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

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NIDCR Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subjects protection training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
BPI	Brief Pain Inventory
BPND	non-displaceable binding potential
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRO	Contract Research Organization
CSF	cerebrospinal fluid
CSOC	Clinical Study Oversight Committee
CT	computerized tomography
DC	diagnostic criteria
DCC	Data Coordinating Center
DEA	Drug Enforcement Agency
DHHS	Department of Health and Human Services
DMFS	Decayed, missing, and filled tooth surfaces
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EEG	electroencephalography
FDA	Food and Drug Administration
FFR	Federal Financial Report
FWA	Federalwide Assurance
GABA	gamma-amino butyric acid
GCP	Good Clinical Practice
HD-tDCS	high-definition transcranial direct current stimulation
HIPAA	Health Insurance Portability and Accountability Act
H.O.P.E.	Headache and Orofacial Pain Effort
IB	Investigator's Brochure
ICBM	International Consortium for Brain Mapping
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption

IND	Investigational New Drug Application
IRB	Institutional Review Board
IRBMED	Institutional Review Boards of the University of Michigan Medical School
ISM	Independent Safety Monitor
M1	primary motor cortex
MCS	motor cortex stimulation
MedDRA®	Medical Dictionary for Regulatory Activities
MNI	Montreal Neurological Institute
MOP	Manual of Procedures
MPQ	McGill Pain Questionnaire
N	Number (typically refers to subjects)
NDA	New Drug Application
NIDCR	National Institute of Dental and Craniofacial Research, NIH, DHHS
NIH	National Institutes of Health
NSAID	non-steroidal anti-inflammatory drug
OCTOM	Office of Clinical Trials Operations and Management, NIDCR, NIH
OHRP	Office for Human Research Protections
PANAS	Positive and Negative Affect Schedule
PET	positron emission tomography
PHI	Protected Health Information
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
QST	quantitative sensory testing
RDC	Research Diagnostic Criteria
RDRC	Radioactive Drug Research Committee
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
tDCS	transcranial direct current stimulation
TMD	temporomandibular disorder
TMJ	temporomandibular joint
TSA	thermal sensory analyzer
UM	University of Michigan
UP	Unanticipated Problem

US	United States
VAS	visual analog scale
WHO	World Health Organization
μOR	μ-opioid receptor

PROTOCOL SUMMARY

Title:

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

Précis:

This is a phase 2, single center, two-arm double-masked, randomized investigation and modulation of the μ-opioid mechanisms in TMD (in vivo). We will enroll 60 patients with chronic TMD (30 for the active M1 HD-tDCS group and 30 for the sham group). Each participant will undergo the sequence of events and evaluations laid out in the Schematic of Study Design (pages 14-15), which will take approximately 3 months (up to 10 weeks for healthy volunteers [HV]). In addition, we will recruit 20 (or more) age- and gender-matched HV. We will use the PET/MRI data from up to 10 healthy controls who were recruited and scanned during the NIDCR-NIHR56 DE022637 project, for a total of 30 HV. These 30 healthy control volunteers will be compared to TMD patients at baseline; however, they will not be part of the clinical trial. Completion of full protocol enrollment and participation is expected to take approximately 5 years. Data will be collected on paper or electronic CRFs, on mobile devices, or electronically on local systems (PET, MRI, QST), then transferred via HIPAA-compliant methods by the Michigan Medicine system for analysis by study staff.

Objectives:

Primary Objective: The primary effectiveness objective is to investigate whether 10 daily sessions of primary motor cortex (M1) HD-tDCS will result in a significant reduction in clinical pain intensity at rest in chronic TMD subjects 4 weeks after completion of HD-tDCS sessions, as measured by a visual analog scale (VAS) pain score.

The secondary objectives are as follows:

- To investigate whether 10 daily sessions of M1 HD-tDCS will result in significant reductions in clinical pain intensity (at rest) and experimental (sustained masseteric pain stress challenge) measures in chronic TMD subjects at 1 week after completion of HD-tDCS sessions, as measured by VAS pain score assessments, obtained during the baseline PET (#1) session and follow-up PET (#2) session.
- To investigate whether 10 daily sessions of M1 HD-tDCS will result in significant short-term and/or long-term changes

in clinical pain intensity and area measures in chronic TMD subjects treated with HD-tDCS compared to those who receive sham treatment, as measured by GeoPain measures.

- To investigate whether repetitive active M1 modulation induces increase of μ-opioid receptor (μOR) non-displaceable binding potential (BP_{ND}) in the thalamus and other pain-related regions in the brains of chronic TMD subjects from the baseline PET (#1) session to the follow-up PET (#2) session, 1 week after completion of HD-tDCS sessions.

- To investigate whether any μOR BP_{ND} changes from baseline PET (#1) session to follow-up PET (#2) session are associated with changes in mean clinical and experimental pain measures, as measured by VAS pain scores in chronic TMD subjects who receive HD-tDCS treatment compared to those subjects who receive sham treatment.

- To investigate whether chronic TMD is associated with μOR BP_{ND} changes as compared to healthy subjects during baseline PET (#1) session at rest, and during experimental sustained masseteric pain stress challenge.

Population:	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.
Phase:	II
Number of Sites:	1
Description of Intervention:	High-definition transcranial direct current stimulation (HD-tDCS)
Study Duration:	5 years

Subject Participation Duration:	Approximately 3 months (up to 10 weeks for healthy volunteers)
Estimated Time to Complete Enrollment:	4 years

Schematic of Study Design (Patients with Chronic TMD):

PreScreening (Up to 8 weeks prior to RND)	Phone Call IRB-Approved Prescreening Checklist/Script	
Screening (Up to 3 weeks prior to RND)	Informed Consent Demographics History and Physical Exam Questionnaires	
PET and MRI #1 (Up to 1 week prior to RND)	QST PET #1 Pre-PET Questionnaires Pregnancy Test and Drug Screen CFN (^{11}C-carfentanil) Injection [Time 0] Masseteric [HT (Hypertonic) Saline] Injection [45-65 min] Post-PET Questionnaires MRI #1 Screening Form (MRI-specific) MRI Questionnaires	
	Randomization	
RND or Enrollment (HD-tDCS Week 1)	TMD Active	TMD Control
HD-tDCS x 10 Daily Sessions (Week 1-2)	Questionnaires ~2 mA current for **20 min/day** x 10 days (M-F over 2 wks) Questionnaires	Questionnaires ~2 mA current for **30 sec at start plus 30 sec at end** of session x 10 days (M-F over 2 wks) Questionnaires
PET and MRI #2 (Week 3)	QST PET #2 Pre-PET Questionnaires Pregnancy Test and Drug Screen CFN (^{11}C-carfentanil) Injection [Time 0] Masseteric [HT (Hypertonic) Saline] Injection [45-65 min] Post-PET Questionnaires MRI #2 Screening Form (MRI-specific) MRI Questionnaires	
Follow Up @ Week 3 (Week 3)	Questionnaires	
Follow Up @ Month 1 (Week 6)	Questionnaires	
Follow Up @ Month 2 (Week 10)	Questionnaires	

Schematic of Study Design (Healthy Volunteers):

PreScreening (Up to 7 weeks prior to PET/MRI)	Phone Call IRB-Approved Prescreening Checklist/Script
Screening (Up to 2 weeks prior to PET/MRI)	Informed Consent Demographics History and Physical Exam Questionnaires
PET and MRI #1	QST PET #1 Pre-PET Questionnaires Pregnancy Test and Drug Screen CFN (^{11}C-carfentanil) Injection [Time 0] HT (Hypertonic) Saline Injection [Time 45-65 Min] Post-PET Questionnaires MRI #1 Screening Form (MRI-specific) MRI Questionnaires

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

2.1.1 *Temporomandibular Disorders (TMD)*

Temporomandibular disorders (TMD) are debilitating chronic conditions affecting the temporomandibular joint (TMJ) and/or masticatory muscles. Prevalence of this disorder ranges from 8% to 15% for women and 3% to 10% for men[1]. A sizable proportion of TMD patients have a tendency for chronicity and aggravation of their symptoms. In a study of 45,711 US households, nearly 11% described TMD symptoms that persisted over a 6-month period[2]. In another large population-based study, 10% of the participants who reported TMD had severe pain on function[3]. Patients suffering from chronic TMD are frequently followed by multiple healthcare professionals and are subjected to various treatment modalities, including medications, occlusal appliances, trigger point injections, physical therapy, behavioral therapy, and surgeries[4,5]. Approximately 10% of TMD patients will not experience an improvement of their symptoms[6], and around 75% of patients who fail to respond to conservative treatments are also not suitable for TMJ surgery[7]. For those for whom surgery is indicated, there is always the risk associated with invasive surgical procedures that can lead to refractory neuropathic or inflammatory pain and further joint dysfunction. Unfortunately, it is not known which patients will benefit from the treatments described above in the early phases of TMD treatment and which will be at risk to experience perpetuation and/or worsening of the TMD symptoms even when the peripheral trigger or etiologic factor is eliminated.

2.1.2 *Investigation and Potential Treatment of TMD Pain*

We aim to investigate the μ-opioid mechanisms of acute and chronic masseteric pain in TMD patients, the main receptor target of opiate therapy, using novel molecular neuroimaging and neuromodulatory models developed in-house. The information available on the dysfunctional μ-opioid activation *in vivo* in TMD patients and how they respond to non-invasive primary motor cortex (M1) stimulation is scarce. We hypothesize that continuous modulation of this crucial neurotransmitter system, which is intimately involved in the pain experience, will be related to TMD sensory dysfunction and to molecular neuroplasticity in the human brain.

In addition, while understanding central mechanisms in TMD using molecular neuroimaging is important, it is equally important to develop novel concepts for future clinical application. The studies proposed here represent a change of paradigm in TMD research in humans as we directly investigate and modulate *in vivo* one of the most important endogenous analgesic mechanisms in the brain.

2.1.3 *Transcranial Direct Current Stimulation*

Transcranial direct current stimulation (tDCS) is based on the application of a weak direct current to the scalp that flows between two electrodes, an anode and cathode. Its effects depend on polarity of stimulation: cathodal stimulation tends to induce a decrease in cortical excitability and anodal stimulation an increase, both of which may last briefly beyond the duration of the stimulation past the session. In our investigations with the μ-opioid-specific radiotracer [^{11}C]carfentanil, conventional M1-supraorbital tDCS application induced strong μ-opioid system activation in several pain-related regions, including the thalamus[8,9,10] **(**Figure 1).

Figure 1: Decreased thalamic μ-opioid receptor availability during active tDCS, represented in the coronal plane. Bar chart illustrating the μOR BP_{ND} in the thalamus during the late phase of the first (Baseline) and second positron emission tomography (PET) scans (Active tDCS).

However, a more concentrated area of stimulation would allow for better investigation and modulation of M1 cortico-thalamic mechanisms and better emulate the successful clinical effects of (implanted) motor cortex stimulation (MCS). This would decrease scattered electric current across the brain, improving the specificity of our translational scientific methods. Therefore, we have developed a high-definition tDCS (HD-tDCS) montage that uses increased focality to selectively target the putative M1 head and facial homuncular region using similar principles as MCS, including postero-anterior stimulation of the precentral gyrus' superficial fibers (Figure 2).

Figure 2: **Brain modulation using 2x2 HD-tDCS Montage. A.** 3D rendered head built from the magnetic resonance imaging (MRI) derived segmentation masks used in the study. Anode electrodes (red) were placed over C3-4 and C5-6 and Cathode electrodes were placed over FC3-4 and FC5-6 (the stimulation was always on the cortical side opposite to the worst pain). **B.** Skin, skull, and cerebrospinal fluid (CSF) masks are suppressed to reveal the underlying gray matter mask. **C.** Induced cortical surface electric-field directional plot for 2 mA stimulation. Red denotes inward (anodal) stimulation while blue denotes outward (cathodal) stimulation. **D.** Induced cortical surface electric-field magnitude plot for 2 mA stimulation.

In a previous study, our M1 HD-tDCS model significantly improved side-specific sensorimotor clinical measures (area and intensity) in chronic TMD pain patients[11], with more general analgesic effects lasting up to four weeks following treatment. This approach selectively modulates M1, as in MCS, but noninvasively to provide better temporary TMD pain relief.

We propose the study described here to investigate whether 10 daily sessions of M1 HD-tDCS will result in a significant reduction in clinical pain intensity 4 weeks after completion of HD-tDCS sessions.

2.1.4 *The HD-tDCS Device*

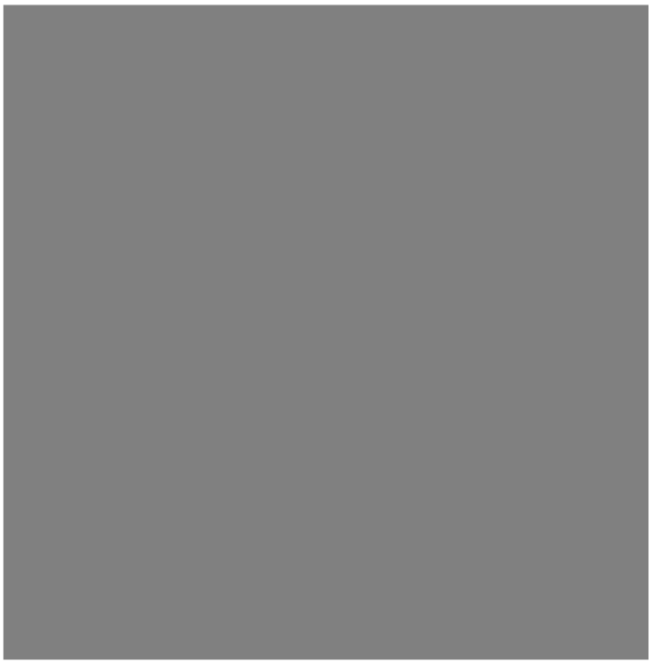
The HD-tDCS in this study will be delivered by an investigational product that delivers HD-tDCS and is publically available for research use only from Soterix Medical. Stimulation will be delivered by 4, 12-mm Ag/AgCl sintered ring electrodes arranged at the corners of a 4 cm x 4 cm square placed over the motor cortex. Total current

provided by the device, ≤2 mA for subjects in the active arm of this study, is equally distributed between the 2 anodes (1 mA per anode). The operation of the electrodes is controlled through a unit on which the current level and treatment time are set by the investigator's unblinded designee before each treatment session. The unit also has a "Relax" feature that, when switched on by the designee, immediately ramps down the current by 0.2 to 0.5 mA for a few seconds if a subject communicates they are experiencing discomfort. This unit has been inspected by the University of Michigan (UM) biomedical engineering unit and found to be in compliance with all regulations. The electrodes are connected to the unit by 4 identical smooth, rounded, red cables measuring 39.5 cm in length. The control unit and cables are shown in Figure 3b.

As shown in Figure 3a, the upper anode will be placed on C3-4, the lower anode on C5-6, and the upper and lower cathodes will be placed anteriorly on FC3-4 and FC5-6, respectively, using the standard International Electroencephalography (EEG) 10-20 system[12]. The vertex will be found by measuring the midpoint between nasion and inion and the midpoint between the pre-auricular areas; then, the midpoint from the vertex to the pre-auricular point on the side contralateral to the patient's worst pain will be marked so that stimulation can be applied to the same spot each day. A perforated fabric cap with a chinstrap will then be placed on the head to secure plastic casings in the desired position of each electrode (Figure 3a), and approximately 3 mL of Lectron II Conductive Gel (K933804) will be injected into the casings. The electrodes will be placed in the gel with the rough surface directed toward the skin and held in place with plastic caps[13]. For subjects in the active HD-tDCS group, ≤2 mA total current stimulation will be applied for 20 min. For subjects receiving the sham-controlled tDCS sessions, current will be applied for 30 seconds at the beginning and at the end of the treatment sessions, as sensations arising from tDCS treatment occur mostly at the beginning and end of application. The control panel will not be visible to subjects or blinded investigators during treatment. The unit will be continually monitored by the designee throughout each treatment session.

Figure 3: **High-definition Transcranial Direct Stimulation Device. A.** Stimulation cap being worn by a patient, including electrodes attached to cables. **B.** Control unit for stimulation device.

A.



B.

2.2 Rationale

The **overall goal** of this project is to provide a detailed understanding *in vivo* of the μ-opioid receptor mediated neurotransmission in brains of chronic TMD patients, with the **long-term objective** of developing more focused neuromechanism-driven methods for TMD research and therapy.

2.3 Potential Risks and Benefits

The following potential risks and benefits are applicable to all subjects enrolling in this study, whether patients or healthy volunteers, except those addressing High-Definition Transcranial Direct Current Stimulation (HD-tDCS). Only patients randomized to the clinical trial (treatment or sham arm) will receive this application.

For a schedule of each procedure, see Section 7, Tables 1 & 2 "Schedule of Events" for TMD patients or healthy volunteers.

2.3.1 *High-Definition Transcranial Direct Current Stimulation (HD-tDCS)*

In our study, only TMD patients will receive (HD)-tDCS application. This study will employ a novel, high-definition transcranial direct current stimulation (HD-tDCS) montage created by our group[14] to assess whether tDCS can modulate the u-opioid dysfunction in TMD patients. Preliminary evidence indicates that HD-tDCS sessions reduced exclusively "contralateral" sensory-discriminative clinical pain measures (intensity/area) in chronic TMD patients by precisely targeting the M1 region[15].

Transcranial DCS has been used increasingly worldwide in recent decades and has been tested and implemented in several research projects in healthy subjects (e.g., cognitive tests, memory) and for the treatment of a variety of conditions from neuropsychiatric illnesses to chronic pain across patients of a wide age range (children, adolescents, adults, and the elderly)[16,17,18]. Chronic pain conditions that have responded effectively to tDCS include spinal cord injury, fibromyalgia, diabetic polyneuropathy, pelvic pain, multiple sclerosis, and back pain.

Transcranial DCS is a noninvasive technique in which weak, constant, direct current (e.g., 1 to 2 mA) is applied to an area of the brain through electrodes placed on the scalp to modify excitability and reduce pain. Generally, these treatments employ tDCS at low current densities and low maximum total charges with minimal side effects.

In 2011, Brunoni et al.[19] published a systematic review of data from tDCS studies performed up to 2010, which included 172 published articles. Although 63% of the articles reported at least 1 adverse effect (AE), systematic analysis revealed that the rates of most common adverse effects did not differ between the active and sham arms in these studies. Common AEs included itching (39.3% vs. 32.9%, respectively), tingling (22.2% vs. 18.3%), headache (14.8% vs. 16.2%), burning sensation (8.7% vs.

10%), and discomfort (10.4% vs. 13.4%). Erythema is significantly more common in the active vs. sham group in multiple studies, which is generally benign but could endanger study masking in randomized, sham-controlled trials. On rare occasions, the tDCS application has led to skin burns; however, this side effect appears to occur only when standard procedures for tDCS application are not followed, such as correct preparation of the skin, humidification of sponges with saline, and limiting of voltage/current. No serious adverse events (SAEs) attributable to tDCS have been reported in more than 10,000 subjects investigated in the contemporary tDCS literature from 1998 through 2014. These results suggest that tDCS implemented according to accepted tDCS safety guidelines and procedures is associated with relatively minor AEs.

One crucial consideration for the safety of tDCS is the current density that is being transmitted during treatment. Liebetanz et al.[20] reported a study conducted in 58 rats that received single cathodal stimulations at 1-1000 μA for up to 270 min through an epicranial electrode (3.5 mm^2) followed by histological evaluation 48 hours following treatment. A threshold estimate for current density was calculated from volumes of the direct current-induced lesions. No pathological brain lesions were observed below a charge density threshold of 52400 C/m^2. This threshold was at least 2 orders of magnitude higher than the charge density currently applied in human clinical studies at that time (171–480 C/m^2). This study provides a valuable guideline when either raising the current density being used for treatment or looking to alter the method of tDCS delivery.

