Investigation and Modulation of the Mu-Opioid Mechanisms in TMD (*in vivo*)

NCT03724032

Date: 7/22/2021

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

Study title: Investigation and Modulation of the Mu-Opioid Mechanisms in TMD (*in vivo*)

Company or agency sponsoring the study:
National Institutes of Health – National Institute of Dental and Craniofacial Research (NIH-NIDCR)

Names, degrees, and affiliations of the researchers conducting the study:
Alexandre DaSilva, DDS, DMedSc – Headache & Orofacial Pain Effort (HOPE), Department of Biologic & Material Sciences, University of Michigan

1.1 Key Study Information

You may be eligible to take part in a research study. This form contains information that will help you decide whether to join the study. All information in this form is important. Take time to carefully review this information. After you finish, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others such as your friends, family, or other doctors about your possible participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you do, be sure you understand what the study is about.

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

This is a research study of temporomandibular disorder (TMD). The purpose is to decide if 10 daily sessions of brain stimulation will cause a significant lowering of pain at one month (28 days) after finishing these sessions. Stimulation will be delivered non-invasively, by a transcranial direct current stimulation device, which might do so by modulating your own pain-killers in the brain. This device is considered investigational by the FDA.

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?

Two groups:

- People with chronic jaw pain (also called “temporomandibular disorder”; TMD) and
- Healthy volunteers

3.2 How many people (subjects) are expected to take part in this study?

- 60 men or women aged 18 to 65 with TMD
- 30 age- and gender-matched healthy subjects, in total:

Twenty (or more) subjects will be recruited from the UMHealthResearch.org database, the TMD and orofacial pain clinics at the University of Michigan (UM), and from other clinics in the region. We will also include the PET/MRI data from up to 10 healthy subjects who were recruited and scanned during the NIDCR-NIHR56 DE022637 project, if they are gender and age-matched.

There are other inclusion/exclusion criteria not listed here that the study team will review with you to make sure you qualify for the study.

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?

4.1.1 Screening Visit

If you would like to take part in this study, we will first make sure you qualify. We will ask you some questions, then ask you to complete some questionnaires*. Parts of this visit may be completed using Zoom for health at U of M, and some questionnaires may be administered electronically:

- All subjects (both TMD patients and healthy people) will complete questionnaires about personal information (such as age, race, education, and occupation) and about their moods and sleep.
- TMD patients will complete additional questionnaires about their pain.
- You may be able to take some of the questionnaires home to complete and return them at your next visit.
- All potential subjects will undergo a baseline exam including a medical/dental history with a limited physical exam, a listing of medication history (6 months) and a review of eligibility for the study. TMD patients will be given a baseline TMD exam.

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

- Healthy people who don't suffer from TMD will be invited for up to 2 more study visits.
- TMD patients will be invited for up to 17 more study visits.
- Due to COVID-19, additional screening measures may be performed before entering university buildings.

4.1.2 MRI #1 Visit

Both TMD patients and healthy subjects

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 80 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.

4.1.3 PET #1 Visit

Both TMD patients and healthy subjects

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:

- 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.

- 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. Algometry (pressure testing) may also be performed in the same areas. This stimulus, though it may feel mildly painful, does not produce any skin damage.

- Hypertonic Saline Challenge**:** During the PET scan your response to pain will be measured by an IV injection of salt water into the large muscle in your jaw. If you have TMD, it will be placed on the side where you feel your worst pain. This injection will be under your control with a computer mouse and you can stop it at any time.

  During the PET scan:
  1. We'll show you how to use a pain rating system.
  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 hypertonic saline pain challenge will begin 45 minutes after we inject the tracer. Each scan will consist of multiple saline pain challenges, which will incorporate limits and safety features.
  6. You will be asked to rate your pain at different time points.

  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. TMD patients will continue to come to our clinic for further study visits.

4.1.4 HD-tDCS Visits #1-10 (High-Definition - Transcranial Direct Current Stimulation)

TMD patients only — 10 daily brain stimulation sessions

High-Definition - Transcranial Direct Current Stimulation (HD-tDCS; "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 fabric 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 mild 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, and a tDCS side effects form to fill out.

During each session, we will place a fabric cap containing electrodes over your head. If you are in the active tDCS subject group, the device will send a mild electrical current (up to 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.

4.1.5 MRI #2 Visit — *TMD patients only*

A second MRI scan will be performed so that we can see if the tDCS treatments resulted in changes in your TMD-related brain functions. The procedures at this visit will be identical to those at the MRI #1 Visit (above).

