicity, sex and medical history might be available for investigators studying your blood. Such information is important for scientific context and sometimes for public health. It is possible that genetic information may be associated with your racial or ethnic group.
f. Genetic research raises difficult issues about informing you and other subjects about any results or of future results. Some people want to know information discovered about them, others do not. We do not anticipate that our findings will be useful for any individual subject. Therefore, We will not inform you about any results, and you agree that: 1) You will not be notified of any future research, test or information generated by future tests or analyses using blood samples and assign any such rights to yourself or other family members. If you are interested in storage of a blood sample for genetic testing, you should consult with a clinician skilled in this area.
g. The results of the genetic study will not be placed in your medical records.

4.2 How much of my time will be needed to take part in this study?

- The screening appointment and 3 follow-up (1 week, 1 month, 2 month) visits will each last approximately 1 hour
- Each MRI scan appointment will last approximately 1.25 hour
- Each PET scan appointment will last approximately 2.5 hours
- Each tDCS appointment will last approximately 1 hour

4.3 When will my participation in the study be over?

Healthy Controls: Your participation in the study will be over when you have completed a screening appointment, one MRI scan, and one PET scan. If a problem (for example, a technical glitch) occurs during the MRI or PET scan you may be asked to complete an additional scan. Most subjects will complete their part in the study within 1 month. The entire study is expected to last 5 years. You may end your participation in this study at any time. If you decide to stop participating, you will not lose any benefits to which you may otherwise be entitled.

Episodic Migraine Patients: Your participation in the study will be over when you have completed a screening appointment, two MRI scans, two PET scans, 10 daily tDCS sessions, and the 1 week, 1 month, and 2 month follow-up visits. If a problem (for example, a technical glitch) occurs during an MRI or PET scan you may be asked to complete an additional scan.

The MRI and PET scans will be scheduled for the week before and week after the 2 weeks (10 daily sessions) of tDCS active or sham treatment. Thus, this portion of the study should be completed over a period of 4 consecutive weeks, followed by the three follow-up visits. Most subjects will complete their part in the study within 4 months. However, if having the MRI and PET scans the week before and week after the tDCS sessions is not possible for some reason, the scans will be scheduled for at most 2 weeks before and 2 weeks after tDCS. The entire study is expected to last 5 years. You may end your participation in this study at any time. If you decide to stop participating, you will not lose any benefits to which you may otherwise be entitled.

4.4 What will happen with my information and/or biospecimens used in this study?

Your biospecimens and collected information may be shared with the National Institutes of Health/National Institute of Neurological Disorders and Stroke.

With appropriate permissions, your samples and collected information may also be shared with other researchers, here, around the world, and with companies.

Your identifiable private information or identifiable biospecimens may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent.

5. INFORMATION ABOUT RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?

The known or expected risks are:

We do not anticipate adverse reactions or side effects as a result of these procedures. The possibility exists of an unexpected reaction in certain individuals. This study involves you being in moderate pain for around 20 minutes during the thermal pain challenge (PET scan). However, it is not associated with pain lasting beyond the study period or any irreversible damage to your body. Participation in multiple studies may be hazardous to you. If you are already participating in another study, please inform us fully. You should not participate in multiple studies, unless you and the investigators agree that your health and the outcome of the study will not be jeopardized.

If you are or may become pregnant during the study, this research may involve unforeseeable risks to the embryo or the fetus. A free pregnancy test will be provided to all reproductive age women.

- **MRI Imaging:**
  1. This type of imaging requires the use of magnetic pulses to obtain information about the structure of your body. This technique is used routinely in clinical practice, and does not involve radiation exposure. Nevertheless, it will interfere with the functioning of any electric or mechanical devices that may be implanted within you. You will be instructed to provide information as to the possibility that any metal fragments, surgical clips, pacemakers or metallic implants may be present in your body.
  2. If you were to have any surgical, electric or mechanical devices in your body during the performance of the MRI scanning study, they may stop functioning, move within your body or break, potentially causing serious injuries. Medication patches may also contain metal and could become very hot during the study, damaging your skin.
  3. MRI scanning is performed within a machine, or scanner, which can feel quite confining. This may cause nervousness or severe claustrophobia in some subjects, which may require your withdrawal from the study, or even medical treatment. The scanner also produces very loud noises. We will provide you with soft earplugs to reduce discomfort from the noise.
  4. There is the potential that a magnetic resonance image may reveal an abnormality that is already in your body, such as a cyst or tumor. Many such abnormalities are not significant, but you may need or want to investigate them further. Such a finding might require additional studies, and maybe even treatment, neither of which would be paid for by the investigators, the sponsor, or the University of Michigan.