Electrical fields generated by conventional tDCS analgesic montages are widely distributed across the brain, lacking specificity on the pain-related structures that are best targeted for the potential relief of TMD pain. High-definition tDCS has been utilized in multiple published studies[21,22,23,24]. A novel HD-tDCS approach was developed by Villamar et al. (2013) to more precisely target the cortical areas of interest. Our group has further optimized the HD-tDCS montage for noninvasive putative M1 modulation for effective analgesia. A pilot study investigating the effect of 5 daily HD-tDCS sessions on the modulation of pain and motor dysfunction in TMD was published by Donnell et al.[25] in 2015. A modified 2x2 HD-tDCS montage was developed and used, with four electrodes arranged at the corners of a 4 cm 4 cm square centered over the caudal portion of the putative M1 (Figure 4), where the homuncular head and facial region is represented. The treatment procedure was identical to that proposed for the study described in this document.

Figure 4: **Brain modulation using 2×2 HD-tDCS Montage.** **A.** 3D rendered head built from the MRI-derived segmentation masks used in the study. Anode electrodes (red) were placed over C4 and C6 and Cathode electrodes were placed over FC4 and FC6. **B.** Skin, skull and CSF masks are suppressed to reveal the underlying gray matter mask. **C.** Induced cortical surface electric-field magnitude plot for 2 mA stimulation. **D.** Induced cortical surface electric-field directional plot for 2 mA stimulation. Red denotes inward (anodal) stimulation while blue denotes outward (cathodal) stimulation.

The previous HD-tDCS study in TMD reported a low rate of mild AEs[26]. The most commonly reported side effects (occurring at least once per patient during the study) were sleepiness, tingling, headache, scalp pain, a burning scalp sensation, and neck pain. No skin lesions were observed. During any given appointment, patients in the active group experienced an average of 3.33 side effects per session, while patients in the sham group experienced an average of 3.32 side effects per session, out of 10 possible side effects.

The current study will implement the technique described above from our lab[27], but will deliver tDCS over 10 days (Monday through Friday for 2 weeks) instead of 5 days. Although mild adverse effects induced by HD-tDCS have been identified, severe and serious AEs are not expected if procedures are followed to ensure that HD-tDCS is conducted within the recommended safety guidelines.

For more safety information on (HD)-tDCS please see the following links:

tDCS (http://www.jove.com/details.php?id=2744)[28]

and

HD-tDCS (http://www.jove.com/video/50309/technique-considerations-use-4x1-ring-high-definitiontranscranial) [29].

2.3.2 ***Hypertonic Saline Challenge***

To observe or measure the response to pain with the PET scan (described in Section 2.3.3), study participants will be subjected to a pain challenge that elicits the release of endogenous opioids and activates the μ-opioid system. This pain challenge will be conducted only during scheduled PET scan(s).

A hypertonic saline challenge will be used to test the capacity of an individual to mobilize neurotransmitters involved in the response to pain. It is hypothesized that this response may be altered using HD-tDCS treatment. Hypertonic saline (5%; less than 5 mL over 20 minutes) will be infused into the masseter muscle during the PET scan, causing persistent pain that fluctuates in nature. The intensity of the pain will be controlled by the individual's experience such that individuals with chronic TMD pain will experience the same subjective pain intensity as those without TMD. The system is calibrated to induce an average target pain intensity of 4 units on a visual analog scale (VAS; 0= no pain, 10= worst possible pain) over a 20-minute period. Other than the risk of experiencing pain, this procedure carries with it the expected local risks, including those due to piercing of the skin with a needle and injection of saline (Figure 5). In performing approximately 70 of these procedures, our group has noticed redness and soreness at the site as the common AEs associated with the procedure.

The hypertonic saline challenge in the masseter muscle was selected for various reasons, including technical elements related to receptor quantification methods (e.g., sustainability and stability over sufficient time so that receptor quantification can

be obtained[30]. In addition, it is a challenge with psychophysical responses that closely mimic those reported by TMD patients[31], as opposed to briefer challenges (e.g., heat pain, ischemic pain model); making it a perfect challenge to compare neuronal mechanisms of pain regulation in healthy controls and TMD patients. In fact, around half of all TMD cases are classified as masticatory myofascial pain, and the masseter muscle appears to be the best target of choice for pain induction, since it is the main site of clinical TMD pain complain[32].

The suggested pain challenge has been extensively employed in our center to elicit the release of endogenous opioids and μ-opioid system activation in previous studies, but never for TMD patients (with the exception of our preliminary data). It is also ecologically consistent with the process under study. Receptor binding measures require the utilization of challenges sufficiently long in duration so that a constant state can be achieved. The subject state does not change substantially during the measurement period, and enough data points are collected to permit quantification. Most pain models do not have those characteristics, because pain declines over time if the stimulus does not adapt to the progressive activation of anti-nociceptive mechanisms.

Pain invariably disappears well within 5-10 min of infusion completion. The total volume of 5% hypertonic saline required to maintain the target pain intensity is also an objective measure of “sustained” pain sensitivity. Of note, momentary ratings of pain intensity still allow for sufficient individual variations in overall assessments of pain sensory and affective qualities (MPQ scale), expectations and effectiveness ratings (0-100 scale) (for placebo/active M1 HD-tDCS evaluation), VAS intensity and unpleasantness, and in emotional responses to the stimulus (PANAS), to allow for the examination of relationships between variable.

Figure 5: **Diagram of System to Induce and Maintain Pain Intensity.** Block diagram to induce and maintain pain intensity between preset VAS scores by infusion of 5% hypertonic saline into the masseter during the PET session. The main feature of the adaptive control delivery system is a proportional-integrative-derivative (PID) controller. It corrects the difference between actual and estimated pain intensities. The adaptive element includes strategies to bring pain intensity back in case the preset bounds are exceeded and recalculates any previously established PID parameters.

2.3.3 *Positron Emission Tomography (PET)*

Positron emission tomography (PET) scans will be used to analyze potential changes in the tissues and organs of interest occurring as a result of treatment with HD-tDCS, particularly potential changes in the thalamic μOR availability in the brains of TMD patients during masseteric pain. The μ-opioid system is arguably the main analgesic resource in the brain and target of many exogenous opiates, and currently there is no translational method in animals that could consistently reproduce the complex human TMD experience. However, PET is able to provide crucial information of the central μ-opioid activity in humans during clinical and experimental TMD pain. A radioactive drug (tracer) [^{11}C] carfentanil is used to visualize this activity by binding to μOR available. Potential PET risks include complications associated with venous cannulation, the administration of study radiopharmaceuticals, and the exposure to low level radiation.

During the PET procedure, an intravenous line will be inserted for injection of the radiotracer and collection of blood. The risks of bruising, bleeding, infection, or soreness associated with intravenous catheter placement are similar to the risks associated with blood draws for routine blood testing. Subjects may also experience dizziness or lightheadedness. Highly trained personnel using standard procedures employed in clinical practice will administer this procedure to minimize the risks. If infection does occur, the subject will be treated with appropriate systemic antibiotic therapy or surgical intervention.

A dose of [^{11}C] carfentanil requires consideration of both the radioactive ('hot') and non-radioactive ('cold') components, as only a very small fraction of molecules of carfentanil injected is radioactive (~1 of every million molecules). There are limits on both 'hot and 'cold' components. The radioactive dose used for each carfentanil scan is 15 mCi, and does not vary with subject weight. The non-radioactive dose (called 'cold' mass) is dependent on subject weight and is limited to <0.03 μg/kg body weight.

[^{11}C]Carfentanil is very short lived, having a half-life of 20.3 min, hence after 2 hours there is less than 2% of the injected dose remaining. A 15 mCi injection of [^{11}C]carfentanil results in a whole-body effective dose equivalent of 0.27 rem, and a critical organ (bladder) mean dose equivalent of ~2.0 rem. Completion of two PET scans will result in a whole-body dose equivalent of ~0.54 rem. This dose is less than that received from a standard chest computerized tomography (CT) scan, which has a dose of ~0.70 rem. Natural background radiation averages ~0.30 rem per year, so the carfentanil dose per scan is slightly less than the exposure from a year of background radiation. The low- level radiation exposure arising from participation in the studies in this project is well within federal guidelines established for participation of normal adult volunteers in medical research involving radiation. All subjects will be encouraged to drink plenty of fluids after the studies to encourage voiding and further diminish radiation exposure to the urinary tract and kidneys. 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, 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 immediately prior to the PET scanning session.

The cold mass of [^{11}C]carfentanil dosed to a patient during a PET scan must be <0.030 µg/kg body weight and is typically <0.015 µg/kg. All clinical research studies are

conducted by authorized user physicians under protocols approved by the US Food and Drug Administration (FDA) / UM Radioactive Drug Research Committee (RDRC), and the UM Institutional Review Board (IRBMED). The UM PET Center holds a Drug Enforcement Agency (DEA) License that covers the necessary supplies for the manufacture of [^{11}C]carfentanil, including des-methyl carfentanil (the precursor to [^{11}C]carfentanil, unscheduled substance. As the mass of [^{11}C]carfentanil made is very small (<5.0µg per 10 mL batch), authentic carfentanil reference standard (schedule 2 substance) is used to confirm identity of the radiolabeled version. Both carfentanil precursor and reference standard are housed in a Class 5 safe per DEA regulations.

Idiosyncratic responses to the study radiopharmaceuticals are unlikely at the tracer doses employed; however, we will exclude subjects with prior history of allergic response to the study tracer or chemically related drugs. A "crash cart" will be immediately available in the PET suite, containing necessary drugs for management of allergic or other drug reactions. The signs of exposure to the PET tracer, carfentanil also include[1]: respiratory depression or arrest, drowsiness, disorientation, sedation, pinpoint pupils, and clammy skin. A physician will be immediately available in the PET suite or in the immediately adjoining Nuclear Medicine Clinic area at all times when research subjects are present.

In summary, [^{11}C]carfentanil is a radiolabeled version of carfentanil for PET scans of the opioid system that is approved for human use in the Department of Radiology / Division of Nuclear Medicine at the UM. The UM PET Center within the Division of Nuclear Medicine has prepared [^{11}C]carfentanil for use in human research PET imaging studies for over 20 years and over 1300 clinical scans have been conducted to date. The Headache and Orofacial Pain Effort (H.O.P.E.) Laboratory (Dr. Alexandre DaSilva, Principal Investigator) at UM has conducted multiple clinical research studies since 2011, enrolling both healthy volunteers and chronic pain patients, including TMD, neuropathic pain and episodic/chronic migraine. In the course of these studies, PET scans employing the radiotracer carfentanil have been conducted more than 80 times with no SAE occurrences.

2.3.4 *Functional Magnetic Resonance Imaging (fMRI)*

Three Tesla functional magnetic resonance imaging (fMRI), without contrast, will be conducted for use in analyzing PET data. The images obtained provide anatomical

[1] https://www.dea.gov/divisions/hq/2016/hq092216.shtml. Accessed 23March2018.

information for structure identification and will be used for the anatomical standardization to the International Consortium for Brain Mapping/Montreal Neurological Institute (ICBM/MNI) atlas coordinate system.

If the TMD pain mechanisms are not through a change in the μ-opioid system, we will explore alternative mechanisms in the future using MRI data: first, the glutaminergic and gamma-amino butyric acid (GABA) systems, the main inhibitory and excitatory systems (respectively); and second, functional connectivity (Resting State), which gives information on how brain areas are functionally connected in chronic TMD patients compared to healthy controls (data which will also be acquired during this study). Hence, the results will still be interesting to report and investigate further.

MRI is a noninvasive imaging technique that does not involve exposure to ionizing radiation. fMRI enables the assessment of functional anatomy of the brain, which cannot be accomplished with other imaging techniques. The MRI examination poses almost no risk to the average patient when appropriate safety guidelines are followed. For this reason, study participants will undergo standard screening to determine if an MRI can be performed safely, and potential participants will be excluded if MRI cannot be performed.

While there are no known health hazards from temporary exposure to the MR environment, the MR environment involves a strong, static magnetic field, a magnetic field that changes with time (pulsed gradient field), and radiofrequency energy, each of which carry specific safety concerns.

The strong, static magnetic field will attract magnetic objects and may cause damage to the scanner or injury to the patient or medical professionals if those objects become projectiles. The magnetic fields that change with time create loud knocking noises which may harm hearing if adequate ear protection is not used. They may also cause peripheral muscle or nerve stimulation that may feel like a twitching sensation. The radiofrequency energy used during the MRI scan could lead to heating of the body. The potential for heating is greater during long MRI examinations. Some patients find the inside of the MRI scanner to be uncomfortably small and may experience claustrophobia. To produce good quality images, patients must generally remain very still throughout the entire MRI procedure.

The MR environment presents unique safety hazards for patients with implants, external devices and accessory medical devices. The strong, static magnetic field of the MRI scanner will pull on magnetic materials and may cause unwanted movement of the medical device. The radiofrequency energy and magnetic fields that change with time may cause heating of the implanted medical device and the surrounding tissue, which could lead to burns. The magnetic fields and radiofrequency energy produced by an MRI scanner may also cause electrically active medical devices to malfunction, which can result in a failure of the device to deliver the intended therapy.

The presence of the medical device will degrade the quality of the MR image, which may make the MRI scan uninformative or may lead to an inaccurate clinical diagnosis, potentially resulting in inappropriate medical treatment. Therefore, patients with implanted medical devices should not receive an MRI exam unless the implanted medical device has been positively identified as MR Safe or MR Conditional. An MR Safe device is nonmagnetic, contains no metal, does not conduct electricity and poses no known hazards in all MR environments. An MR Conditional device may be used safely only within an MR environment that matches its conditions of safe use. Any device with an unknown MRI safety status should be assumed to be MR Unsafe.

Adverse events for MRI scans are very rare. Millions of MRI scans are performed in the US every year, and the FDA receives around 300 adverse event reports for MRI scanners and coils each year from manufacturers, distributors, user facilities, and patients. The majority of these reports describe heating and/or burns (thermal injuries). Second degree burns are the most commonly reported patient problem. Other reported problems include injuries from projectile events (objects being drawn toward the MRI scanner), crushed and pinched fingers from the patient table, patient falls, and hearing loss or a ringing in the ear (tinnitus). The FDA has also received reports concerning the inadequate display or quality of the MR images.[33]

An MRI scan may reveal an abnormality that is already present in a subject's body, such as a cyst or tumor. Subjects will be advised that such a finding might require additional studies, and maybe even treatment, neither of which would be paid for by the investigators, the sponsor, or UM.

2.3.5 *Quantitative Sensory Testing (QST)*

For both TMD subjects and healthy volunteers, quantitative sensory testing will be performed (thermal and algometry) in four areas: right and left superficial masseter muscle, and dorsum of the hands. This stimulus, though it may feel mildly painful, does not produce any skin damage.

Thermal stimulation

We will use a standard clinical evaluation program designed for the Pathway system (MEDOC-Israel). This program is comprised of a series of hot and cold stimuli that are delivered from a baseline temperature of 32°C, bilaterally. The subject will control the heating/cooling unit with a computer mouse. They will be instructed to tap the mouse button at the first perception of pain. Each stimulus (hot and cold) will be delivered three times in each location, and the Pathway program records the average temperature.

Algometry

We will use an algometer (Somedic, Sweden) to define pressure pain threshold and tolerance in the four regions bilaterally, and in a randomized fashion. Each area will be

evaluated three times, and the ultimate pressure pain threshold and tolerance 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.

2.3.6 *Collection of Blood Samples for Biomarkers and/or Genetic Analysis*

Serial biomarker blood draws and a blood sample for genetic testing will be collected for this study. Serial 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 a separate intravenous line placed into the vein of the arm that is opposite the arm used for the tracer injection. One additional, individual collection for genetic analysis will be performed for future studies. The blood for genetic analysis will be collected prior to tracer administration and will not exceed 25 mL (2.4 Tbsp) per scan. No more than 70 mL of blood will be collected per subject per day; therefore, a total of 140 mL blood will be collected, per subject, for following the study per protocol. These samples will be stored for potential analyses after the study. This procedure carries with it the expected risks associated with a blood draw, particularly the chance of mild bruising and pain. Trained personnel will perform blood collection using standard procedures to reduce the risks. No repeated phlebotomy is planned. If the second IV stops working or cannot be started, the scan will be canceled. Movement during data capture is not tolerable.

2.3.7 *Administration of Pregnancy (Urine Dipstick) & Drug Screening Tests*

Pregnancy tests (urine dipstick) will be asked of female participants to assure that they are not pregnant prior to each PET scan. The results are immediately recorded in the research record (only) and are shared with the subject.

The multi-drug screening test employed is also a dipstick and uses monoclonal antibodies to selectively detect specific drugs and drug metabolites in urine. If a positive result is obtained, a repeat test may be performed on a second sample.

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 coding the data. Additionally, the results for the drug screen will be recorded in the research record (not in the clinical record) and shared only with the subject.

2.3.8 *Administration of Questionnaires*

Subjects 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.

2.3.9 *Collection of Medical/Dental History*

At the initial Screening visit (after completion of a written informed consent process) a review of the subject's medical/dental history, with emphasis on TMD pain will be performed by the Investigators. This will include a review and evaluation of the inclusion and exclusion criteria, and the determination of eligibility for the subject.

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 the subject. Subject data will be coded. Research records will be kept confidential to the extent provided by federal, state and local law. Subjects 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 subjects.

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 subjects, 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.

2.3.10 *Conclusion*

After careful consideration of all the neuroimaging, neuromodulatory, and associated methods outlined above, which our lab has applied and published on for several years, we firmly believe that this study is of non-significant risk to the patients. It has the capacity to provide vital information to increase our understanding of the central mechanisms of TMD pathophysiology as well as lead to potential new treatments for those patients where currently available treatments have failed.

2.3.11 **Potential Benefits**

There is no direct benefit to the participants in this project. Subjects will be informed that the medical significance of these studies is presently unknown and that the results will not influence their subsequent medical care. However, these studies may help to

determine the molecular mechanisms to suppress pain in subjects suffering from TMD via the μ-opioid system.

3 OBJECTIVES

3.1 Study Objectives

3.1.1 *Primary Objective*

The primary effectiveness objective is to investigate whether 10 daily sessions of primary motor cortex (M1) HD-tDCS will result in a significant reduction in clinical pain intensity at rest in chronic TMD subjects 4 weeks after completion of HD-tDCS sessions, as measured by a visual analog scale (VAS) pain score.

3.1.2 *Secondary Objectives*

The secondary objectives are as follows:

- To investigate whether 10 daily sessions of M1 HD-tDCS will result in significant reductions in clinical pain intensity (at rest) and experimental (sustained masseteric pain stress challenge) measures in chronic TMD subjects at 1 week after completion of HD-tDCS sessions, as measured by VAS pain score assessments, obtained during the baseline PET (#1) session and follow-up PET (#2) session.

- To investigate whether 10 daily sessions of M1 HD-tDCS will result in significant short-term and/or long-term changes in clinical pain intensity and area measures in chronic TMD subjects treated with HD-tDCS compared to those who receive sham treatment, as measured by GeoPain measures.

- To investigate whether repetitive active M1 modulation induces increase of μ-opioid receptor (μOR) non-displaceable binding potential (BP_{ND}) in the thalamus and other pain-related regions in the brains of chronic TMD subjects from the baseline PET (#1) session to the follow-up PET (#2) session, 1 week after completion of HD-tDCS sessions.

- To investigate whether any μOR BP_{ND} changes from baseline PET (#1) session to follow-up PET (#2) session are associated with changes in mean clinical and experimental pain measures, as measured by VAS pain scores in chronic TMD subjects who receive HD-tDCS treatment compared to those subjects who receive sham treatment.