4.1.6 PET #2 Visit — *TMD patients only*

A second PET scan will be performed so that we can see if the tDCS treatments resulted in changes in your TMD-related brain functions. The procedures at this visit will be identical to those at the PET #1 Visit (above).

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

Appointments will be scheduled for 1 week, 1 month, and 2 months following the last HD-tDCS day. During these appointments, we will ask about your pain 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. These follow-up visits might be done remotely using electronic surveys.

4.1.8 Subject Participation and Compensation

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.

Table 1. Subject Participation and Compensation

Type of Visit*	**Screening**	**fMRI* #1**	**PET* #1**	**HD-tDCS 10 Daily Sessions**	**fMRI #2**	**PET #2**	**Follow Up Visits**
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 1 Month 2 Months After HD-tDCS
Duration	1 hr	1 hr and 20 minutes	2.5 hr	1 hr ea x 10 visits	1 hr and 20 minutes	2.5 hr	1 hr ea x 3 visits
Compensation	$25	$50	$100	$25/ea x 10	$50	$100	$25/ea x 3
*Healthy Volunteers: Screening, 1st fMRI, 1st PET only							

4.1.9 Genetic Data Sharing

We will collect and store information about your genes. The DNA contained in your genes holds the instructions that your body uses to grow and function. Your genes are responsible for your physical features such as eye color, blood type, and how your body breaks down medications. Genes can also be responsible for some medical conditions.

Genomic information relates to the structure and function of all of the genetic material in the body.

We will submit your genomic information to a repository to be used for scientific purposes. A repository contains information from many people. Some repositories are maintained by the University of Michigan, some are maintained by the federal government, and some are maintained by private companies.

Researchers all over the world can take information from the repository and use it in their studies. Their studies may be similar to this one or may be completely different.

Because this research receives funding from the National Institutes of Health (NIH), we will submit your genomic information to a controlled-access NIH-designated data repository such as the NIH Database of

Genotypes and Phenotypes (dbGaP) or other NIH-designated data repository. NIH is a national research agency and is part of the federal government.

We will label your genomic information with a code, instead of your name or other information that people could use to directly identify you. Even so, there is a possibility that when your genomic information is combined with other information available to researchers, either now or in the future, they may be able to identify a group you belong to (like an ethnic group or a disease population) or, less likely, you personally. NIH prohibits people from trying to identify individuals whose genomic information is in an NIH-designated repository.

Researchers will have *controlled access* to your specific genomic information. Controlled access means that researchers will need approval from an NIH Data Access Committee in order to obtain genomic information from the repository. Researchers with an approved study may be able to see and use your de-identified information, along with that from many other people. However, your personally identifiable information (such as your address or social security number) will never be placed into a scientific database).

If you allow us to put your genomic information in the repository, you can change your mind later and ask us to remove it. To make this request, please use the contact information in Section 10 of this document. Keep in mind, however, that we cannot take back information that other researchers have already obtained from the repository.

4.1.10 Optional Substudy for Biomarker Analyses

We would like your permission to study your blood and medical information to find out how genetic profiles and inflammatory markers can affect the way people become more susceptible to chronic pain. You can take part in this study even if you decide not to let us analyze your blood to find out about the types of genetic profiles and biomarkers.

During each PET scan, 30 mL (~2 Tbsp) of blood will be collected; 6 mL at 20 minute intervals for serial biomarker analysis. Healthy volunteers are scheduled to undergo one PET scan (30 mL [2 Tbsp] total per protocol); TMD subjects are scheduled to undergo two PET scans (60 mL [4 Tbsp] total per protocol).

For the collection of blood samples post-[11C]carfentanil (CFN) injection, we will use an arterial pressure tubing that will collect approximately 4mL (~0.3 Tbsp) of blood for each PET scan. The total volume of blood collected, per scan, will not exceed 70mL (~4.7 Tbsp) per subject.

There is no limit for the amount of time we may store your samples. Even if you give us permission now to keep some of your blood and medical information, you can change your mind later and ask us to destroy it. To make this request, please use the contact information in Section 10 of this document. Keep in mind, however, that once we have analyzed your blood, we may not be able to take the information out of our research. Also, if we have shared some of your blood and medical information with other researchers, we will not be able to get it back.

We will not tell you the results of the analysis of your blood. Allowing us to study your blood and medical information to find out genetic profiles and inflammatory markers of chronic pain will not benefit you directly.

If the researchers decide to take you out of the study after completing blood collection for the reasons listed below, then your blood wil be stored as part of the regular study protocol unless you ask for it to be destroyed.

- ✓ 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.