- **PET Imaging:** Potential PET risks include potential complications or inconveniences associated with venous cannulation, the administration of study radiopharmaceuticals, and the exposure to low level radiation. The radiation exposure resulting from these studies is well within that associated with routine radiological procedures and is not associated with adverse health consequences.

  - **Intravenous line (IV) for tracer injections and blood collection**: There is an infrequent risk of bruising, bleeding, infection, or soreness associated with intravenous catheter placement, similar to the risks associated with routine blood testing. You might feel dizzy or lightheaded or may rarely even faint when the tube is put in or taken out. There is a small chance of infection or clotting in the area from which the blood was taken. The risk of these side effects is minimized by using highly trained personnel. If persisting pain or redness in the area is noted, this may require medical or surgical treatment.

- **PET Tracers**: You could theoretically experience an allergic reaction to CFN. This could involve itching, skin rash or shortness of breath shortly after injection. However, because of the very small tracer amounts used in PET imaging, the risk is very rare. The combined experiences of multiple research centers using these tracers in hundreds of research volunteers have identified no known reactions. A physician will be available and an emergency cart is located in the PET Facility for treatment of any adverse reactions that may occur.

- **Low-level radiation exposure:** During the course of this study, you will be exposed to radiation from the PET tracer, CFN. A 15 mCi injection of [11C]CFN per PET scan will result in a whole body effective dose equivalent of 0.27 rem, which is less than 6% of the dose that occupationally exposed individuals are permitted to receive each year, and a critical organ (liver) mean dose equivalent of 0.89 rem. If you complete a second PET scan for this study, the total radiation you will be exposed to will result in a whole body effective dose equivalent of 0.546 rem and a critical organ (liver) mean dose equivalent of 1.79 rem. If a problem occurs during a PET scan and you are asked to complete an additional, third PET scan, the total radiation you will be exposed to will result in a whole body effective dose equivalent of 0.81 rem and a critical organ (liver) mean dose equivalent of 2.67 rem. The proposed PET methods have no alternatives for collection of the necessary data at the present time. The effects on the body of this radiation exposure will be added to subject's overall lifetime radiation risk. Each individual's life-time radiation risk includes the background radiation they are exposed to naturally like everyone else living on this planet, which is on the average 0.6 rem per year. The US Federal Government requires that the annual amount of radiation exposure of radiation workers does not exceed 5 rem per year. The risk of a side effect from this level of radiation exposure is very rare. The risk from radiation exposure of this amount is considered to be similar to other every day risks, such as driving a car. An individual's lifetime radiation risk also includes any radiation they may have received in the past for diagnosis or treatment, and any such radiation they may be exposed to in the future. Subjects are asked to inform the investigators if they have had any major radiation exposure in the past, particularly in the past year, such as medical treatment with X-rays or radioactivity, or diagnostic X-rays, CT-scans or nuclear medicine scans. No PET studies will be performed on pregnant, nursing, or potentially pregnant women, as determined by pregnancy testing within 48 hours prior to PET the scanning session.

- tDCS (Non-Invasive Brain Stimulation) Testing: This research team has conducted several tDCS trials and has had no report of significant side effects or incidents with any of our research subjects or healthy controls. Mild or benign adverse effects, such as mild headache, have been reported in a small number of subjects. The likelihood of these incidences is rare. Potential changes can be avoided if the safety guidelines are followed. You will fill out a tDCS Side Effects questionnaire after each session you receive the treatment. This data will be used to assess safety and adverse events.

- **Drug Testing:** There is a risk of loss of confidentiality and/or feeling uncomfortable about sensitive information such as drug use status. Such information could be inadvertently and inappropriately shared with third parties. These risks will be minimized by using an anonymous code that only the study team can use to identify you. Additionally, the results for the drug screen will be shared with you only and will not appear in your medical record.

- **Questionnaires**: You will be asked to complete several questionnaires at each visit. Although each questionnaire is not stressful when answered alone, completing multiple surveys in a row may lead to a low level of mental fatigue.

The researchers will try to minimize these risks as described above.

- **Genetic analysis:** The kind of genetic information analyzed is not likely to have any direct effect on your health. There is the unlikely risk that if people other than the researchers got your genetic information they could misuse

it. However, the chance of this ever happening to you is very small.