- To investigate whether chronic TMD is associated with μOR BP_{ND} changes as compared to healthy subjects during baseline PET (#1) session at rest, and during experimental sustained masseteric pain stress challenge.

3.2 Study Outcome Measures

3.2.1 *Primary*

The primary effectiveness endpoint will be as follows:

Change in clinical VAS pain score from baseline (Screening Day) to 4 weeks after completion of HD-tDCS sessions (Follow Up #2).

3.2.2 *Secondary*

The secondary effectiveness endpoints will include the following:

- Change in clinical VAS pain score at rest and during sustained masseteric pain stress challenge from baseline PET (#1) session to follow-up PET (#2) session, 1 week after completion of HD-tDCS sessions.
- Short- and long-term changes in GeoPain measures (pain area, intensity, and their summation) from baseline daily over the treatment period and through follow-up (1, 4, and 8 weeks after completion of HD-tDCS sessions).
- Change in μOR BP_{ND} levels and clinical VAS pain score from baseline PET (#1) session to follow-up PET (#2) session, 1 week after completion of HD-tDCS sessions.
- Change in μOR BP_{ND} levels at rest and during experimental sustained masseteric pain stress challenge during PET (#1) in chronic TMD patients as compared to healthy subjects.

3.2.3 *Safety*

All adverse events (AEs) will be solicited via generalized questioning at each study visit, beginning after informed consent.

In addition, questionnaires for PET Screening and HD-tDCS AEs will solicit information about the following symptoms/side effects of specific interest for HD-tDCS: headache, neck pain, scalp pain, scalp burns, tingling, skin redness, sleepiness, trouble concentrating, acute mood changes, and “other (specify).” These AEs were chosen because comprehensive reviews and a consensus article regarded them as common[34,35].

4 STUDY DESIGN

This is a phase 2, single center, 2-arm, double-masked, randomized investigation HD-tDCS treatments for modulation of the μ-opioid mechanisms in TMD (*in vivo*). The population for the study will consist of 60 subjects with chronic TMD (30 in the active M1 HD-tDCS group, and 30 in the sham group).

We will also include a total of 30 healthy volunteer subjects, comprised of two populations. We will recruit at least 20 age and gender-matched healthy volunteers (HV) who will be enrolled in parallel, who might be supplemented if matched by PET/MRI data from up to 10 additional healthy controls, who were previously recruited and scanned during the NIDCR-NIHR56 DE022637 project.

A visual of the study design is provided in the Study Schema (Figure 6). Details about each study visit are provided in the study schedule (Section 7).

Figure 6.a Study Schema for Healthy Volunteers

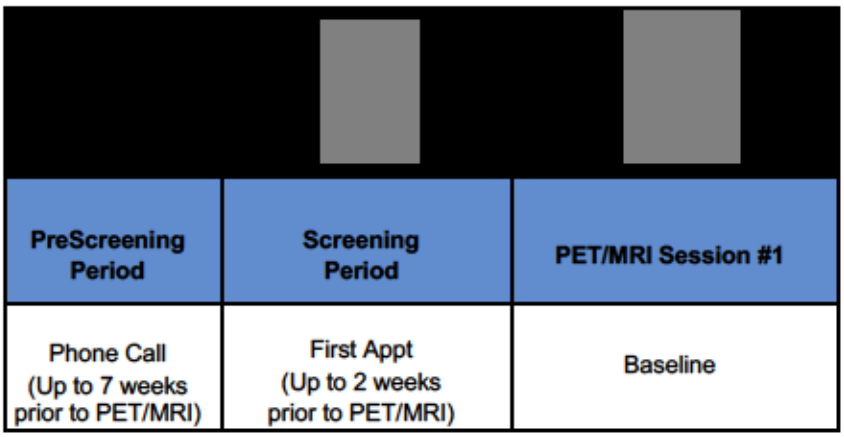
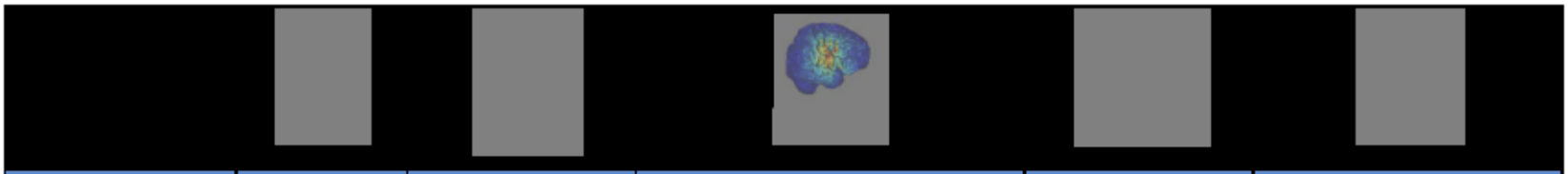


Figure 6.b Study Schema for TMD Subjects



PreScreening Period	Screening Period	PET/MRI Sessions #1 (Baseline)	Active/Sham Neuromodulation M1 HD-tDCS (10 Daily Sessions) M-F x2		PET/MRI Sessions #2 (Follow-up)	Follow-up Period for pain assessments ⇒
Phone Call Up to 8 weeks before M1 HD-tDCS sessions	First Appt up to 3 weeks before M1 HD-tDCS sessions	1 week before M1 HD-tDCS sessions	5 Daily Sessions, Week 1-5	5 Daily Sessions, Week 2	1 Week after completion of M1 HD-tDCS sessions	Follow-up at 1, 4 and 8 weeks after completion of M1 HD-tDCS sessions

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Subject Inclusion Criteria

To be eligible to participate in this study, an individual must meet all of the following criteria:

- Provide signed and dated informed consent form;
- Male or female, aged 18 to 65 (inclusive);
- tDCS naïve; and
- Willing to comply with all study procedures and be available for the duration of the study.

In addition, **TMD subjects** must qualify as**:**

- Diagnosed with chronic TMD as defined by the Diagnostic Criteria (DC) for TMD and the American Academy of Orofacial Pain (DC/TMD)[36]:

  "Chronic TMD pain and dysfunction for at least one year from the clinical exam session (DC/TMD: Masticatory myofacial pain with/without referral) not adequately controlled by previous therapies (eg, NSAIDs, muscle relaxants)"

- TMJ open-surgery naïve;
- TMD maximum pain score pain of greater than or equal to 3 (moderate to severe) on a 0-10 VAS, despite existing treatment, for 3 days in the 7 days preceding study consent, based on report at the screening session;
- If taking pain medications, the dose regimen must be stable for at least 4 weeks prior to screening; and
- Willing to halt the introduction of new medications for chronic TMD symptoms during the study.

Emphasis is therefore placed on generalizability and chronicity of symptoms.

OR

To qualify as a **Healthy Volunteer**, subjects must be:

- Without self-reported history of systemic disorders or other chronic pain disorders, including migraine.

5.2 Subject Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Existence of chronic pain disorder(s) other than TMD
- VAS rating lower than 3 during Screening Visit (week -3)
- History of a traumatic brain injury
- History or current evidence of a psychotic disorder (e.g. schizophrenia) or substance abuse (self-reported)
- Bipolar or severe major depression, as evidenced by a Beck Depression Inventory[37] score of ≥ 30
- Ongoing, unresolved disability litigation (self-reported)
- History of neurological disorder (e.g. epilepsy, stroke, neuropathy, neuropathic pain; self-reported)
- Opioid pain medications taken within the past 3 months
- Past allergic response to opioids or chemically related drugs (e.g., carfentanil)
- Excluded by MRI Center or PET Center safety screening checklist (as administered by study staff)
- Drug test positive for opioid or recreational drug (e.g., cannabis) at the time of the PET scan visits
- Pregnant or lactating (negative urine pregnancy test must be available before any PET procedures are initiated)
- Treatment with an investigational drug, device or other intervention within 30 days of study enrollment
- Anything that would place the individual at increased risk or preclude the individual's full compliance with or completion of the study (e.g., medical condition, laboratory finding, physical exam finding, logistical complication).

5.3 Strategies for Recruitment and Retention

We will recruit 60 chronic TMD pain patients divided into 2 groups: 30 for the active M1 HD-tDCS group and 30 for the sham HD-tDCS group. We will also include a total of 30

healthy volunteer subjects between the following two groups, if they are gender and age-matched to the active M1 HD-tDCS group:

1. We will use the PET/MRI data from up to 12 healthy controls and 12 TMD patients who were recruited and scanned during the NIDCR-NIHR56 DE022637 project.

2. We will recruit the balance of the healthy volunteer population, for a total of 30 subjects as detailed below.

Recruited patients will be screened from the UMhealthresearch.org recruitment network and the TMD and Orofacial Pain Clinic at the University of Michigan (from which ~90% of the 1,572 patients report TMD pain). In addition to active referral from these centers and others, advertisements will be placed in other pain clinics in the region. In-hospital advertisements will be placed in other departments at the institution, as well as across the university.

Subjects recruited will be prescreened by phone using an initial IRB-approved questionnaire. Those who pass the phone screening will be scheduled for an in-person screening visit, which will commence with a verbal and written informed consent process. Once informed consent has been obtained, subjects will undergo further screening; those subjects who are determined to be eligible to enter the study will be enrolled into either the TMD or healthy volunteer pools.

Study duration is expected to be approximately 3 months for each TMD patient; up to 10 weeks for healthy volunteers. Due to the repeated scheduling of PET and MRI visits, reminders (eg, phone and/or email; subject preference) may be implemented to help with retention.

During the course of participation, subjects will be compensated according to amounts stated in the informed consent form and approved by the IRB (Table 1). Subjects will be paid for visits completed until they finish the study or withdraw. Allowance for travel expenses may be provided in very specific situations when needed, and will be decided on case-by-case basis.

Table 1. Subject Compensation

VISIT NAME	*NUMBER of Visits*	*COMPENSATION*
Screening	1	$25
PET #1	1	$100
MRI #1	1	$50
HD-tDCS Session	10 Planned	$25 x 10 = $250
PET #2	1	$100
MRI #2	1	$50
Follow-Up @ 1 Wk**	1	$25
Follow-Up @ 1 Mo	1	$25
Follow-Up @ 2 Mo	1	$25
TOTAL		$650
		*$175 for Healthy Volunteers

***Healthy Volunteers will have completed the protocol after PET/MRI #1.**
****Follow-Up @ 1 Wk is during the week following the final HD-tDCS session.**

5.4 Treatment Assignment Procedures

5.4.1 *Randomization Procedures*

Participants initially will be screened by phone. After clinical exam and diagnosis of the DC/TMD Axis I Group, participants will be randomized to the treatment HD-tDCS or sham groups using the Taves covariate adaptive randomization method[38]. Using this method, a new participant will be sequentially assigned to a group based upon the previous assignments of other participants and certain covariates[39]. The first eight TMD participants will be randomized by coin flip and the remaining TMD participants will be randomized by age and gender, following the Taves covariate adaptive randomization protocol.

5.4.2 *Masking Procedures*

The PI, Co-Investigator, and any members of the research staff who will be analyzing study data (with the exception of the coordinator[s]/biostatistician) will be masked to participant treatment. The research coordinator and any study staff who will be NOT involved in the treatment of the study participants in the HD-tDCS study component will be unmasked in order to promptly address any emergency directly or indirectly associated with the procedure for safety reasons. The research coordinators are not masked, and thus are able to blind the machines prior to administration of the stimuli. The biostatistician transmits the code to the coordinator in a manner that keeps the investigators and co-I's blinded. Patients will be allowed to know the type of stimulation they received, active or sham, at the end of the study if requested.

5.5 Subject Withdrawal

5.5.1 *Reasons for Withdrawal*

Subjects are free to withdraw from participation in the study at any time upon request. An investigator may terminate a study subject's participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

5.5.2 *Handling of Subject Withdrawals or Subject Discontinuation of Study Intervention*

Subjects wishing to withdraw from the study at any time may do so and should notify the study team. For payment to these subjects, see Section 5.3.

Withdrawals need not be replaced, but may be on a case-by-case basis, at the PI's discretion. The power calculations allow for a 20% dropout rate.

5.6 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator, funding agency, the sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Insufficient adherence to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Determination of futility.

6 STUDY INTERVENTION

6.1 Study Procedural Intervention(s) Description

We will conduct a single-center, sham-controlled, double-blinded study to prospectively investigate the neuromodulatory effects of M1 HD-tDCS in pain intensity and brain molecular neuroplasticity in a cohort of chronic TMD patients. The subjects will participate in 10 daily sessions (e.g., Monday – Friday for two weeks), either active or sham M1 HD-tDCS.

6.2 Administration of Procedural Intervention

For the M1 HD-tDCS, four electrodes arranged at the corners of a 4 cm x 4 cm square will be centered over the motor cortex contralateral to the side with the worst TMD pain. The upper anode will be placed on C3/C4 and lower anode on C5/C6, and the upper and lower cathodes will be placed anteriorly on FC3/4 and FC5/6, respectively, using the International Electroencephalography (EEG) 10-20 system and confirmed by TMS to determine the precise scalp position[40]. The vertex will be found by measuring the midpoint between nasion and inion and the midpoint between the pre-auricular areas. Then the midpoint from the vertex to the pre-auricular point on the side contralateral to the patient's worst pain will be marked so that stimulation could be applied to the same spot each day. A perforated cloth cap with a chinstrap will be placed on the patient's head to secure plastic casings of each electrode in the desired position. Approximately 3 mL of Lectron II Conductivity Gel will be injected into the electrode casings. Ag/AgCl sintered ring electrodes with the rough surface directed towards the skin will be placed into the gel and held in place with plastic caps. In the active HD-tDCS group, 2 mA current stimulation will be applied for 20 min. For sham-controlled tDCS sessions current will be applied for 30 sec only—this is a frequent method of sham stimulation[41] as sensations arising from tDCS treatment occur mostly at the beginning and end of application. Nonetheless, groups will be composed of different, tDCS-naïve patients to avoid comparison between sham and active tDCS from ongoing and previous experiences.

These HD-tDCS sessions will be conducted by study staff trained in the technique by the PI. Sessions will occur at the University of Michigan. A licensed physician will be available by pager at all times.

6.3 Procedures for Training of Clinicians on Procedural Intervention

All study clinicians will be trained in HD-tDCS technique by the PI (or trained designee) according to the study Manual of Procedures.

6.4 Assessment of Clinician and/or Subject Compliance with Study Procedural Intervention

Study staff performing each procedural administration will be trained in a standardized manner so as to assure compliance with the protocol. Likewise, the team will reassess clinician and subject compliance with study procedures and instructions at a study level during weekly meetings to assure quality control.

7 STUDY SCHEDULE

See Table 2. Schedule of Events. Adverse events will be recorded from the time that the subject signs the informed consent until the subjects leaves the study. Any AE reported voluntarily by the patients after the study, potentially associated with the procedures, will be documented and shared with the IRB.

7.1 Healthy Volunteers

Prescreening
(Study Week -8)

Subjects interested in the study will be prescreened via a phone interview using an IRB-approved checklist.

Screening
(Study Week -3)

The activities assigned to the Screening Visit will be completed within ~21 days prior to the second of two scans (see Baseline PET/MRI). Following the informed consent process, subjects will undergo a baseline assessment comprised of a medical/dental history with limited physical, listing of medication history (6 months) and review of eligibility. They will then complete questionnaires, as listed in the study schedule (Table 2).

Baseline PET/MRI
(Study Week -1)

Within 7 days of each other, subjects will undergo an MRI, as well as a PET scan that uses an [^{11}C]carfentanil radioligand, with a masseter muscle pain challenge via a 5% hypertonic saline intramuscular infusion. Pain questionnaires will also be completed during this visit window. Completion of all procedures may require more than one clinic visit and an additional week window will be allowed to account for scheduling issues.

At this point, all Healthy Volunteer subjects will have completed participation in the study.

7.2 TMD Patients

Prescreening
(Study Week -8)

Chronic TMD subjects interested in the study will be prescreened via a phone interview using an IRB-approved checklist.

Screening
(Study Week -3)

The activities assigned to the Screening Visit will be completed within 3 weeks prior to the first session of Week 1. Following the informed consent process, subjects will undergo a baseline assessment and the completion of questionnaires, as listed in the study schedule (Table 2). The baseline visit will include a medical/dental history with limited physical that involves clinician assessed DC/TMD (Diagnostic Criteria/Temporomandibular Disorder) status. Also covered are a comprehensive medication history (6 months) and a review of eligibility.

Baseline PET/MRI
(Study Week -1)

Within 7 days preceding randomization and the first study treatment, subjects will undergo an MRI, as well as a PET scan that uses an [^{11}C]carfentanil radioligand, with a masseter muscle pain challenge via a 5% hypertonic saline intramuscular infusion. Pain questionnaires will also be completed during this visit window. All procedures are targeted for the week prior to HD-tDCS; however, due to occasional scheduling difficulties, they may be completed within 14 days prior to Day 1 of HD-tDCS. Completion of all procedures may require more than one clinic visit.

Treatment HD-tDCS
(Study Weeks 1 through 2)

Beginning at Day 1 of HD-tDCS, subjects will be randomized to active treatment or sham procedure. They will then attend 10 sessions, 1 each weekday (Monday through Friday) over a 2-week period, and will receive either the M1 HD-tDCS treatment or the sham treatment, preceded and followed by questionnaires. Missed days can be doubled and/or rescheduled within the 2-week schedule, as necessary, with study team approval.

Follow-up PET
Follow-up MRI &
First Follow-up Visit
(Study Week 3)

Within 7 days following the last study treatment, subjects will undergo an MRI as well as a PET scan that uses an [^{11}C]carfentanil radioligand with a masseter muscle pain challenge via a 5% hypertonic saline intramuscular infusion. Pain questionnaires will also be completed during this visit window. All procedures are targeted for the week following completion of HD-tDCS; however, due to occasional scheduling difficulties, they may be completed within 14 days following Day 10 of HD-tDCS. Completion of all procedures may require more than one clinic visit.

Follow-Up #2 & #3
(Study Weeks 6 and 10)

Pain questionnaires will be completed again at 4 weeks (Follow-Up #2) and 8 weeks (Follow-Up #3) after the final treatment day (Study Weeks 6 and 10, respectively).

Table 2

SCHEDULE OF EVENTS – I. Procedures

Procedures	Phone PreScreening	Screening	PET/MRI #1 (Baseline)[1,2]	HD-tDCS #1-10[8]	PET/MRI #2/ Follow-up #1[1,2]	Follow-up #2	Follow-up #3	Early Termination[3]
Visit	P	1	2	3A-J	4	5	6	ET
Study Week	-8	-3	-1	1 – 2	3	6 (1 mth)	10 (2 mths)	N/A
Prescreening Script/Checklist	X[5]							
Informed Consent		X[5]						
Adverse Events		X[5]	X[5]	X	X	X	X	X
Medical/Dental History and Physical		X[5]						
Medication History/ Concomitant Medications		X[5]	X[5]	X	X	X	X	
Quantitative Sensory Testing (QST)			X[5]		X			
Eligibility Assessment[4]		X[5]						
PET Scan • Pregnancy Test (Dip)[7] • Drug Screen[7] • Blood sample for biomarkers • Masseteric Pain Challenge (5% hypertonic saline)			X[5]		X			
Blood sample for genetic testing			X[5]					
MRI Scan			X[5]		X			
RANDOMIZATION				Week 1				
HD-tDCS (M-F for 2 weeks)				X[6]				

[1] Target dates for PET/MRI are the week prior to Day 1 HD-tDCS session (Baseline) and the week after completion of HD-tDCS sessions (Follow-up); an additional week window is allowed to account for scheduling issues.
[2] Procedures may require more than one clinic visit.
[3] Applicable if subject completes an in-person visit.
[4] If subject is deemed eligible, schedule subject visits and provide subject with instructions for PET & MRI.
[5] Healthy Volunteer subjects complete only these procedures indicated.
[6] Missed days can be doubled in the (M-F) x 2 schedule, with study team approval. See Section 7.
[7] Completed within 24 hours prior to PET session
[8] HD-tDCS sessions will be scheduled M-F. See Section 7.2.