As part of this study, your samples and collected information may be shared with the NIH. However; samples will be coded to protect your identity, and only the Principal Investigator (or other appropriate person) will have access to the code. If the samples or data from the samples are shared with other researchers, the information shared will not include information that identifies you.

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.

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.

4.1.11 Optional Substudy for Future Research

Besides the information about the main study, the following information is specific to unspecified future use of identifiable data and/or biospecimens. We would also like your permission to keep some of your blood and medical information collected in the main study, so that we may study it in future research. The future research may be similar to this study or may be completely different.

Blood samples that do not exceed a total of 45mL (3 Tbsp) will be collected during the PET scan for biomarker analysis. This blood will be collected from the arm that is opposite the arm used for the tracer injection. In addition, one blood sample for genetic analysis will be collected for future studies. This will not exceed 25 mL (1.7 Tbsp) per scan. No more than 70 mL (4.7 Tbsp) of blood will be collected per subject per PET scan; therefore, a total of 140 mL (9.5 Tbsp) blood will be collected, per TMD subject. Trained personnel will perform blood collection using standard procedure to reduce the likelihood of bruising or pain.

You can take part in the main study even if you decide not to let us keep your blood and medical information for future research.

If you give us your permission, we will use your blood and medical information for future research. Even if you give us permission now to keep some of your blood and medical information, you can change your mind later and ask us to destroy it. To make this request, please use the contact information in Section 10 of this document. Keep in mind, however, that once we have analyzed your blood, we may not be able to take the information out of our research.

Once we have your permission, researchers can keep your blood and medical information even after a decision was made to take you out of the study unless you request the samples to be destroyed.

We may share your blood and medical information with other researchers, so that they can use it in their research. Their research may be similar to this study or may be completely different. Once we have shared your blood and medical information with other researchers, we will not be able to get it back.

Future use of your identifiable data and/or specimens will be conducted in compliance with applicable regulatory requirements.

You will not find out the results of future research on your blood. Allowing us to do future research on your blood and medical information will not benefit you directly.

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.

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.

4.2 How much of my time will be needed to take part in this study?
Approximately 3 months

4.3 When will my participation in the study be over?

- The screening appointment and 3 follow-up visits (1 week, 1 month, 2 month) will each last approximately 1 hour
- Each MRI scan appointment will last approximately 1 hour & 20 minutes
- Each PET scan appointment will last approximately 2.5 hours
- Each tDCS appointment will last approximately 1 hour
- Due to COVID-19, additional screening measures may be performed before entering university buildings.

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

Your biospecimens and collected information may be shared with NIH-NIDCR.

With appropriate permissions, your biospecimens 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?

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 pain challenge (during the 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 function and anatomy 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.

1. **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 bruise 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.

2. **PET Tracers**: The signs of exposure to the PET tracer, carfentanil (CFN) include : respiratory depression or arrest, drowsiness, disorientation, sedation, pinpoint pupils, and clammy skin. You could theoretically experience an allergic reaction to the radioactive tracer (dye) carfentanil (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.

3. **Low-level radiation exposure:** During the course of this study, you will be exposed to radiation from the PET tracer, CFN. A single PET scan will result in a dose of 0.27 rem. Each individual's life-time radiation risk includes the background radiation they are exposed to naturally, which is on the average 0.3 rem per year. The proposed PET methods have no alternatives for collection of the necessary data at the present time. 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.

   Hypertonic Saline Challenge: During the PET scan your response to pain will be measured by an IM injection of salt water into the large muscle in your jaw. If you have TMD, it will be placed on the side where you feel your worst pain. The intention of this procedure is to induce (20min) a moderate level of pain that will persists long enough for the PET session. This injection will be under your control with a computer mouse and you can stop it at any time. The risks associated with this procedure are similar to those of an IV line placement for blood draws (see #1 above), and include infrequent bruising, bleeding, infection, or soreness associated with placement. You might feel dizzy or lightheaded or may rarely even faint when it is put in or taken out. There is a small chance of infection or clotting in the area where the line was placed. The condition is usually treated by icing and typically resolves in a few days.

- **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. The potential minor risks of HD-tDCS include brief headache, itching, tingling, burning sensation (not injury), discomfort, skin redness, sleepiness, trouble concentrating, acute mood changes, scalp and neck pain. If present, they usually subside soon after session without physical harm. 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.

- **Quantitative Sensory Testing (QST)**:

  Thermal QST will be performed in four areas of the skin (face and hands, both left and right sides) to test your sensitivity to cold and warm temperatures. We will produce both warm and cold sensations (0-50° Celsius; approximately 32-120° Fahrenheit) 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 or cold sensation will be delivered 3 times in each location. This stimulus, though it may feel mildly painful, does not produce any skin damage.