The federal Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Under this law:

- Health insurance companies and group health plans may not request your genetic information that we obtain from this research
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums
- Employers with 15 or more employees may not use your genetic information that we obtain from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment

GINA does not apply to the following groups, however these groups have policies in place that provide similar protections against discrimination:

- Members of the US Military receiving care through Tricare
- Veterans receiving care through the Veteran's Administration (VA)
- The Indian Health Service
- Federal employees receiving care through the Federal Employees Health Benefits Plans

As with any research study, there may be additional risks that are unknown or unexpected.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?
The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 about any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors**.**

5.3 If I take part in this study, can I also participate in other studies?
Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?
You may not receive any personal benefits from being in this study other than to help advance scientific knowledge. The types of scans we will use are not very sensitive to many abnormalities. The scanning procedures used for this study will not be read by a specialist trained to make medical diagnoses from the scan. That is, even if there is an abnormality in your head, it is likely that it would not be discovered by the people who inspect the images. Therefore, it is likely that any abnormality that you may currently have will not be revealed by the images obtained in this experiment. If you have any current health concerns, you should consult your doctor. However, some subjects in the study who receive brain stimulation treatment may experience migraine pain relief. Hopefully this research will allow us to gain a better understanding of the behavior of the brain of migraine sufferers and the effectiveness of brain stimulation as a treatment for migraine.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?

Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. OTHER OPTIONS

6.1 If I decide not to take part in this study, what other options do I have?

Your participation in this project is voluntary, and participation will not help in diagnosis of and may not help in treatment of any medical condition. The alternative to experiencing these procedures is not to participate. You should feel free to choose or reject this study or to withdraw from any portion of this study at any time without penalty or loss of benefits to which you may otherwise be entitled. The physicians and other staff of the University Hospital will continue to offer their best medical care regardless of your decision. You may want to discuss additional treatment options with the study team or your current physicians.

Additionally, if you have migraines there may be other ways of treating your condition. These include, but are not limited to, over-the-counter and prescription pain medications. Although tDCS is available as part of this clinical study, you should check with the researcher and/or your primary care physician to discuss your options including how to obtain any alternative treatments and whether they must be obtained through a physician or require medical supervision.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?

You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 “Contact Information” (below).

7.2 Could there be any harm to me if I decide to leave the study before it is finished?

There is no inherent risk in leaving the study early. If you decide to leave the study early, the researchers may ask your reason for doing so.

7.3 Could the researchers take me out of the study even if I want to continue to participate?

Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

- ✓ The researcher believes that it is not in your best interest to stay in the study.
- ✓ You become ineligible to participate.
- ✓ Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- ✓ You do not follow instructions from the researchers.
- ✓ The study is suspended or canceled.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?

The study will pay for research-related items or services that are provided only because you are in the study. If you are not sure what these are, see Section 4.1 above or ask the researchers for a list. If you get a bill you think is wrong, call the researchers’ number listed in section 10.1.

The study team has given you instructions about this research study. It is important that you follow these instructions carefully. If you get sick, have a medical complication, or are injured as a result of your being in the study, call the

Principal Investigator listed in Section 10 immediately. The doctor will either treat you or send you to another doctor for treatment.

You will get free medical care at the UMHS for any hospitalization or ER visits directly caused by the study procedures. The UMHS and the study doctor are responsible for determining whether your condition was the result of your participation in the study. The UMHS will pay for your treatment only if the need for treatment has been caused by the study procedures. This means that you or your health plan must pay for any treatment that is part of your usual medical care or that is related to a medical condition you had before participating in the study.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care
- Items or services needed to give you study drugs or devices
- Monitoring for side effects or other problems
- Deductibles or co-pays for these items or services.

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan's medical reviewer.

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

8.2 Will I be paid or given anything for taking part in this study?

You will be compensated $25.00 for your screening appointment, $50.00 per MRI scan, and $100.00 per PET scan. Episodic migraine patients will also receive $25.00 for each brain stimulation session and $25.00 for each follow-up visit. All compensation will be paid in cash upon the completion of each visit. The total compensation provided for this study is $175.00 for healthy controls and $650.00 for episodic migraine patients. However, this total may be exceeded if a problem occurs during one of your MRI or PET scans and you are asked to complete an additional scan. Allowance for travel expenses may be provided in very specific situations when needed and will be decided on case-by-case basis. If a visit ends early, you may be paid less; this also will be decided on a case-by-case basis.

8.3 Who could profit or financially benefit from the study results?

The University of Michigan is an owner and Dr. Alex DaSilva is an inventor of a tool being used in this research. This tool is licensed to MoxyTech, Inc., which is partially owned by Dr. DaSilva. This means the University of Michigan, Dr. DaSilva, and MoxyTech, Inc. could financially benefit from this study.

Research can lead to new discoveries, such as new tests, drugs, or devices. Researchers, their organizations, and other entities, including companies, may potentially benefit from the use of the data or discoveries. You will not have rights to these discoveries or any proceeds from them.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how your privacy and the confidentiality of your research records will be protected in this study.