Table 2
SCHEDULE OF EVENTS – II. Questionnaires

Questionnaires	Phone PreScreening	Screening	PET/MRI #1 (Baseline)[1,2]	HD-tDCS #1-10[8]	PET/MRI #2/ Follow Up#1[1,2]	Follow Up #2	Follow Up #3	Early Termination[3]
Visit	P	1	2	3A-J	4	5	6	ET
Study Week	-8	-3	-1	1 – 2	3	6 (1 mth)	10 (2 mths)	N/A
Demographics		X[7]						
Beck Depression Inventory		X[7]						
DC/TMD Examination Form		X[7]				X	X	
Expectation of Effect VAS		X						
McGill Pain Questionnaire (MPQ) (Long Form)		X						
MPQ (Short Form)[6]		X	X	X	X	X	X	
Positive and Negative Affect Schedule (PANAS)[6]		X[7]	X[7]	X	X	X	X	
GeoPain (via mobile device)[6]		X	X	X	X	X	X	
Visual Analog Scale (VAS)[6]		X	X	X	X	X	X	
Graded Chronic Pain Scale		X			X	X	X	
Brief Pain Inventory (BPI; Short)		X			X	X	X	
Pittsburgh Sleep Quality Index		X[7]			X	X	X	
PET Subject Information Sheet			X[7]		X			
tDCS Effects Questionnaire				X	X	X	X	
HD-tDCS Sham/Placebo Assessment				X				
DC for TMD Symptom Questionnaire		X[7]			X	X	X	

[1] Target dates for PET/MRI are during the week prior to Day 1 HD-tDCS session (Baseline) and during the week after completion of HD-tDCS sessions (Follow-up); an additional week window is allowed to account for scheduling issues. The "Magnetic Resonance (MR) Safety Screening Form" is completed prior to each MRI scan. See Section 2.3.4.
[2] Procedures may require more than one clinic visit.
[3] Applicable if subject completes an in-person visit.
[4] If subject is deemed eligible, schedule subject visits and provide subject with instructions for PET & MRI.
[5] Missed days can be doubled in the (M-F) x 2 schedule, with study team approval. See Section 7.
[6] These assessments will be conducted at Screening, before and after MRI/PET and tDCS Sessions, and at Follow-up visits.
[7] Questionnaires to be completed by healthy volunteer subjects at the timepoints indicated.
[8] HD-tDS sessions will be scheduled M-F. See Section 7.2.

7.3 Withdrawal Visit

If a subject terminates the study early for one of the reasons listed in Section 5.5 or 5.6, and is willing to return to the site for a final study visit, the following will be completed:

- Record adverse events as reported by subject or observed by investigator
- Provide final instructions to subject (e.g., follow-up of ongoing adverse events)

If the subject cannot be reached or is not willing to return to the study site for a final study visit, the subject will be considered lost to follow up.

7.4 Repeated Screening Visit

If a subject completes a Screening Visit (ie, signs informed consent), but does not complete a Randomization Visit (first session of HD-tDCS Week 1) within 3 weeks, the subject may continue participation by repeating a limited to full Screening visit.

Informed consent must be re-obtained if there have been changes to the informed consent document since the version that was originally signed. These changes might include:

- New “reasonably foreseeable” risks or side effects judged to be “definitely related” to the research.
- Changes are made to the protocol such as additional tests or research procedures that may affect subjects’ willingness to participate, rights, welfare, or safety.
- New information included that may affect subjects’ willingness to participate.
- A change in principal investigator and contact information.

The remaining Screening evaluations and questionnaires to be repeated are to be determined based on clinical relevance by the PI.

7.5 Unscheduled Visit

If a subject returns to the study site on a date that is significantly outside a visit window, the following assessments will be completed:

- Record adverse events as reported by subject or observed by investigator

8 STUDY PROCEDURES /EVALUATIONS

8.1 Study Procedures/Evaluations

8.1.1 *Quantitative Sensory Test (QST)*

For both TMD subjects and healthy volunteers, QST will be performed in four areas: right and left superficial masseter muscle, and dorsum of the hands.

Thermal stimulation: We will use a standard clinical evaluation program devised by MEDOC (Israel) on a thermal stimulation device of their design. The program is comprised of a series of hot and cold stimuli that are delivered from a baseline temperature of 32°C bilaterally. Subjects will control the heating/cooling unit with a computer mouse and they will be instructed to tap the mouse button at the first perception of pain. Each stimulus (hot and cold) will be delivered three times in each location, and the MEDOC program records the average temperature.

Algometry: We will use an algometer (Somedic, Sweden) to define pressure pain threshold and tolerance in the four regions bilaterally, and in a randomized fashion. Each area will be evaluated three times, and the ultimate pressure pain threshold and tolerance levels will be the average of the three measurements recorded. For the evaluation of motor function, we will perform the exam according to the DC/TMD guidelines and forms (e.g., range of motion).

8.1.2 *Sustained Masseteric Pain Model for TMD Research – Positron Emission Tomography and Hypertonic Saline Challenge*

Positron emission tomography (PET) scans with [^{11}C]carfentanil and infusion of hypertonic saline during the scan will be conducted twice during the study for each TMD subject and only once for each healthy volunteer.

PET scans will be used for the clinical trial with TMD patients to analyze potential changes in the brain occurring as a result of treatment with HD-tDCS, particularly potential changes in the thalamic μOR availability in the brains of TMD patients during masseteric pain. In addition, we will investigate whether chronic TMD is associated with μOR BP_{ND} changes as compared to healthy subjects during baseline PET (#1) session at rest, and during experimental sustained masseteric pain stress challenge.

A hypertonic saline challenge will be used to test the capacity of an individual to mobilize neurotransmitters involved in the response to pain. It is hypothesized that this response may be altered using HD-tDCS treatment in TMD patients. Hypertonic saline (5%; less than 5 mL over 20 minutes) will be infused into the masseter muscle by a computer-controlled closed loop system and a syringe pump[42] during the PET scan, causing persistent pain that fluctuates in nature. The intensity of the pain will be controlled by the individual's experience such that individuals with chronic TMD pain will

experience the same subjective pain intensity as those without TMD. The system is calibrated to induce an average target VAS intensity of 40 units (0= no pain at all, 100= most pain imaginable) over 20 min **(Figure 7)**.

Figure 7. Diagram of System to Induce and Maintain Pain Intensity. Block diagram to induce and maintain pain intensity between preset VAS scores by infusion of 5% hypertonic saline into the masseter during the PET session. The main feature of the adaptive control delivery system is a proportional-integrative-derivative (PID) controller. It corrects the difference between actual and estimated pain intensities. The adaptive element includes strategies to bring pain intensity back in case the preset bounds are exceeded and recalculates any previously established PID parameters.

Pain invariably disappears well within 5-10 min of infusion completion. The total volume of 5% hypertonic saline required to maintain the target pain intensity is also an objective measure of "sustained" pain sensitivity.

A 90min PET session of [^{11}C]carfentanil[43] will be performed, where 45min of baseline will be followed by a 45min challenge period, in which controlled moderate masseteric pain **will be induced for only 20 min.**

PET Protocol	**Early Phase [^{11}C]Carfentanil 5-40min**	**Late Phase [^{11}C]Carfentanil 45-90min**
TMD Active Group	Baseline	Masseteric Pain 20min
TMD Sham Group	Baseline	Masseteric Pain 20min
Healthy Control Group	Baseline	Masseteric Pain 20min

PET scans will be acquired with a Siemens HR+ scanner in 3-D mode (reconstructed FWHM resolution ~5.5mm in-plane/5.0mm axially) with septa retracted and scatter correction. Subjects will be positioned in the PET scanner gantry and two intravenous (antecubital) lines placed.

[^{11}C]carfentanil (CFN), a selective and specific μ-opioid receptor radioligand, is synthesized at high specific activity (> 2000 Ci/mmol) by the reaction of ^{11}C-methyl triflate with desmethyl carfentanil as previously described. 15±1 mCi are administered to each subject with a maximum mass injection of 0.03 μg/kg to ensure that the compound is administered in true tracer quantities, eliminating significant receptor occupancy. The percent occupancy of μ-opioid receptors at peak regional carfentanil concentrations has been calculated at 0.2%-0.6% by utilizing the average mass of carfentanil administered and the known concentration of μ-opioid receptors in the postmortem human brain. Fifty percent of the [^{11}C]CFN dose will be administered as a bolus, and the remainder will be administered as a continuous infusion by using a computer-controlled automated pump to achieve steady-states between (non-)specific binding areas (5-7min post-tracer administration with Logan plots, and full equilibrium conditions and Logan plots at 40min post-tracer administration) for baseline (resting-state) and 20min of **masseteric pain challenge** for μ-opioid system activation analysis. Twenty-eight frames will be acquired over 90min.

Subsequently, dynamic image data for each of the receptor scans are transformed on a voxel-by-voxel basis into three sets of parametric maps, which are co-registered to each other. These are **(1)** a tracer transport measure (K_1 ratio, proportional to cerebral blood flow; tracer transport = blood flow x tracer extraction) and receptor-related measures (non-displaceable binding potential, BP_{ND}), encompassing data from **(2)** 10-40 min (baselines) and **(3)** 45-90 post tracer administration (pain or saline control). These parametric images are calculated using a modified Logan graphical analysis (Logan et al., 1996) with the occipital cortex (a region devoid of μ-opioid receptors) as the reference region. The Logan plot becomes linear well within 10 minutes after the start of radiotracer administrations with a slope proportional to the Bmax/Kd + 1 for this receptor site. Bmax/Kd is the “receptor related” measure BP_{ND}. If noise-related underestimations in BP_{ND} measures are observed, these can be further corrected utilizing published methods[44]. In addition, late scan periods will be assessed using ratios of specific to non-specific binding at full equilibrium [(specific –nonspecific)/nonspecific] to ensure that biases are not introduced by the use of Logan plots[45].

8.1.3 *MRI Acquisition*

Magnetic resonance imaging (MRI), without contrast, will be conducted twice during the study on each TMD subject and only once on each healthy volunteer. MRI scans are acquired on a 3 T scanner (General Electric, Milwaukee, WI). These images provide anatomical information for structure identification and will be utilized for the anatomical standardization to the ICBM/MNI atlas coordinate system. This will establish the linear and non-linear warping transformation matrices to be applied to the co-registered receptor binding maps. The acquisition sequence is axial T1 FAST SPGR MR (TE = 3.4, TR = 10.5, TI = 200, flip angle 25 deg, FOV 24cm, 1.5mm thick slices, NEX = 1), acquisition matrix 256x256, 60 slices. T1-weighted MR and PET images of each subject are then co-registered to each other using a mutual information algorithm[46]. For this purpose, K_1 ratio images are first aligned to the MR, and the transformation matrix

applied to the co-registered BP_{ND} scans of the same image set. The MR scans are then anatomically standardized to ICBM brain atlas stereotactic coordinates by non-linear warping, and the resulting transformation matrix applied to both K_1 ratio and BP_{ND} image sets[47],[48],[49],[50]. As an alternative approach for Aim3, ^{1}H-MRS spectra will be collected from the ACC (3x2x3cm) based on our prior work showing Glx alterations in this region following tDCS therapy. Single-voxel point resolved spectroscopy (PRESS)(TR/TE=2000/35ms) will be performed using 'VAPOR' water suppression with 32 averages to measure Glx and NAA levels. A MEGAPRESS experiment, which edits out the overlapping creatine peak at 3.0ppm will measure GABA levels[51]. The MEGA-PRESS experiment will use: TE=68ms (TE_1=15ms/TE_2=53ms); TR=1.8s; 256 transients of 2k datapoints; spectral width=2kHz; frequency selective editing pulses (14ms) applied at 1.9ppm (ON) and 7.46ppm (OFF).

8.1.4 *Questionnaires*

To assess the primary effectiveness endpoint, clinical pain intensity at rest will be measured using the VAS at study visits shown in Table 2, Schedule of Events – II. Questionnaires. Other questionnaires listed in Table 2 will be used to address the secondary objectives of the study.

8.2 Laboratory Procedures/Evaluations

8.2.1 *Clinical Laboratory Evaluations*

Pregnancy and urine drug screen testing will be performed by dipstick analysis to assess eligibility criteria prior to PET scans #1 and #2.

8.2.2 *Blood Samples for Study-Specific Analyses*

If the subject consents to participate in this part of the study, serial blood samples that do not exceed a total of 45 mL (3 Tbsp) will be collected during each PET scan for analysis of inflammatory biomarkers. This blood will be collected from a separate intravenous line placed into the vein of the arm that is opposite the arm used for the tracer injection. Approximately 6 mL (0.4 Tbsp) of blood will be drawn during each PET scan at time 0, 20, 45, 65 and 80 for analysis of biomarkers. See details in MOP Section 6.6.3. The blood samples will be frozen for future testing to look at biological substances in the blood and potential hereditary traits associated with migraine.

One additional, individual collection for genetic analysis will be performed for future studies. The blood for genetic analysis will be collected prior to tracer administration and will not exceed 25 mL (2.4 Tbsp) per scan.

The total blood volume collected per scan will not exceed 70 mL per subject.

Details can be found in the Manual of Procedures.

8.2.3 *Specimen Preparation, Handling, and Storage*

Blood samples will be collected according to the schedule in Section 7, and will be prepared, handled and stored for future studies following protocols set forth in the study Manual of Procedures.

8.2.4 *Specimen Shipment*

No shipping of specimens is planned for this protocol.

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

9.1.1 *Unanticipated Problem (UaP)*

The Office for Human Research Protections (OHRP) considers unanticipated problems, in general, to include any incident, experience, or outcome that meets all of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

If the IRB concurs that an event is an unanticipated problem the IRB will follow the policies and procedures outlined in the University of Michigan Human Research Protection Plan Operations Manual, part 12. (PDF)[52].

9.1.2 *Adverse Events*

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

9.1.3 *Serious Adverse Events*

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization

- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.2 Time Period and Frequency for Event Assessment and Follow-Up

Unanticipated problems will be recorded in the data collection system throughout the study.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit.

9.3 Characteristics of an Adverse Event

9.3.1 *Relationship to Study Intervention*

To assess relationship of an event to study intervention, the following guidelines are used:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention.
    b. There is a temporal relationship between the intervention and event onset.
    c. The event abates when the intervention is discontinued.
    d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the intervention and event onset.
    b. An alternate etiology has been established.

9.3.2 *Expectedness of SAEs*

The Study PI will be responsible for determining whether an SAE is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or

frequency of the event is not consistent with the risk information previously described for the intervention.

9.3.3 *Severity of Event*

The Common Terminology Criteria for Adverse Events (CTCAE) v4.03[2] scale will be used to grade adverse events:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE. A Semi-colon indicates 'or' within the description of the grade. A single dash (-) indicates a grade is not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

[2] https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed 28Apr2017; Last updated 11/14/16)

9.4 Reporting Procedures

9.4.1 *Unanticipated Problem Reporting to IRB and NIDCR*

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. OHRP recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- a detailed description of the adverse event, incident, experience, or outcome;
- an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the IRB and to NIDCR within 7 calendar days of the problem or of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB and to NIDCR within 14 calendar days of the problem or of the investigator becoming aware of the problem.
- If the unanticipated problem involved one or more persons experiencing actual harm, the event will be reported to the IRB as an adverse event.
- If a person did not experience actual harm but an unanticipated problem entailed potential harm, and/or risk of harm to subjects or others, the event will be reported to the IRB as an Other Reportable Information or Occurrence (ORIO).

All unanticipated problems will be reported to NIDCR's centralized reporting system via Rho Product Safety:

- Product Safety Fax Line (US): 1-888-746-3293
- Product Safety Fax Line (International): 919-287-3998
- Product Safety Email: rho_productsafety@rhoworld.com

General questions about SAE reporting can be directed to the Rho Product Safety Help Line (available 8:00AM – 5:00PM Eastern Time):

- US: 1-888-746-7231
- International: 919-595-6486

9.4.2 *Serious Adverse Event Reporting to the IRB and NIDCR*

Any AE meeting the specified Serious Adverse Event criteria will be submitted on an SAE form to NIDCR's centralized safety system via Rho Product Safety. This report may be sent by fax or email. Once submitted, Rho Product Safety will send a confirmation email to the investigator within 1 business day. The investigator should contact Rho Product Safety if this confirmation is not received. This process applies to both initial and follow-up SAE reports.

SAE Reporting Contact Information:

- Product Safety Fax Line (US): 1-888-746-3293
- Product Safety Fax Line (International): 919-287-3998
- Product Safety Email: rho_productsafety@rhoworld.com

General questions about SAE reporting can be directed to the Rho Product Safety Help Line (available 8:00AM – 5:00PM Eastern Time):

- US: 1-888-746-7231
- International: 919-595-6486

The study clinician will complete a Serious Adverse Event Form and submit via fax or email to NIDCR via Rho Product Safety within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the Serious Adverse Event Form and submitted to Product Safety within 24 hours of site awareness.
- Serious adverse events other than death and immediately life-threatening events, regardless of relationship, will be reported by fax within 72 hours of site awareness.

All SAEs will be followed until resolution or stabilization.

The study clinician will report SAEs to the IRB in the Adverse Event form via eResearch system within the following timelines:

- All deaths and life-threatening outcomes that are related and unexpected should be submitted as soon as possible, but within 7 calendar days of site awareness.
- Serious adverse events other than death and life-threatening outcomes that are related and unexpected should be submitted within 14 calendar days of site awareness.
- Serious adverse events that are unrelated and expected should be submitted within 14 calendar days of site awareness.
- All other unrelated and unexpected events should be submitted in aggregate form in conjunction with completion of the scheduled continuing review.

9.4.3 *Reporting of UaPs and SAEs to NIDCR*

A copy of all SAE reports will be provided in a timely fashion to NIDCR/Rho Inc (see Section 9.4.2 for details).

Any UaP must be reported by the investigator to NIDCR/Rho Inc and the reviewing Institutional Review Board (IRB) as soon as possible but no later than 7 calendar days after the investigator first learns of the effect. NIDCR, the Investigator, and Rho Product Safety shall immediately conduct an evaluation of any reported SAE to determine whether it meets UaP reportable criteria. If they determine that a UaP presents an unreasonable risk to subjects, then NIDCR and the Investigator shall terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur no later than 5 working days after this determination is made and no later than 15 working days after Rho first receives notice of the effect.

9.4.4 *Reporting of Pregnancy*

Any pregnancy occurring after consent has been signed until the subject has completed the protocol will be reported to UM IRBMED and will be reported according to all other applicable procedures in Section 9. This includes following the pregnancy through outcome.

9.5 Halting Rules

If we see a pattern of worsening in symptoms across patients including severe levels on pain measures, we will halt the study to guarantee the safety of all patients.

10 STUDY OVERSIGHT

In addition to the PI's responsibility for oversight, study oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of members with expertise in neuromodulation, neuroimaging and neurology. The DSMB will meet at least annually to assess safety and efficacy data, study progress, and data integrity for the study. If safety concerns arise, more frequent meetings may be held. The DSMB will operate under the rules of a NIDCR-approved charter that will be approved at the organizational meeting of the DSMB. At this time, most data elements that the DSMB needs to assess will be clearly defined. The DSMB will provide recommendations to the NIDCR.