  Algometry, another type of QST, will be performed to define pressure pain threshold in the same four areas. Each area will be tested three times, and the ultimate pressure pain threshold levels will be the average of the three measurements recorded. For the evaluation of motor function, we will perform the exam according to the Research Diagnostic Criteria (RDC) guidelines and forms (e.g., range of motion). The QST is not associated with pain lasting beyond the study period or any irreversible damage to the body.

- **Drug and Pregnancy Screening:** There is a risk of loss of confidentiality and/or feeling uncomfortable about sensitive information such as drug use status or discovering an unknown pregnancy. 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 and pregnancy screens 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 that might be presented electronically. Although each questionnaire is not stressful when answered alone, completing multiple surveys in a row may lead to a low level of mental fatigue. You may be offered the opportunity to take some of the questionnaires home to complete, then return them to the researchers at your next visit.

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

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.

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 pain relief. Hopefully, this research will allow us to gain a better understanding of the behavior of the brain of TMD sufferers and the effectiveness of brain stimulation as a treatment for TMD.

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 TMD there may be other ways of treating your condition. These include, but are not limited to over-the-counter and prescription pain medications. Although brain stimulation 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 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.

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.

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 Dr. DaSilva immediately at 734-615-3807. 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 drug, device, or procedure. 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 drug, device or procedure. 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.

It is not the policy of the federal funding agencies to compensate or provide medical treatment for human subjects in federally funded studies.

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. TMD 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 TMD 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. Visits terminated early may be compensated by a reduced fee (ie, $25) and allowance for travel expenses may be provided in very specific situations when needed; each circumstance will be decided on 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. DaSilva is an inventor of a tool being used in this research. This tool is licensed by 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. You will not receive any proceeds, profits, or other benefits from any commercial product that may result 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. Research records will be kept confidential to the extent provided by federal, state and local law. You will not be identified in any reports on this study; however, the National Institutes of Health, the United States Food and Drug Administration, and the institutional review board monitoring this study may inspect the records of this investigation. Genetic research may provide information about who is at risk to develop a disease. Some people may find this information stressful or uncomfortable. While our research is focused primarily on pain mechanisms through new genetic technologies that allow us to look at all of the information across the genome, we may learn information about subjects regarding diseases not related to pain. We do not intend to release the results of the genetic testing to you. If multiple members of a family are enrolled in research, information from this research may identify previously undisclosed biological relationships (i.e. non-paternity or non- maternity). There is an unlikely but possible risk of a breach of confidentiality. To reduce this risk, the databases developed for this project will not contain information that is traditionally used to identify you, such as name, address, telephone number, or social security number. It is also possible that there could be violations to the security of the computer systems used to store the codes linking genetic and medical information to subjects. These codes will be maintained only at UM.

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 the SPONSOR 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.

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

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
- Demographic information
- Personal 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, auditors, and/or the IRB 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.
- Information about your study participation may be included in your regular UMHS medical record.

- If you receive any payments for taking part in this study, the University of Michigan accounting department may need your name, address, social security number, payment amount, and related information for tax reporting purposes.
- 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:	Dr. Alexandre F. DaSilva, DDS, DMedSc
Mailing Address:	1011 N. University Ave, #1014A Ann Arbor, MI 48109-1078
Telephone:	734-615-3807
Research Coordinator:	Jacqueline Dobson
Mailing Address:	205 Zina Pitcher Place, Room 1021 Ann Arbor, MI 48109-5720
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 a signed and dated copy 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 [NAME OF STUDY TEAM MEMBER OBTAINING CONSENT] _____. 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.

Print Legal Name: _____

Signature: _____

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

Consent/Assent to Collect for Unspecified Future Research

This project involves the option to allow the study team to keep your identifiable specimens/data for use in future research. I understand that it is my choice whether or not to allow future use of my specimens. 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 let the study team keep my specimens for future research.

_____ No, I do not agree to let the study team keep my specimens for future research.

Print Legal Name: _____

Signature: _____

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

Consent/Assent for Participating in an Optional Sub-Study: BLOOD SAMPLES FOR BIOMARKER STUDIES
This project involves optional participation in a 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.

Print Legal Name: _____

Signature: _____

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

Consent/Assent for Participating in an Optional Sub-Study: GENETIC BLOOD SAMPLE
This project involves optional participation in a 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.

Print 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): _____

Impartial Witness

I observed the above subject (or his/her legally authorized representative, if applicable) sign this consent document.

Legal Name: _____

Title: _____

Signature: _____

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