9.1 How will the researchers protect my privacy?

Research records will be kept in a separate research file that does not include names, registration numbers, or other information that is likely to allow someone other than the researchers to link the information to you. Instead, you will be assigned a unique code that is used on all your research records, and only the investigators will be able to link the information to you using this code. We shall keep your research record confidential, to the extent provided by

federal, state and local law. You will not be identified in any reports on this study. Nevertheless, the National Institutes of Health, the United States Federal Food and Drug Administration, and the Institutional Review Board monitoring this study may inspect the records of this investigation.

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

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

The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document.

9.2 What information about me could be seen by the researchers or by other people? Why? Who might see it?
Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study. Information about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- All records relating to your condition, the treatment you have received, and your response to the treatment
- Billing information

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- University, Food and Drug Administration (FDA), and/or other government officials may need the information to make sure that the study is done in a safe and proper manner.
- Study sponsors or funders, or safety monitors or committees, may need the information to:
    - Make sure the study is done safely and properly
    - Learn more about side effects
    - Analyze the results of the study
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The researchers may need to use the information to create a databank of information about your condition or its treatment and to use in future IRB-approved research studies.
- Information about your study participation may be included in your regular UMHS medical record.

- If you receive payments of $600 or more for taking part in this study, the University of Michigan accounting department will collect your name, address, social security number, payment amount, and related information. For tax reporting purposes this information must be sent to the Internal Revenue Services (IRS).
- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

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.

9.3 What happens to information about me after the study is over or if I cancel my permission?
As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over.

Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the University of Michigan "Notice of Privacy Practices". This information is also available on the web at http://www.uofmhealth.org/patient+and+visitor+guide/hipaa. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.4 When does my permission expire?
Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below).

10. CONTACT INFORMATION

10.1 Who can I contact about this study?
Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: Alexandre DaSilva, D.D.S.,D.Med.Sc.
Mailing Address: Biologic & Material Sciences, School of Dentistry
1011 N. University, Room 1014A
Ann Arbor, MI 48109-0720
E-mail: adasilva@umich.edu
Telephone: (734) 763-5280

Study Coordinator: Dalya Saleem, BSPH
Mailing Address: The Molecular & Behavioral Neuroscience Institute (MBNI)
205 Zina Pitcher Place, Room 1021
Ann Arbor, MI 48109-5720
E-mail: dsaleem@umich.edu
Telephone: (734) 763-8469

You may also express a concern about a study by contacting the Institutional Review Board listed below.

University of Michigan Medical School Institutional Review Board (IRBMED)
2800 Plymouth Road
Building 520, Room 3214
Ann Arbor, MI 48109-2800
Telephone: 734-763-4768 (For International Studies: US Country Code: 001)
Fax: 734-763-1234
e-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy or concerned about a study you may contact the University of Michigan Health System Compliance Help Line at 1-866-990-0111.

When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?

Your signature in the next section means that you have received copies of all of the following document:

This "Consent to be Part of a Research Study" document. (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.)*

12. SIGNATURES

Consent/Assent to Participate in the Research Study

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with _____. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

For use only if required by sponsor:

Date of Birth (mm/dd/yy): _____

ID Number: _____

Consent/Assent for Participating in Genetic Sub-Study Testing

This project involves optional participation in a genetic sub-study. I understand that it is my choice whether or not to take part in the sub-study. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

_____ Yes, I agree to take part in the optional sub-study.

_____ No, I do not agree to take part in the optional sub-study.

Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Consent/Assent for Participating in the Sub-Study: Optional Retention of Research Data
This project involves optional participation in a substudy that involves the retention of research data for future studies on migraines. I understand that it is my choice whether or not to take part in the sub-study. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

_____ Yes, I agree to take part in the optional sub-study.

_____ No, I do not agree to take part in the optional sub-study.

Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Consent/Assent for Participating in the Sub-Study: Optional Retention of Research Samples
This project involves optional participation in a substudy that involves the retention of research samples for future studies on migraines. I understand that it is my choice whether or not to take part in the sub-study. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

_____ Yes, I agree to take part in the optional sub-study.

_____ No, I do not agree to take part in the optional sub-study.

Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Principal Investigator or Designee

I have provided this participant and/or his/her legally authorized representative(s) with information about this study that I believe to be accurate and complete. The participant and/or his/her legally authorized representative(s) indicated that he or she understands the nature of the study, including risks and benefits of participating.

Legal Name: _____

Title: _____

Signature: _____

Date of Signature (mm/dd/yy): _____