11 CLINICAL SITE MONITORING

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Monitoring for this study will be performed by NIDCR's Clinical Research Operations and Management Support (CROMS) contractor. The monitor will evaluate study processes and documentation based on NIDCR standards and the International Conference on Harmonisation (ICH), E6: Good Clinical Practice guidelines (GCP).

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by the CROMS contractor, in collaboration with the NIDCR Office of Clinical Trials and Operations Management (OCTOM) and the NIDCR Program Official. The CMP will specify the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of subject data to be reviewed), and the distribution of monitoring reports. Some monitoring activities may be performed remotely, while others will take place at the study site(s). Staff from the CROMS contractor will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the CMP. Documentation of monitoring activities and findings will be provided to the site study team, the study PIs, OCTOM, and the NIDCR. The NIDCR reserves the right to conduct independent audits as necessary.

12 STATISTICAL CONSIDERATIONS

Intent-to-treat Population: An intent-to-treat analysis will be performed including all subjects who complete at least 1 set of post-treatment assessments following HD-tDCS treatment for the primary and secondary effectiveness objectives of the study.

Safety Population: Safety measures will be reported for all subjects who receive at least 1 session of sham or active HD-tDCS treatment.

Healthy Volunteers: An analysis will be performed including all subjects who complete 1 set of PET sessions. TMD patients will be compared with healthy controls to test for differences in μOR BPND at the baseline level in the thalamus and other pain-related regions.

12.1 Study Hypotheses

There are 6 hypotheses regarding the outcomes of this study.

12.1.1 *Hypothesis #1*

In chronic TMD subjects, ten daily sessions of active M1 modulation will result in a significant reduction in clinical pain intensity at rest compared to sham treatment, as measured by VAS scores at 4 weeks after completion of the HD-tDCS sessions.

12.1.2 *Hypothesis #2*

Ten daily sessions of M1 HD-tDCS will result in reductions in clinical (at rest) and experimental (sustained masseteric pain stress challenge) pain intensity measures in chronic TMD subjects at the time of the follow-up PET session, 1 week after completion of the HD-tDCS sessions.

12.1.3 *Hypothesis #3*

Ten daily sessions of M1 HD-tDCS will result in significant reductions in clinical pain intensity and area measures in chronic TMD subjects treated with HD-tDCS compared with those treated with a sham treatment over the short and long terms, measured by GeoPain.

12.1.4 *Hypothesis #4*

Ten daily sessions of M1 HD-tDCS will result in an increase of μOR BP_{ND} in the thalamus and/or other pain-related regions in the brains of chronic TMD subjects from the baseline PET (#1) session to the follow-up PET (#2) session, 1 week after completion of HD-tDCS sessions.

12.1.5 *Hypothesis #5*

Ten daily sessions of M1 HD-tDCS will result in μOR BP_{ND} changes from baseline PET (#1) session to follow-up PET (#2) session, 1 week after completion of HD-tDCS sessions that are inversely correlated with changes in mean clinical and experimental pain measures in chronic TMD subjects.

12.1.6 *Hypothesis #6*

TMD patients, compared to healthy controls, will be associated with reduction in μOR BPND at the baseline level in the thalamus and other pain-related regions. The activation of μOR neurotransmission, calculated as reductions in regional μOR BPND during a sustained masseteric experimental pain challenge, will also be lower than the controls. Both these measures will be negatively correlated with clinical and experimental pain ratings. There will be no clinical trial with HD-tDCS involvement for this particular hypothesis. Hence, healthy subjects will not have stimulation and for TMD patients we will use the first, pretrial PET session (#1).

12.2 Sample Size Considerations

For the primary objective, a sample size of 24 in each group will have 80% power to detect group differences in change in VAS pain scores with an effect size of 1.2 using a 2-group t-test with a 0.05 two-sided significance level. Our sample size of 30 subjects per group is a conservative number that takes a 20% drop-out rate into consideration.

To demonstrate correlations between changes we observe in the μOR BP_{ND} and changes in clinical and experimental measures of pain, we will be reporting correlation coefficients for baseline levels and change scores. With 60 subjects, the confidence intervals of these correlation coefficients will be reasonably narrow for 95% confidence in these estimates. For example, an observed Pearson product-moment correlation of $\rho = 0.8$ would have 95% confidence interval of (0.69, 0.88).

In addition, for secondary objectives 4 and 5 we will use the PET/MRI data from up to 12 healthy controls and 12 TMD patients who were recruited and scanned during the NIDCR-NIHR56 DE022637 project.

12.3 Planned Interim Analyses

An interim analysis will be conducted after one year to examine the initial relationships between μORBP_{ND}, HD-tDCS, and neuropsychological results. The more complex statistical models for network analysis and HD-tDCS will be developed in subsequent years as we recruit subjects for ongoing assessment. The predictability of effects by the combination of neuropsychological and clinical tests will be used at the end of sample accrual.

12.3.1 *Safety Review*

Adverse events will be summarized by treatment group and categorized by severity and relationship to study procedures. If a subject has more than one occurrence of the same AE, he/she will be counted only once for that preferred term in the summary tables. The most severe occurrence of an AE and the most extreme relationship of the AE to the study procedures will be indicated in cases of multiple occurrences of the same AE.

The safety of the HD-tDCS procedure will be tested by comparing the proportion of subjects with each solicited AE in the HD-tDCS treatment group and the sham treatment group.

12.3.2 *Efficacy Review*

12.3.2.1 Primary Objectives

A mixed model of variance will be employed to investigate changes from baseline in clinical pain (VAS score) after 10 active daily HD-tDCS treatments including treatment group, time, and their interaction as fixed effects.

12.3.2.2 Secondary Objectives

We will examine changes from baseline in μOR BP_{ND} and in the activation of μ-opioid neurotransmission following 10 active daily HD-tDCS treatment. A mixed model of variance will be employed to examine change over time across the treatment groups.

Correlation will be assessed between (1) changes in μOR BP_{ND} in the thalamus and other pain-related regions following ten M1 HD-tDCS sessions or sham treatment and (2) patient-reported changes in clinical pain (at rest) and experimental pain intensity and area measures. Correlation will be assessed using Pearson or Spearman correlation analysis, depending on the distribution of the observed data.

12.4 Final Analysis Plan

The final analysis plan will be detailed in the Statistical Analysis Plan.

13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Study staff will permit authorized representatives of NIDCR and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

The studies proposed here incorporate four types of data, documents and biological samples: (1) PET/MRI, (2) clinical/questionnaire data, (3) QST, and (4) biological samples. PET/MRI neuroimaging and derived data are stored on external hard-drives, under local control, in locked rooms in an access-controlled building. A similar process occurs to the clinical/questionnaire data, whose copies are kept in locked offices. In addition, the information is transferred to a REDCap database to which access is limited to IRB-approved study personnel. The database is encrypted and password-protected. Electronic data from QST and the mobile application are kept in password- and access-protected devices and on backed up systems. All patient data, with the exception of the PreScreening form and QST data, are coded. The PreScreening forms contain protected health information, but are stored separately from the rest of the patient data and in another access-controlled space. Coded blood samples are stored in -80°F freezers in locked rooms on an access-controlled floor.

14 QUALITY CONTROL AND QUALITY ASSURANCE

This study will have a separate Quality Management Plan, which will address:

- How data will be evaluated for compliance with the protocol and for accuracy in relation to source documents.
- The documents to be reviewed (eg, CRFs, specimen tracking logs, questionnaires), who is responsible, and the frequency for reviews.
- Who will be responsible for addressing quality assurance issues (correcting procedures that are not in compliance with protocol) and quality control issues (correcting errors in data entry).
- Staff training methods and how such training will be tracked.

15 ETHICS/PROTECTION OF HUMAN SUBJECTS

15.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

15.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

15.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to subjects and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the subject. Consent forms will be IRB-approved, and the subject is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any study-related assessments or procedures. Subjects will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The consent process will be documented in the clinical or research record.

15.4 Exclusion of Women, Minorities, and Children (Special Populations)

15.4.1 *Inclusion of Women*

We will recruit and study two groups of patients diagnosed with chronic TMD, targeting a total of 40 women and 20 men with an approximate F/M ratio based on our recruitment experience and published epidemiological studies in the field. TMD prevalence ranges from 8%-15% for women and 3%-10% for men[53].

15.4.2 *Inclusion of Minorities*

We will recruit without regard to ethnicity, and anticipate that this will reflect the racial characteristics of the general population in this region of the country. According to 2000 census data, the demographic composition of Washtenaw County is 75% White, 12% Black, 5% Asian/Pacific Islanders, 12% Hispanic or Latino (of any race), <1% American Indian/Eskimo/Aleut, and 1% Other.

15.4.3 *Inclusion of Children*

We are proposing to study subjects between the ages of 18-65. Young children would be unable to participate because of blood volume limits and the utilization of ionizing radiation (PET). We draw up to approximately 70 mL of blood in these studies, which is over the allowable guidelines for younger children. In addition, we utilize daily sessions of HD-tDCS that require careful monitoring of internal states and accurate reporting, which may be difficult to tolerate and perform for children.

15.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to any study information relating to subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study subjects. The clinical study site will permit access to such records after the study monitor has signed a University of Michigan confidentiality agreement.

15.6 Future Use of Stored Specimens and Other Identifiable Data

Blood samples may be stored for potential analyses, including genetic investigation, after completion of this study.

The informed consent document provides information to subjects regarding the option of participation in a future study, as well as their rights as subjects, and the responsibilities of the investigative team with regard to the samples and the related data.

15.7 NIH Genomic Data Sharing Policy

In accordance with the National Institutes of Health (NIH), Genomic Data Sharing (GDS) Policy issued on August 27, 2014 (https://osp.od.nih.gov/scientific-sharing/genomic-data-sharing/), we will implement the following GDS plan.

Data generated from HUM00110179 human samples will be shared through **controlled-access** NIH-designated data repositories; individuals who do not give consent for sharing data will be excluded from the study. Genomic data include individual-level and aggregate-level data from whole genome sequencing. The study will be registered in dbGaP and the following data and information will be shared through an NIH-designated repository**:**

- Study documents
- Individual-level sequence data
- Aggregate-level sequence data
- Associated phenotypic data

All data will be de-identified. Data will be given a unique participant code that contains no information about the identity of the individual. Only "Investigation and Modulation of the Mu-Opioid Mechanisms in TMD (in vivo)" investigators will hold the key to other study identifiers. Researchers who request access to the data will have to agree not to try to identify any individuals who have participated in the study. If any of the following identifiers are collected in this study, the identifier will be removed:

1. Names.
2. All geographic subdivisions smaller than a state, including street address, city, county, precinct, ZIP Code, and their equivalent geographical codes, except for the initial three digits of a ZIP Code if, according to the current publicly available data from the Bureau of the Census:
    a. The geographic unit formed by combining all ZIP Codes with the same three initial digits contains more than 20,000 people.
    b. The initial three digits of a ZIP Code for all such geographic units containing 20,000 or fewer people are changed to 000.
3. All elements of dates (except year) for dates directly related to an individual, including birth date, test date; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older.
4. Telephone numbers.
5. Facsimile numbers.
6. Electronic mail addresses.
7. Social security numbers.
8. Medical record numbers.
9. Health plan beneficiary numbers.
10. Account numbers.
11. Certificate/license numbers.
12. Vehicle identifiers and serial numbers, including license plate numbers.

13. Device identifiers and serial numbers.
14. Web universal resource locators (URLs).
15. Internet protocol (IP) address numbers.
16. Biometric identifiers, including fingerprints and voiceprints.
17. Full-face photographic images and any comparable images.
18. Associated genetic and phenotypic data including screening, behavioral and fMRI results as well as any results deriving from samples collected for future studies (e.g. RNA, DNA methylation, cytokines, proteomics).

The sequence data will be shared once the quality control procedures are completed, which is expected to be completed no more than 3 months after the data have been generated. Data will be generated across all years of the study protocol and submitted in scheduled releases as the sequencing data become available. The draft consent form provides consent for the data to be used for future research purposes and to be shared broadly through a controlled access NIH-designated data repository. The Institutional Certification signed by the Institutional Signing Official will be submitted prior to award, along with any other Just-in-Time information.

The sequence data produced through this award may be shared through controlled access NIH-designated data repositories, consistent with data sharing under the NIH GDS Policy.

The IRB will review the protocol of this project and will assure that:

A. The protocol for the collection of genomic and phenotypic data is consistent with 45 CFR Part 46;
B. Data submission and subsequent data sharing for research purposes are consistent with the informed consent of study participants from whom the data were obtained;
C. Consideration was given to risks to individual participants and their families associated with data submitted to NIH-designated data repositories and subsequent sharing;
D. To the extent relevant and possible, consideration was given to risks to groups or populations associated with submitting data to NIH-designated data repositories and subsequent sharing; and
E. The investigator's plan for de-identifying datasets is consistent with the standards outlined in the GDS Policy.

16 DATA HANDLING AND RECORD KEEPING

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study subjects, including accurate case report forms (CRFs), and source documentation.

16.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

16.2 Data Capture Methods

Data will be recorded on paper Case Report Forms as well as by electronic systems from which research data will be transferred to study databases.

16.3 Types of Data

Data will be captured in three primary formats:

- By hand, on paper (ie, questionnaires)
- Electronically, on eCRFs (ie, questionnaires)
- Electronically, by instruments of the study.

These may be transferred to a study database, which will be analyzed by study staff.

16.4 Schedule and Content of Reports

The schedule and content of reports will be agreed upon by the PI, DSMB, and NIH-NIDCR.

16.5 Study Records Retention

Study records will be maintained for at least three years from the date that the grant federal financial report (FFR) is submitted to the NIH.

These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

16.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol or Good Clinical Practice requirements. The noncompliance may be on the part of the subject, the investigator, or study staff. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

These practices are consistent with investigator and sponsor obligations in ICH E6:

- Compliance with Protocol, Sections 4.5.1, 4.5.2, 4.5.3, and 4.5.4.
- Quality Assurance and Quality Control, Section 5.1.1
- Noncompliance, Sections 5.20.1 and 5.20.2.

All deviations from the protocol must be addressed in study subject source documents and promptly reported to NIDCR and the local IRB, according to their requirements.

17 PUBLICATION/DATA SHARING POLICY

This study will comply with the *NIH Public Access Policy*, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy requires that all clinical trials be registered in a public trials registry such as *ClinicalTrials.gov*, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIDCR grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801 mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials:"

Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation;

Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.

NIH grantees must take specific *steps to ensure compliance* with NIH implementation of FDAAA.

18 SUPPLEMENTAL MATERIALS

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

- Statistical Analysis Plan
- Manual of Procedures
- Blood Sampling and Processing Instructions
- Case Report Forms ("CRFs"; aka Questionnaires)
- Quality Management Plan
- Data Management Plan
- Clinical Monitoring Plan
- Site Roster
- DSMB Charter

APPENDICES: KEY STUDY QUESTIONNAIRES

DEMOGRAPHIC QUESTIONNAIRE

BECK DEPRESSION INVENTORY

DC/TMD EXAMINATION FORM

TMD_SQ FORM

EXPECTATION OF EFFECT

MCGILL PAIN QUESTIONNAIRE (LONG)

MCGILL PAIN QUESTIONNAIRE (SHORT)

PANAS-X

GEOPAIN

VISUAL ANALOG SCALE

GRADED CHRONIC PAIN SCALE

PITTSBURGH SLEEP QUALITY INDEX

PET SUBJECT INFORMATION SHEET

tDCS SIDE EFFECTS QUESTIONNAIRE

HD-tDCS SHAM/PLACEBO ASSESSMENT

DEMOGRAPHIC QUESTIONNAIRE

Demographic Questions

1. When were you born _____/_____/_____?
   Month Day Year

2. What is your gender? **(Circle one answer)**
   - Male 1
   - Female 2

3. How would you describe your ethnicity? **(Circle one answer)**
   - Hispanic or Latino 1
   - Not Hispanic or Latino 2
   - Decline to answer 3

4. How would you describe your race? **(Circle all that apply)**
   - American Indian or Alaska Native 1
   - Asian 2
   - Black or African American 3
   - Native Hawaiian or Other Pacific Islander 4
   - White 5
   - Decline to answer 6

5. What is your marital status? **(Circle one answer)**
   - Never married 1
   - Married 2
   - Living with someone as if you were married 3
   - Separated 4
   - Divorced 5
   - Widowed 6

6. What is the highest grade or degree in school you completed? _____
   (The G.E.D. counts as grade 12)

7. What is your occupation or line of work? If you are unemployed, what was your last job?

OCCUPATION OR LAST JOB

8. Are you currently employed? **(Circle one answer)**

Yes, Full-time	1
Yes, Part-time	2
No	3

9. If unemployed, what is the **main** reason you are not currently employed? **(Circle one answer)**

Student	1
Poor health or disabled	2
Retired	3
Homemaker	4
Laid off	5
Other (please describe in the space below)	6

10. Do you have a valid driver's license? **(Circle one answer)**

Yes	1
No	2

11. Do you have an automobile available for your use? **(Circle one answer)**

Yes	1
No	2

12. Which category **best** describes your living situation at this time? **(Circle one answer)**

A house or apartment	1
A rooming house or hotel	2
A halfway house or group home	3
Other	4

Please Describe_____

13. With whom do you live now? **(Circle one answer on each line)**

	YES	NO
Alone	1	2
With spouse or partner	1	2
With children	1	2
With brothers or sisters	1	2
With parents	1	2
With other relatives	1	2
With friends	1	2
With other boarders	1	2
Other	1	2

14. How many children under the age of 16 are currently living with you? _____ children
(If none, enter 0)

15. Do you have enough money to take care of your financial needs? **(Circle one answer)**

Definitely yes	1
Mainly yes	2
Mainly no	3
Definitely no	4

BECK DEPRESSION INVENTORY

BECK DEPRESSION INVENTORY

Please read each group of statements carefully. Then pick out the one statement in each group that best describes the way you have been feeling the PAST WEEK, INCLUDING TODAY. Circle the number besides the statement you picked. If several statements in the group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

1. [0] I do not feel sad.
   [1] I feel sad.
   [2] I am sad all of the time and can't snap out of it.
   [3] I am so sad or unhappy that I can't stand it.

2. [0] I am not particularly discouraged about the future.
   [1] I feel discouraged about the future.
   [2] I feel I have nothing to look forward to.
   [3] I feel that the future is hopeless and that things cannot improve.

3. [0] I do not feel like a failure.
   [1] I feel I have failed more than the average person.
   [2] As I look back on my life, all I can see is a lot of failure.
   [3] I feel I am a complete failure as a person.

4. [0] I get as much satisfaction out of things as I used to.
   [1] I don't enjoy things the way I used to
   [2] I don't get real satisfaction out of anything
   [3] I am dissatisfied or bored with everything.

5. [0] I don't feel particularly guilty
   [1] I feel guilty a good part of the time.
   [2] I feel quite guilty most of the time
   [3] I feel guilty all of the time.

6. [0] I don't feel I am being punished.
   [1] I feel I may be punished.
   [2] I expect to be punished.
   [3] I feel I am being punished.

7. [0] I don't feel disappointed in myself.
   [1] I am disappointed in myself.

[2] I am disgusted with myself.
[3] I hate myself

8. [0] I don't feel I am any worse than anybody else.
[1] I am critical of myself for my weaknesses or mistakes.
[2] I blame myself all the time for my faults.
[3] I blame myself for everything bad that happens.

9. [0] I don't have any thoughts of killing myself.
[1] I have thoughts of killing myself but I would not carry them out.
[2] I would like to kill myself.
[3] I would kill myself if I had the chance.

10. [0] I don't cry any more than usual.
[1] I cry more now than I used to.
[2] I cry all the time now.
[3] I used to be able to cry but now I can't cry even though I want to.

11. [0] I am no more irritated now than I ever was.
[1] I get annoyed or irritated more easily than I used to.
[2] I feel irritated all the time now.
[3] I don't get irritated at all by the things that used to irritate me.

12. [0] I have not lost interest in other people.
[1] I am less interested in other people than I used to be.
[2] I have lost most of my interest in other people.
[3] I have lost all of my interest in other people.

13. [0] I make decisions about as well as I ever could.
[1] I put off making decisions more than I used to.
[2] I have greater difficulty in making decisions than before.
[3] I can't make decisions at all anymore.

14. [0] I don't feel I look any worse than I used to.
[1] I am worried that I am looking old or unattractive.
[2] I feel that there are permanent changes in my appearance that make me look unattractive.
[3] I believe that I look ugly.

15. [0] I can work about as well as before.

[1] It takes an extra effort to get started at doing something.
[2] I have to push myself very hard to do anything.
[3] I can't do any work at all.

16. [0] I can sleep as well as usual.
[1] I don't sleep as well as I used to.
[2] I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
[3] I wake up several hours earlier than I used to and cannot get back to sleep.
17. [0] I don't get more tired than usual.
[1] I get tired more easily than I used to.
[2] I get tired from doing almost anything.
[3] I am too tired to do anything.

18. [0] My appetite is no worse than usual.
[1] My appetite is not as good as it used to be.
[2] My appetite is much worse now.
[3] I have no appetite at all anymore.

19. [0] I haven't lost much weight, if any, lately.
[1] I have lost more than 5 pounds.
[2] I have lost more than 10 pounds.
[3] I have lost more than 15 pounds.

I am purposefully trying to lose weight by eating less. YES [ ] NO [ ]

20. [0] I am no more worried about my health than usual.
[1] I am worried about physical problems such as aches and pains, upset stomach or constipation.
[2] I am very worried about physical problems and it's hard to think of much else.
[3] I am so worried about my physical problems that I cannot think about anything else.

21. [0] I have not noticed any recent change in my interest in sex.
[1] I am less interested in sex than I used to be.
[2] I am much less interested in sex now.
[3] I have lost interest in sex completely.

DC/TMD EXAMINATION FORM

DC/TMD Examination Form

Date filled out (mm-dd-yyyy) ___-___-_____

Patient _____ Examiner _____

1a. Location of Pain: Last 30 days (Select all that apply)

RIGHT PAIN				LEFT PAIN			
O None	O Temporalis	O Other m muscles	O Non-mast structures	O None	O Temporalis	O Other m muscles	O Non-mast structures
	O Masseter	O TMJ			O Masseter	O TMJ	

1b. Location of Headache: Last 30 days (Select all that apply)

O None	O Temporal	O Other	O None	O Temporal	O Other

2. Incisal Relationships **Reference tooth** O US #8 O US #9 O Other

Horizontal Incisal Overjet O If negative ___ mm

Vertical Incisal Overlap O If negative ___ mm

Midline Deviation Right O Left O N/A O ___ mm

3. Opening Pattern (Supplemental; Select all that apply)

O Straight O Corrected deviation

Uncorrected Deviation: O Right O Left

4. Opening Movements

A. Pain Free Opening ___ mm

B. Maximum Unassisted Opening ___ mm

C. Maximum Assisted Opening ___ mm

D. Terminated? Ⓝ Ⓨ

	RIGHT SIDE				LEFT SIDE			
		Pain	Familiar Pain	Familiar Headache		Pain	Familiar Pain	Familiar Headache
B. Maximum Unassisted Opening	Temporalis	Ⓝ Ⓨ	Ⓝ Ⓨ	Ⓝ Ⓨ	Temporalis	Ⓝ Ⓨ	Ⓝ Ⓨ	Ⓝ Ⓨ
	Masseter	Ⓝ Ⓨ	Ⓝ Ⓨ		Masseter	Ⓝ Ⓨ	Ⓝ Ⓨ	
	TMJ	Ⓝ Ⓨ	Ⓝ Ⓨ		TMJ	Ⓝ Ⓨ	Ⓝ Ⓨ	
	Other M Musc	Ⓝ Ⓨ	Ⓝ Ⓨ		Other M Musc	Ⓝ Ⓨ	Ⓝ Ⓨ	
	Non-mast	Ⓝ Ⓨ	Ⓝ Ⓨ		Non-mast	Ⓝ Ⓨ	Ⓝ Ⓨ	
C. Maximum Assisted Opening	Temporalis	Ⓝ Ⓨ	Ⓝ Ⓨ	Ⓝ Ⓨ	Temporalis	Ⓝ Ⓨ	Ⓝ Ⓨ	Ⓝ Ⓨ
	Masseter	Ⓝ Ⓨ	Ⓝ Ⓨ		Masseter	Ⓝ Ⓨ	Ⓝ Ⓨ	
	TMJ	Ⓝ Ⓨ	Ⓝ Ⓨ		TMJ	Ⓝ Ⓨ	Ⓝ Ⓨ	
	Other M Musc	Ⓝ Ⓨ	Ⓝ Ⓨ		Other M Musc	Ⓝ Ⓨ	Ⓝ Ⓨ	
	Non-mast	Ⓝ Ⓨ	Ⓝ Ⓨ		Non-mast	Ⓝ Ⓨ	Ⓝ Ⓨ	

5. Lateral and Protrusive Movements

A. Right Lateral ___ mm

B. Left Lateral ___ mm

C. Protrusion ___ mm

O If negative

	RIGHT SIDE				LEFT SIDE			
		Pain	Familiar Pain	Familiar Headache		Pain	Familiar Pain	Familiar Headache
A. Right Lateral	Temporalis	Ⓝ Ⓨ	Ⓝ Ⓨ	Ⓝ Ⓨ	Temporalis	Ⓝ Ⓨ	Ⓝ Ⓨ	Ⓝ Ⓨ
	Masseter	Ⓝ Ⓨ	Ⓝ Ⓨ		Masseter	Ⓝ Ⓨ	Ⓝ Ⓨ	
	TMJ	Ⓝ Ⓨ	Ⓝ Ⓨ		TMJ	Ⓝ Ⓨ	Ⓝ Ⓨ	
	Other M Musc	Ⓝ Ⓨ	Ⓝ Ⓨ		Other M Musc	Ⓝ Ⓨ	Ⓝ Ⓨ	
	Non-mast	Ⓝ Ⓨ	Ⓝ Ⓨ		Non-mast	Ⓝ Ⓨ	Ⓝ Ⓨ	
B. Left Lateral	Temporalis	Ⓝ Ⓨ	Ⓝ Ⓨ	Ⓝ Ⓨ	Temporalis	Ⓝ Ⓨ	Ⓝ Ⓨ	Ⓝ Ⓨ
	Masseter	Ⓝ Ⓨ	Ⓝ Ⓨ		Masseter	Ⓝ Ⓨ	Ⓝ Ⓨ	
	TMJ	Ⓝ Ⓨ	Ⓝ Ⓨ		TMJ	Ⓝ Ⓨ	Ⓝ Ⓨ	
	Other M Musc	Ⓝ Ⓨ	Ⓝ Ⓨ		Other M Musc	Ⓝ Ⓨ	Ⓝ Ⓨ	
	Non-mast	Ⓝ Ⓨ	Ⓝ Ⓨ		Non-mast	Ⓝ Ⓨ	Ⓝ Ⓨ	
C. Protrusion	Temporalis	Ⓝ Ⓨ	Ⓝ Ⓨ	Ⓝ Ⓨ	Temporalis	Ⓝ Ⓨ	Ⓝ Ⓨ	Ⓝ Ⓨ
	Masseter	Ⓝ Ⓨ	Ⓝ Ⓨ		Masseter	Ⓝ Ⓨ	Ⓝ Ⓨ	
	TMJ	Ⓝ Ⓨ	Ⓝ Ⓨ		TMJ	Ⓝ Ⓨ	Ⓝ Ⓨ	
	Other M Musc	Ⓝ Ⓨ	Ⓝ Ⓨ		Other M Musc	Ⓝ Ⓨ	Ⓝ Ⓨ	
	Non-mast	Ⓝ Ⓨ	Ⓝ Ⓨ		Non-mast	Ⓝ Ⓨ	Ⓝ Ⓨ	

6. TMJ Noises During Open & Close Movements

RIGHT TMJ

	Examiner: Open	Examiner: Close	Patient	Pain w/ Click	Familiar Pain
Click	N Y	N Y	N Y	N Y	N Y
Crepitus	N Y	N Y	N Y		

LEFT TMJ

	Examiner: Open	Examiner: Close	Patient	Pain w/ Click	Familiar Pain
Click	N Y	N Y	N Y	N Y	N Y
Crepitus	N Y	N Y	N Y		

7. TMJ Noises During Lateral & Protrusive Movements

RIGHT TMJ

	Examiner	Patient	Pain w/ Click	Familiar Pain
Click	N Y	N Y	N Y	N Y
Crepitus	N Y	N Y		

LEFT TMJ

	Examiner	Patient	Pain w/ Click	Familiar Pain
Click	N Y	N Y	N Y	N Y
Crepitus	N Y	N Y		

8. Joint Locking

RIGHT TMJ

	Locking	Reduction: Patient	Reduction: Examiner
While Opening	N Y	N Y	N Y
Wide Open Position	N Y	N Y	N Y

LEFT TMJ

	Locking	Reduction: Patient	Reduction: Examiner
While Opening	N Y	N Y	N Y
Wide Open Position	N Y	N Y	N Y

9. Muscle & TMJ Pain with Palpation

RIGHT SIDE

(1 kg)	Pain	Familiar Pain	Familiar Headache	Referred Pain
Temporalis (posterior)	N Y	N Y	N Y	N Y
Temporalis (middle)	N Y	N Y	N Y	N Y
Temporalis (anterior)	N Y	N Y	N Y	N Y
Masseter (origin)	N Y	N Y		N Y
Masseter (body)	N Y	N Y		N Y
Masseter (insertion)	N Y	N Y		N Y

TMJ	Pain	Familiar Pain	Referred Pain
Lateral pole **(0.5 kg)**	N Y	N Y	N Y
Around lateral pole **(1 kg)**	N Y	N Y	N Y

LEFT SIDE

(1 kg)	Pain	Familiar Pain	Familiar Headache	Referred Pain
Temporalis (posterior)	N Y	N Y	N Y	N Y
Temporalis (middle)	N Y	N Y	N Y	N Y
Temporalis (anterior)	N Y	N Y	N Y	N Y
Masseter (origin)	N Y	N Y		N Y
Masseter (body)	N Y	N Y		N Y
Masseter (insertion)	N Y	N Y		N Y

	Pain	Familiar Pain	Referred Pain
Lateral pole **(0.5 kg)**	N Y	N Y	N Y
Around lateral pole **(1 kg)**	N Y	N Y	N Y

10. Supplemental Muscle Pain with Palpation

RIGHT SIDE

(0.5 kg)	Pain	Familiar Pain	Referred Pain
Posterior mandibular region	N Y	N Y	N Y
Submandibular region	N Y	N Y	N Y
Lateral pterygoid area	N Y	N Y	N Y
Temporalis tendon	N Y	N Y	N Y

LEFT SIDE

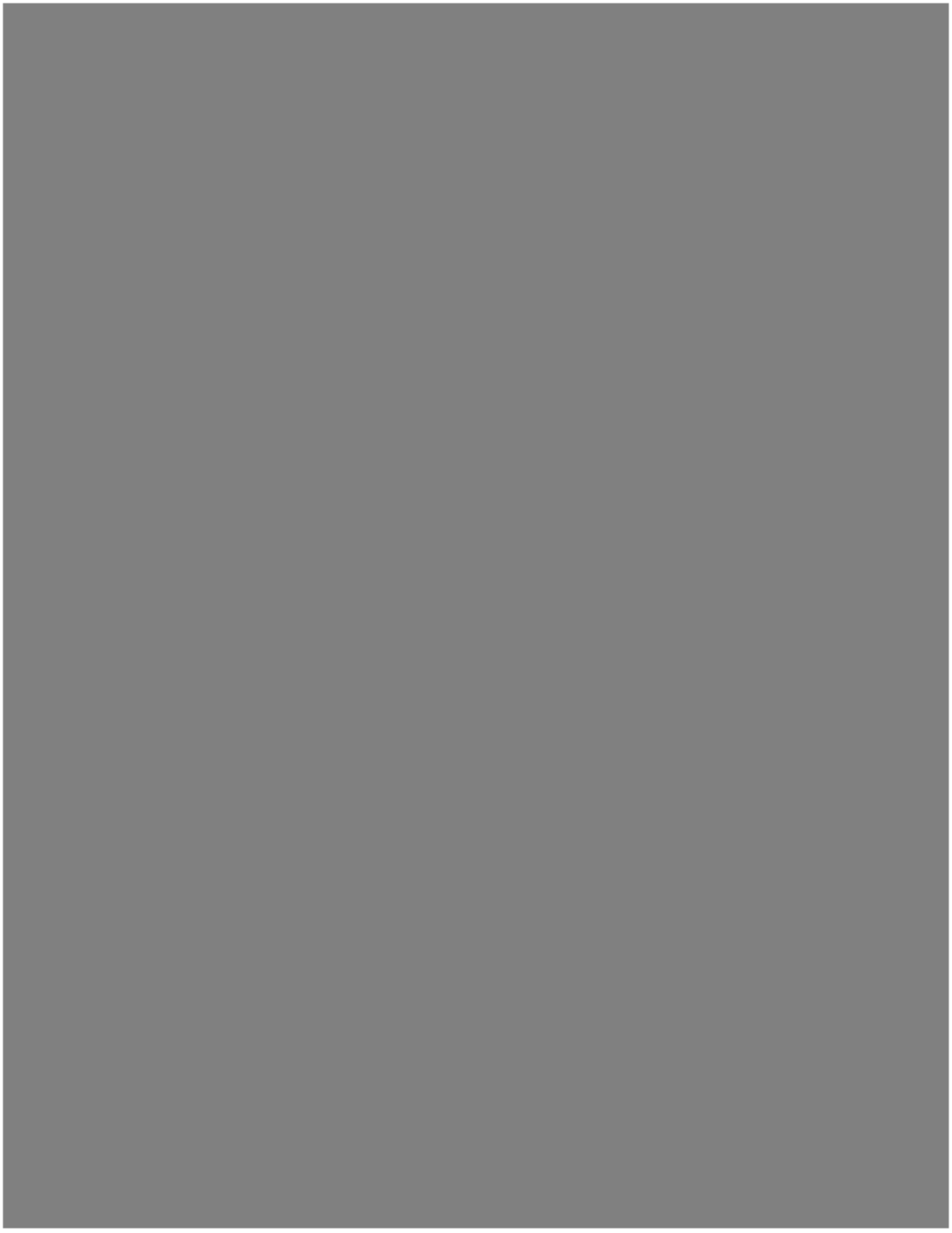
(0.5 kg)	Pain	Familiar Pain	Referred Pain
Posterior mandibular region	N Y	N Y	N Y
Submandibular region	N Y	N Y	N Y
Lateral pterygoid area	N Y	N Y	N Y
Temporalis tendon	N Y	N Y	N Y

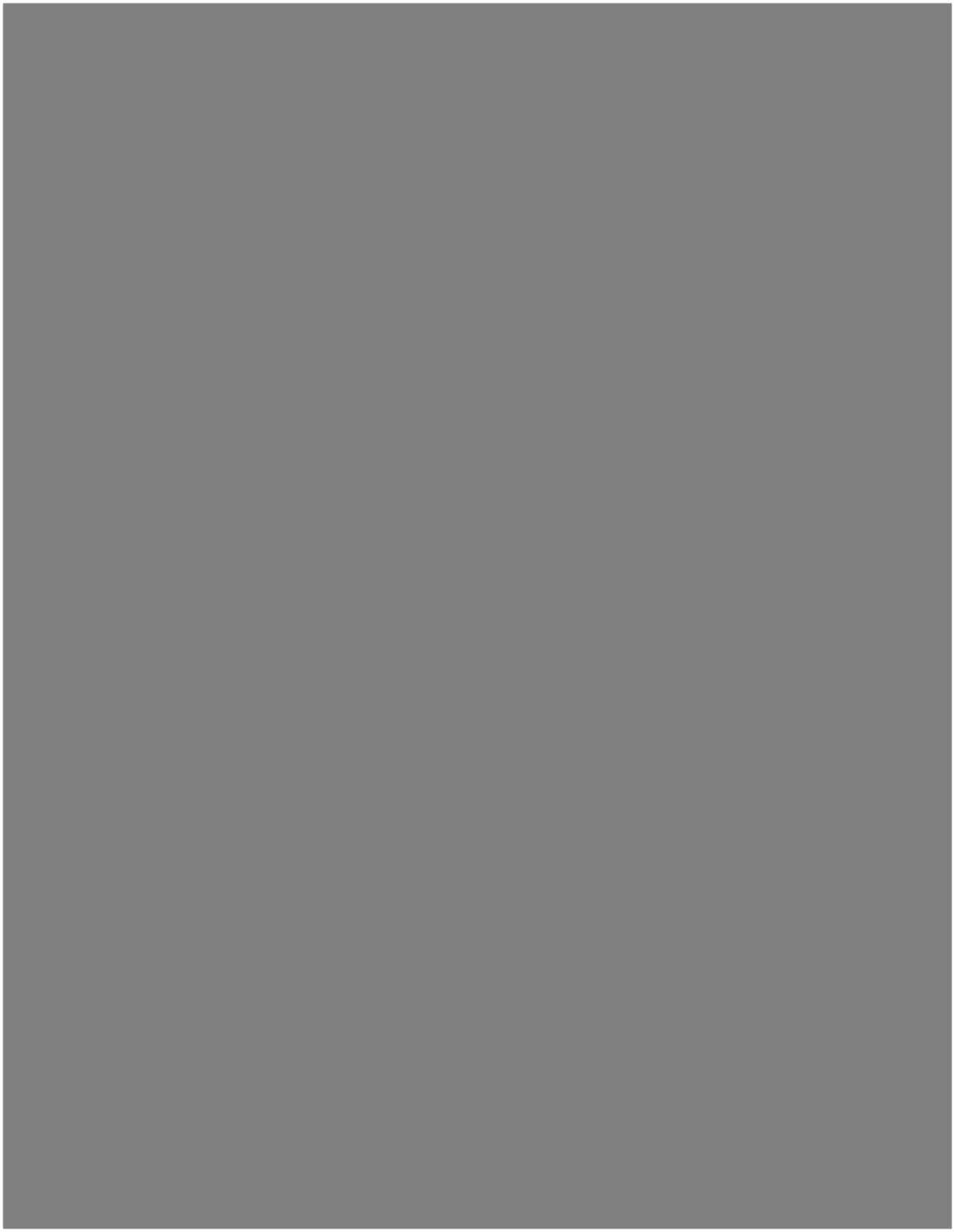
11. Diagnoses

Pain Disorders	Right TMJ Disorders	Left TMJ Disorders
○ None	○ None	○ None
○ Myalgia	Disc displacement (select one)	Disc displacement (select one)
○ Myofascial pain with referral	○ ...with reduction	○ ...with reduction
	○ ...with reduction, with intermittent locking	○ ...with reduction, with intermittent locking
○ Right Arthralgia	○ ... without reduction, with limited opening	○ ... without reduction, with limited opening
○ Left Arthralgia	○ ... without reduction, without limited opening	○ ... without reduction, without limited opening
	○ Degenerative joint disease	○ Degenerative joint disease
○ Headache attributed to TMD	○ Subluxation	○ Subluxation

12. Comments

TMD_SQ FORM





EXPECTATION OF EFFECT

Subject ID : _____

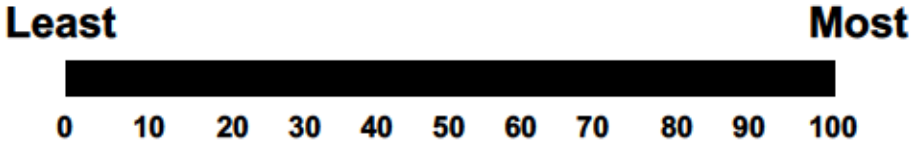
Date: _____

Expectation of Effect

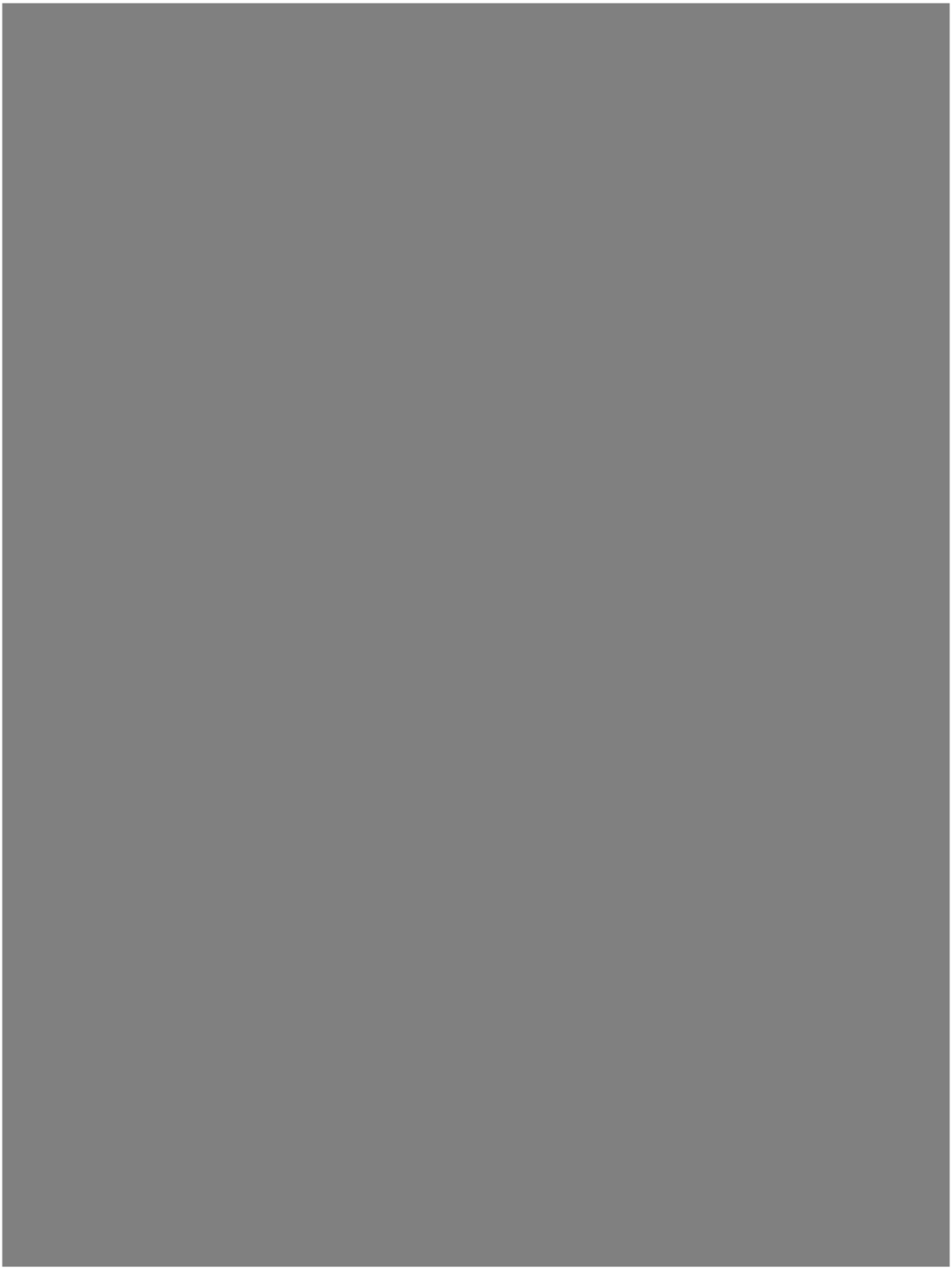
Visual Analog Scale

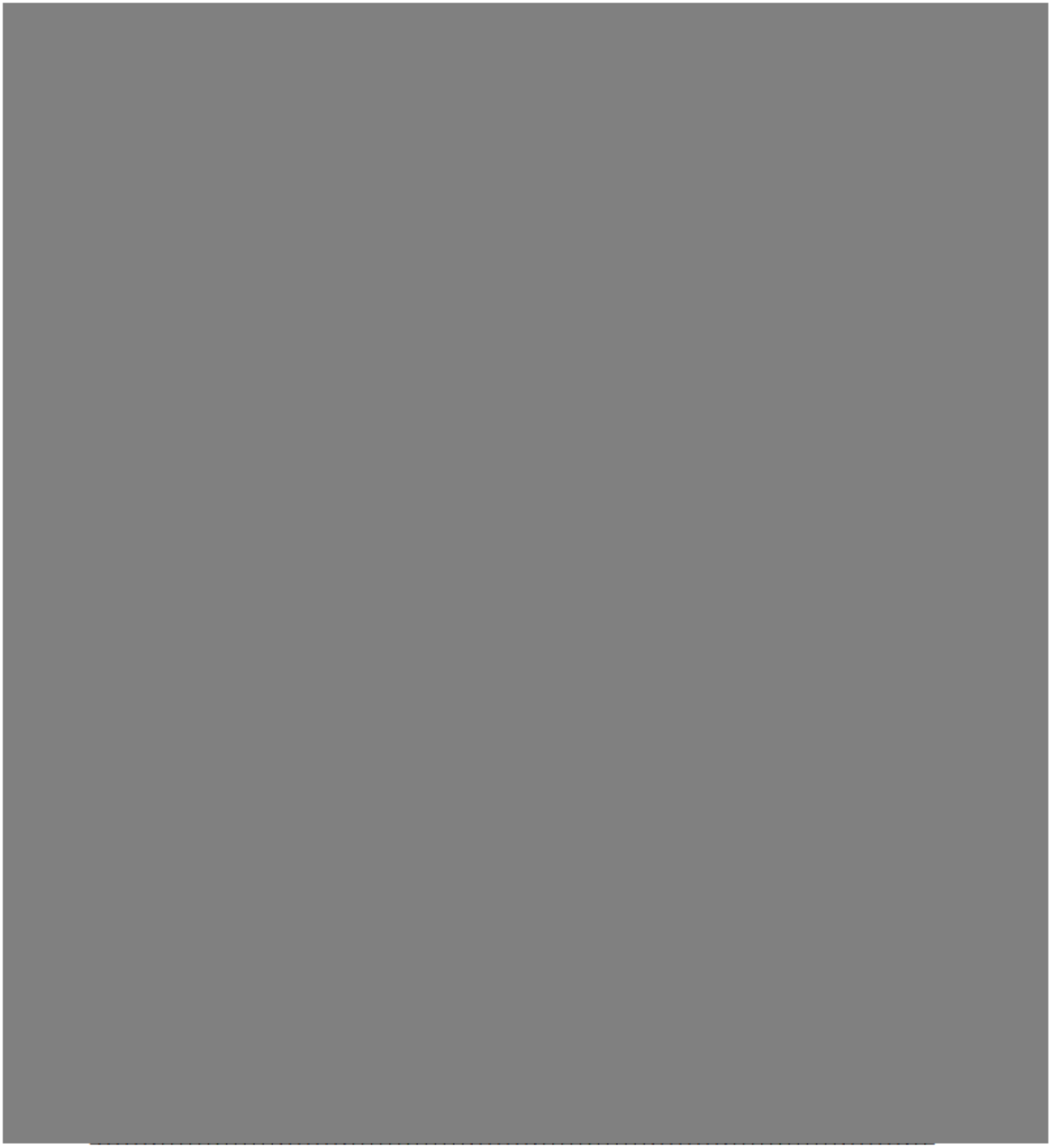
Please rate how effective you think the therapy will be:

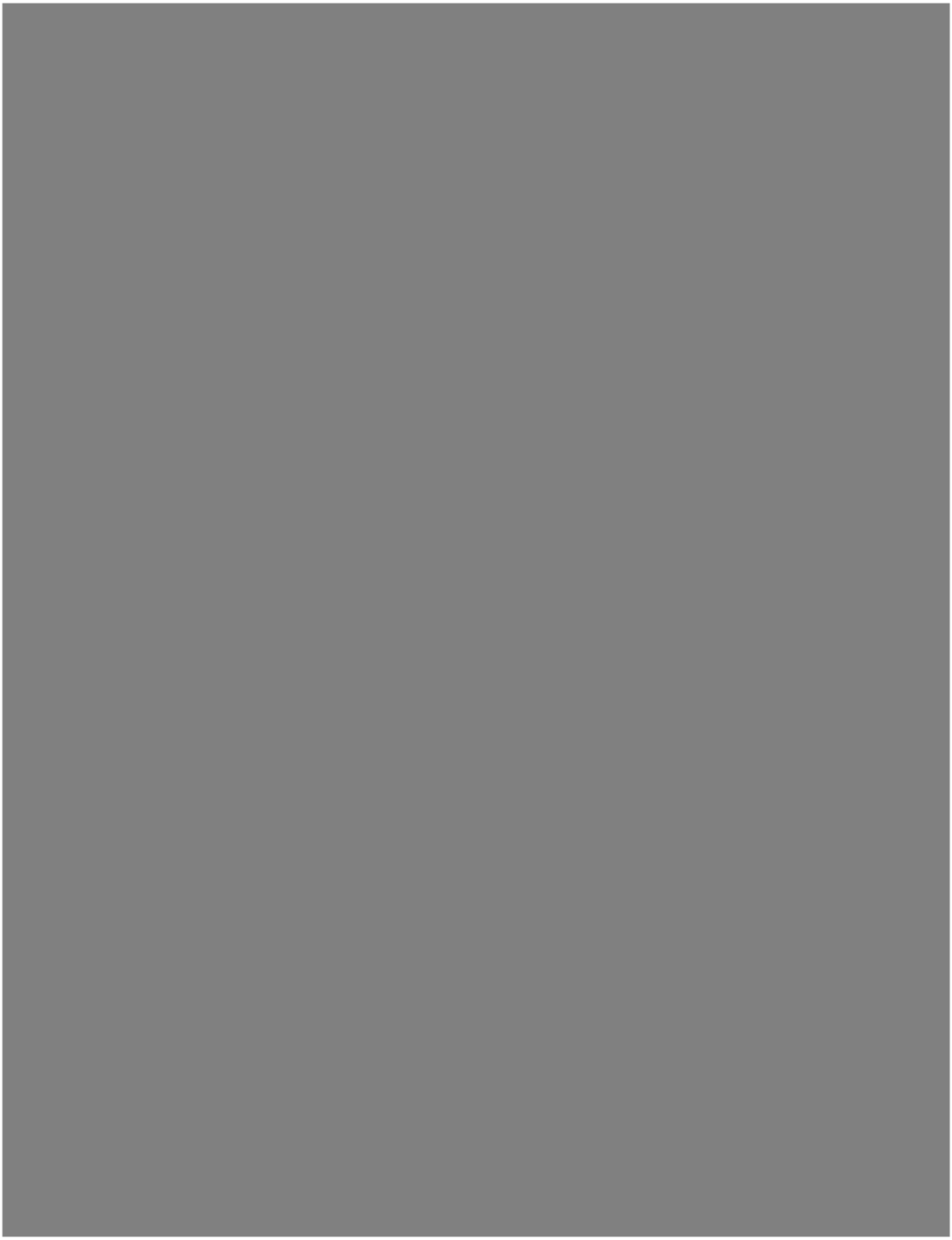
(Circle corresponding number)



MCGILL PAIN QUESTIONNAIRE (LONG FORM)

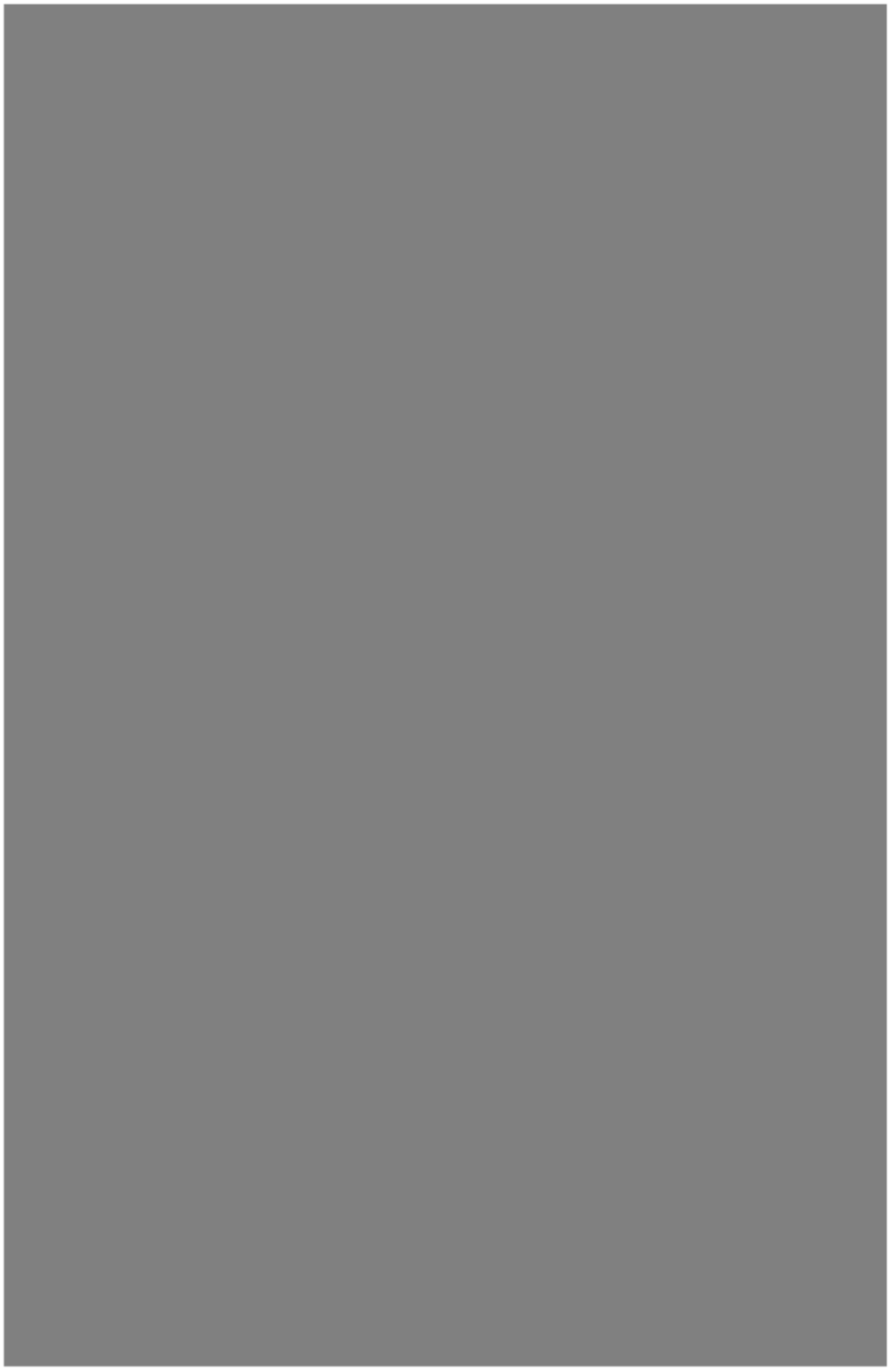






GEOPAIN™

GeoPain™



Disclaimer: Dr. Alexandre DaSilva and Eric Maslowski are the creators of PainTrek (now GeoPain), and also co-founders of MoxyTech LLC, which licensed the technology from University of Michigan.

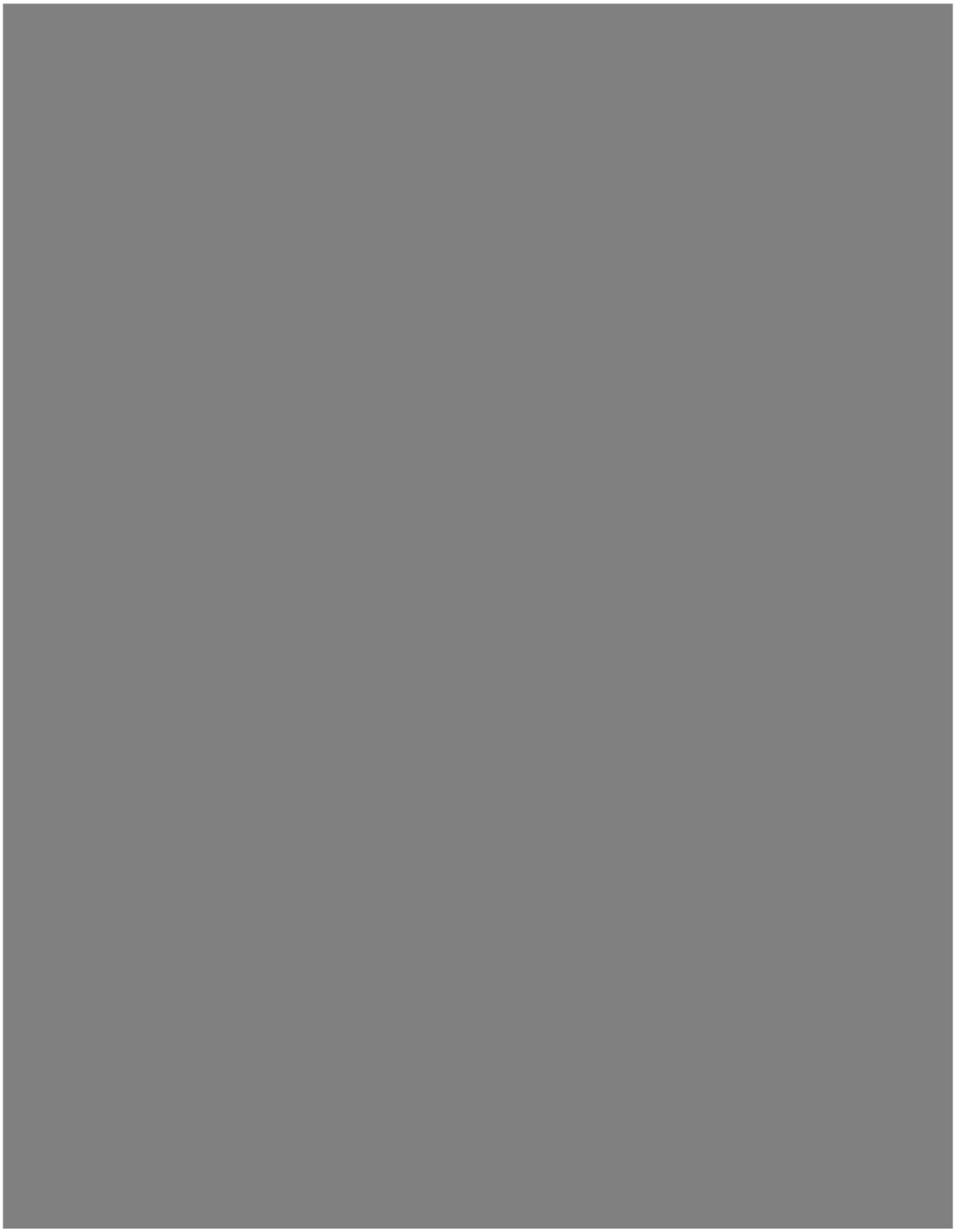
VISUAL ANALOG SCALE

Subject ID : _____

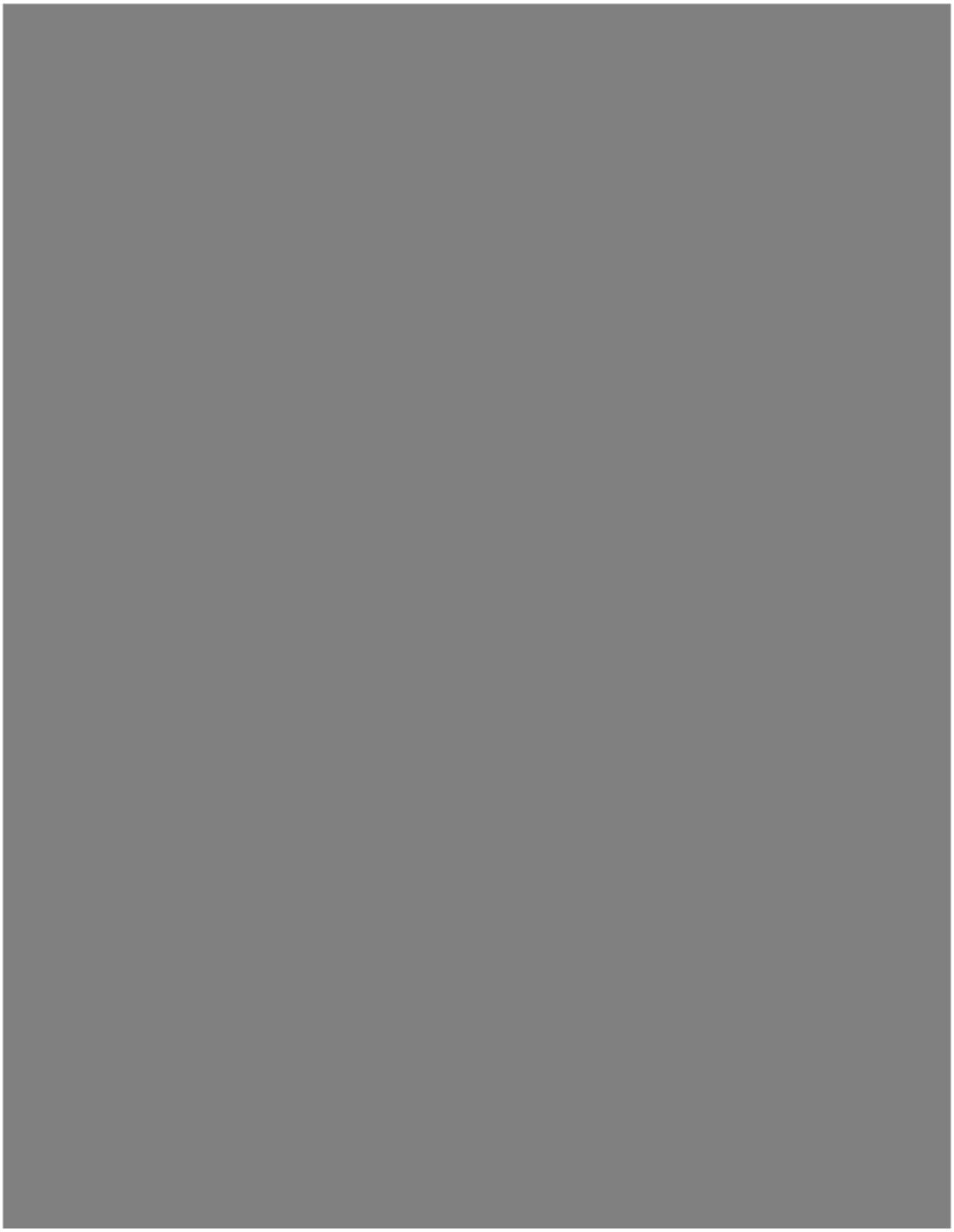
Date: _____

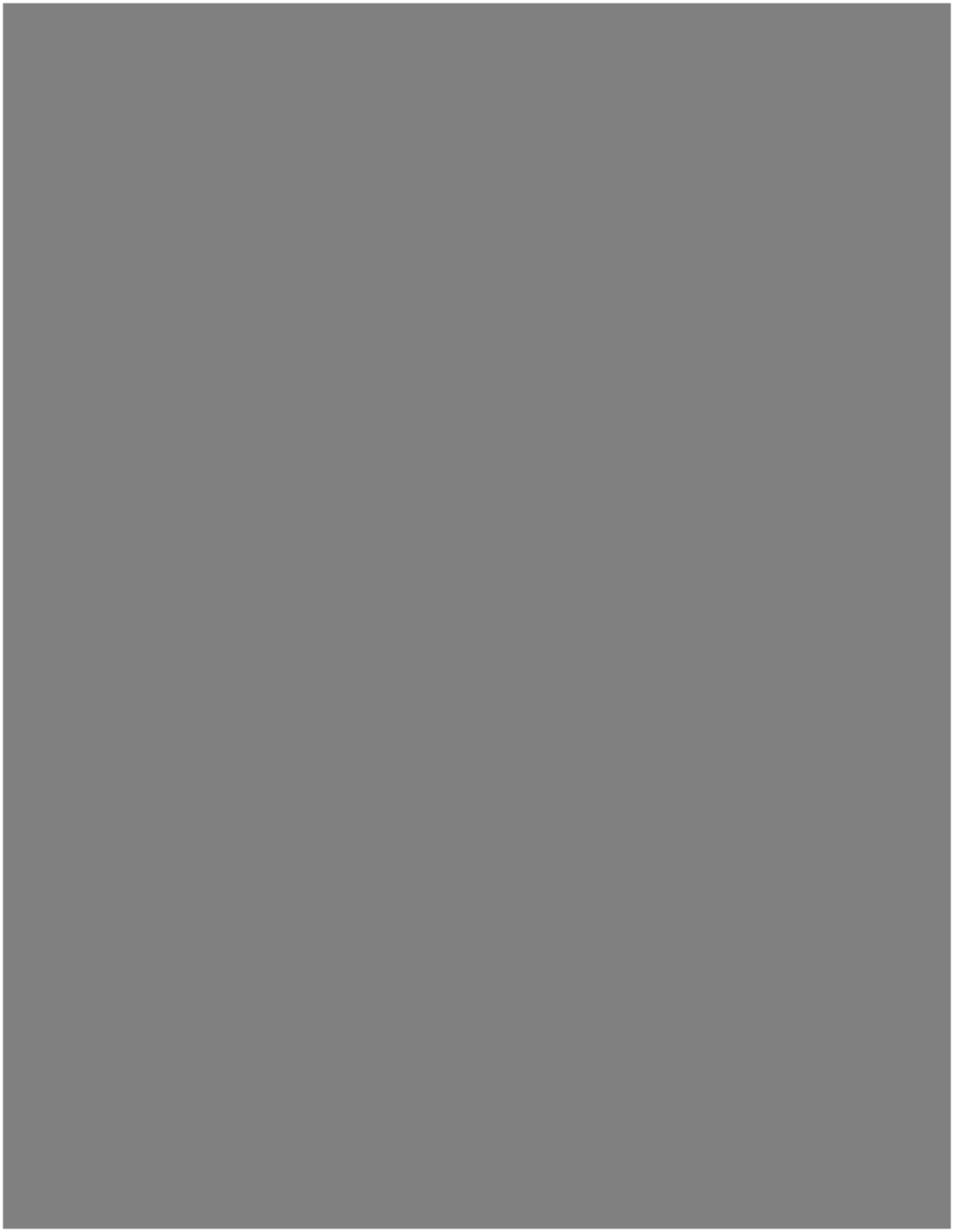
Visual Analog Scale

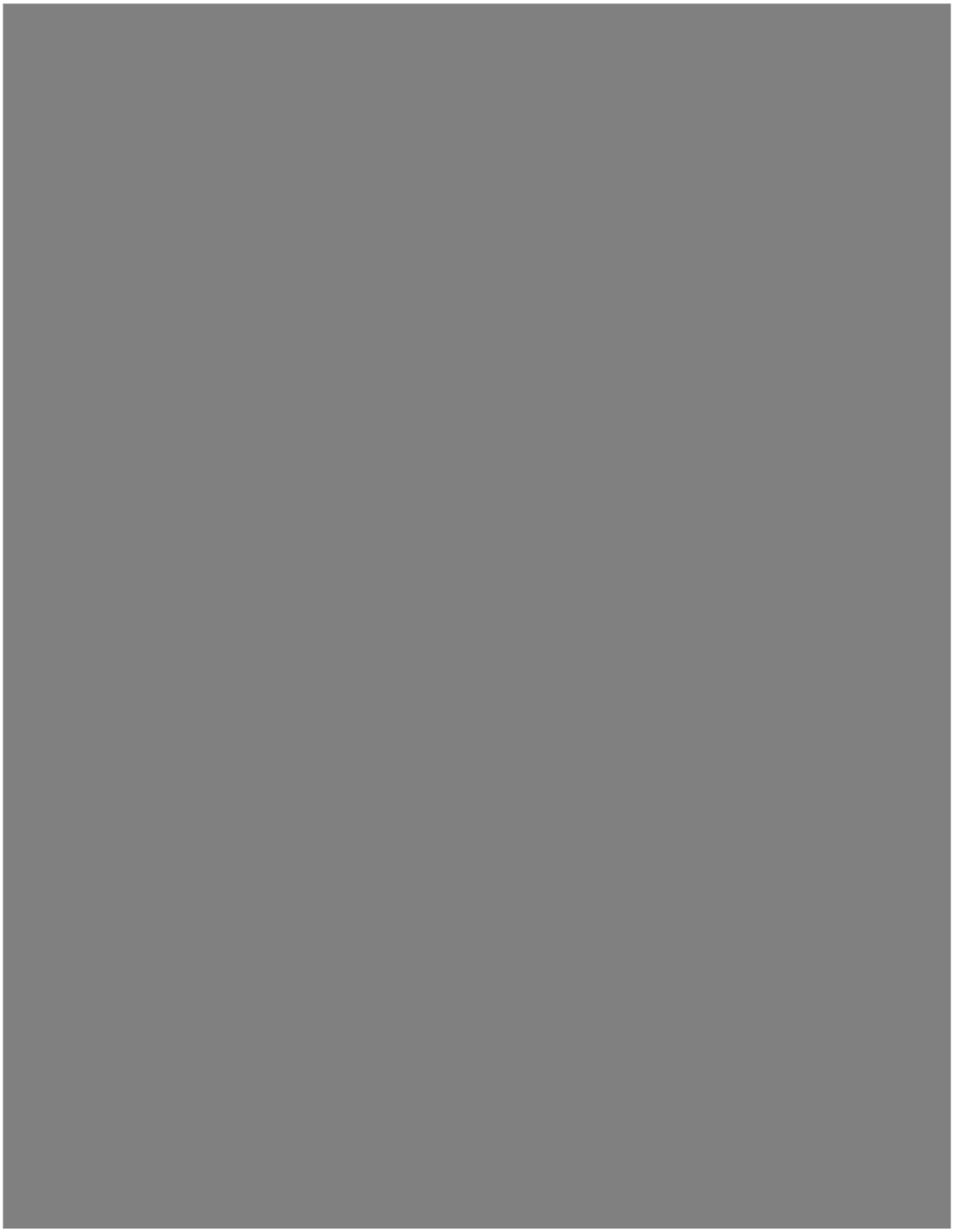
GRADED CHRONIC PAIN SCALE

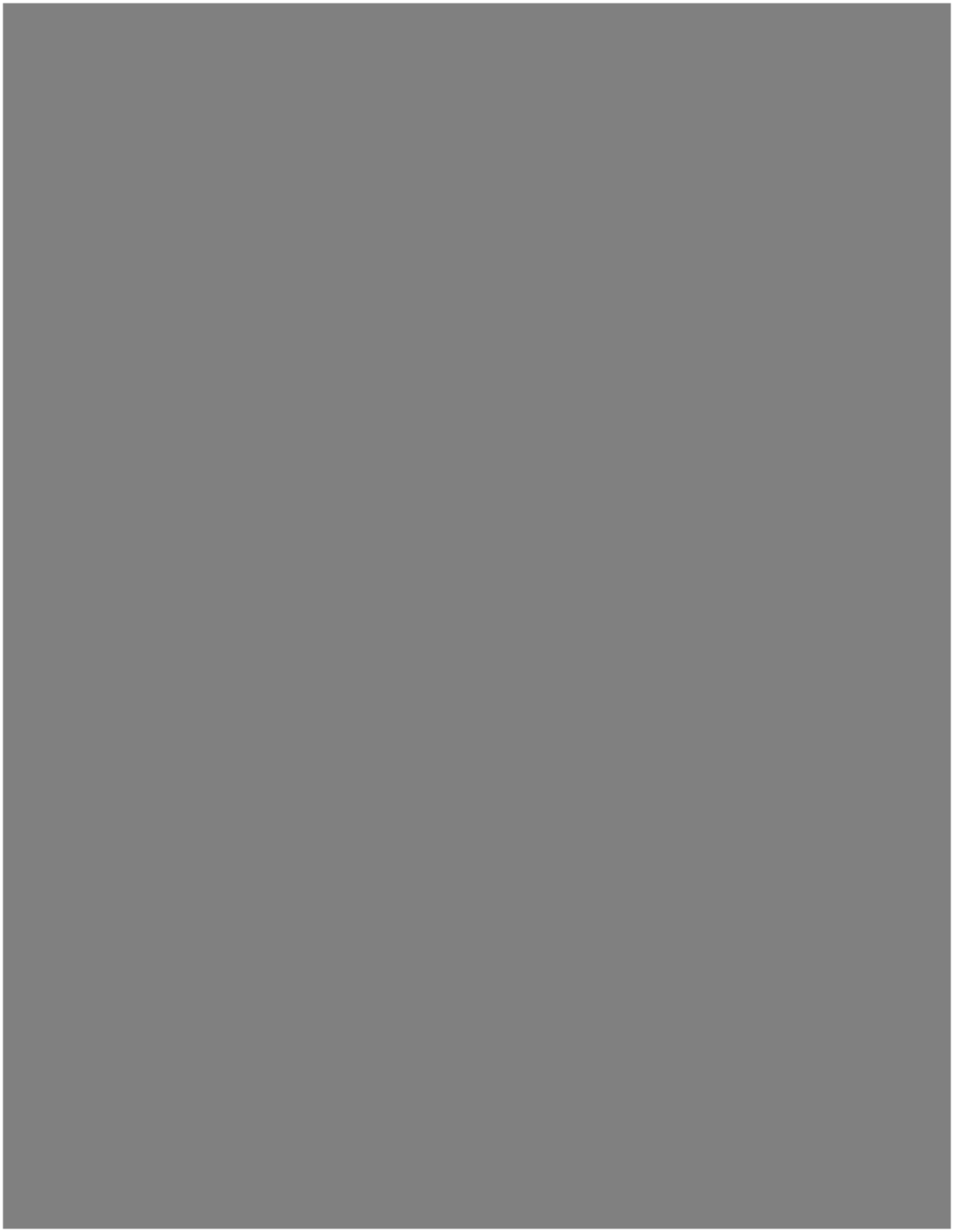


PITTSBURGH SLEEP QUALITY INDEX

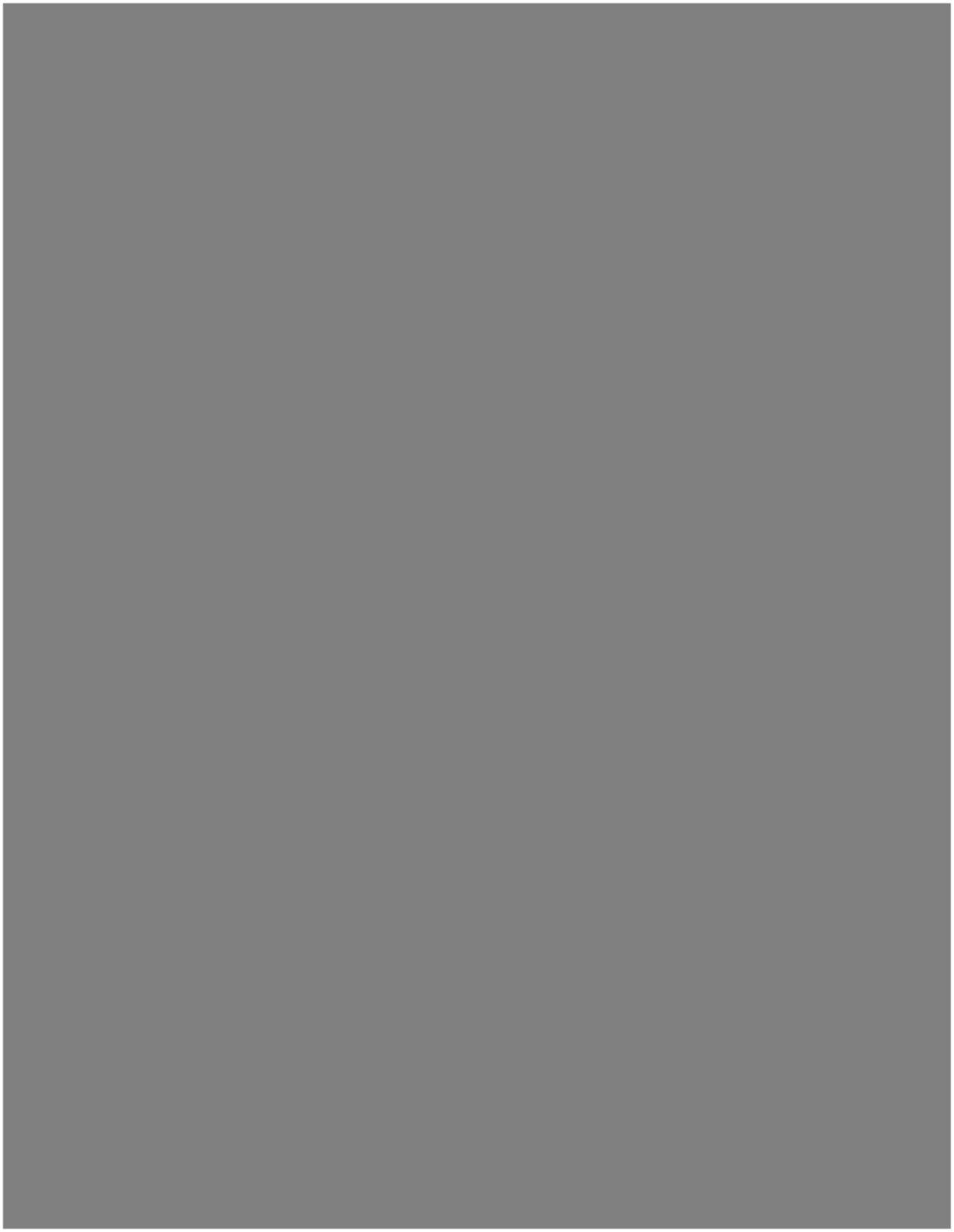








PET SUBJECT INFORMATION SHEET



TDCS SIDE EFFECTS

tDCS Side Effects

Do you experience any of the following symptoms or side effects?	*Enter a value (1-4) in the space below.* *1-Absent* *2-Mild* *3-Moderate* *4-Severe*	*If present: Is this related to tDCS?* *1-None* *2-Remote* *3-Possible* *4-Probable* *5-Definite*	*Notes*
Headache			
Neck Pain			
Scalp Pain			
Scalp Burns			
Tingling			
Skin Redness			
Sleepiness			
Trouble Concentrating			
Acute Mood Change			
Other (specify):			

HD-tDCS Sham/Placebo Assessment

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