Pain Control Using Neuromodulation in Patients Undergoing Definitive Chemoradiotherapy or Radiation Therapy for Locally Advanced Head and Neck Cancer

MAY-21-2019

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1.0 Introduction

More than 50,000 Americans (and more than 750,000 people worldwide) are diagnosed with head and neck cancer (HNCa) every year. HNCa impacts oral intake, speech, physical appearance, and emotional well-being. Despite advancements in treatment technology, which improves patient lifestyle and comfort, HNCa patient quality of life (QoL) still suffers. [1-3]

In nearly all of these patients, there is unintentional weight loss, which is associated with lower survival rates and is an independent predictor of mortality in patients with stage III and IV tumors.[4] The cause of the weight loss is multifactorial. The disease itself often results in significant weight loss and poor performance status before treatment begins, as up to 18% of patients require pre-treatment enteral feeding tube placement.[5] Mucositis as a result of concurrent chemoradiotherapy occurs in up to 80% of patients and further decreases oral intake, resulting in additional weight loss with nadir at the end of treatment.[6-9] These factors also function in a cycle, as poor nutritional status pre-disposes patients to toxicity development and compromises treatment effectiveness.[10] Numerous strategies have been tried to reduce mucositis, the resulting pain and odynophagia, and/or the resulting weight loss, including narcotic pain medicines, biologically-targeted agents, and feeding tubes, with limited success.

Transcranial direct current stimulation (tDCS) offers a unique analgesic modality of central pain neuromodulation by altering the activity key sensory and motor cortical structures.[11, 12] tDCS has been demonstrated to be safe and effective in several chronic pain conditions, including fibromyalgia and multiple sclerosis[13]. However, tDCS pain neuromodulation has never been used in acute pain settings, such the temporary mucositis associated with head and neck cancer radiation and chemoradiotherapy. tDCS pain neuromodulation could offer significant mucositis and odynophagia relief, thereby reducing weight loss, improving performance status, and reducing the need for narcotics.

This study will be a randomized controlled trial of tDCS pain neuromodulation to relieve odynophagia. The randomization will be performed and documented by the statistician. Patients will be randomized to active tDCS or standard care. Measured outcomes will be both objective and subjective, including patient-reported pain, weight loss, and narcotic pain medication requirement.

Therapy-related oropharyngeal mucositis and odynophagia

Oral mucositis , a complication of combined radiation and chemotherapy for nearly all patients with HNCa, presents a significant clinical and economic problem. Severe oral mucositis can halt treatment and affect clinical outcome; pain and swallowing dysfunction can lead to weight loss, dehydration and hospitalization. Advanced planning techniques, such as IMRT, increase tissue sparing and allow dose intensification to improve disease outcomes. Ironically, though, mucositis/odynophagia rates have actually increased as significant portions of mucosa are often within the radiotherapy target [14, 15]. A large retrospective study reported rates of Grade 3-4 mucositis of 80% and 34% for altered and conventional fractionation, respectively, with 16% of patients requiring hospitalization.[8] The increasing use of concurrent chemotherapy also increases mucositis/odynophagia rates.[9]

The consequences of mucositis and odynophagia, in addition to the pain itself, are far-reaching. Odynophagia, combined with compromised swallowing function also as a result of therapy, often leads to decreased oral intake and resulting weight loss. In a retrospective study of 200 patients receiving head and neck radiotherapy with or without chemotherapy, oral mucositis was correlated with increased $\geq$5% weight loss from 17% to 60%.[16] Mucositis and odynophagia also have significant economic and quality of life impacts, including the estimate that oral mucositis has an incremental cost of $17,000 per patient.[16-19] These numbers demonstrate the tremendous morbidity and mortality related to mucositis.

Odynophagia and weight loss mitigation therapies

Narcotics and local anesthetics are standard therapies for acute mucositis and odynophagia, however, their efficacy is modest and they are associated with significant side effects in this generally elderly patient population.[20] Recently, newer approaches have been tried with biologically-targeted mucosa-protective agents and by modifying pain perception.

Amifostine is a pro-drug that supplies sulfhydryl groups as alternative oxidative targets to DNA, thereby reducing the DNA damage induced by radiotherapy. This raises the possibility that amifostine would also be radioprotective for tumor cells. Despite being adopted as a reasonable radioprotective treatment by ASCO in 2008 guidelines,[21] the randomized data supporting this is mixed. Two studies showed a benefit with amifostine,[22, 23] while two studies showed no benefit.[24, 25]

Recombinant human keratinocyte growth factor (KGF, palifermin) stimulates proliferation and repair of the aerodigestive mucosa. Palifermin was found to significantly reduce oral mucositis due to conditioning for stem cell transplant. [26, 27] Results were unfortunately less in Phase I and II studies of its use in head and neck cancer patients receiving radiotherapy, though there was a trend towards benefit.[28] Phase III randomized trials comparing a higher dose of palifermin against placebo showed modest reductions in clinician-assessed mucositis rates and duration in both definitive and post-operative settings. Patient-reported outcomes and opioid use were similar between the groups.[29, 30] Unfortunately, the benefit of mucosal protection with amifostine or palifermin has been limited.

Another strategy includes oral rinse with the anti-depressant doxepin which addresses the patient's perception of pain from mucositis, rather than reducing mucositis directly.[31] Preliminary results have been reported for a Phase III randomized cross-over trial comparing doxepin oral rinse against placebo in the relief of oral mucositis pain during radiotherapy for head and neck cancer. The doxepin mouth rinse significantly reduced patient-reported pain scores in both the initial and cross-over phases, though placebo alone also resulted in pain reduction. Most compellingly, 64% of the trial participants chose to continue use of the doxepin mouth rinse in the optional continuation phase. The authors also noted that the doxepin mouth rinse was associated with increased burning/stinging, unpleasant taste, and drowsiness, but was generally well-tolerated.[32] This study confirms that therapies to address the perception of pain, other than opioids, can be a successful strategy.

Several different approaches have targeted treatment-related weight loss directly, though randomized evidence comes from only a few small trials.[33] Nutritional support without a feeding tube had mixed results in several trials.[33]. Early enteral feeding tube placement has been advocated by some, and appeared to have some benefit in one trial.[5, 34] Enteral feeding offers an effective but less than ideal intervention of last resort for patients with severe ongoing weight loss.

tDCS pain neuromodulation

Therapies that directly modulate brain activity in specific neural networks might be particularly suited to relieve chronic pain in individuals with cancer. Ultimately, this underlies the interest in neurostimulation approaches, which are being explored at multiple levels of the neuroaxis, including the peripheral nerves, spinal cord, deep brain structures, and cortex [35]. Among the methods of central neurostimulation, two of them, repetitive transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), are particularly appealing as they can change brain activity in a non-invasive, painless and safe way. TMS is a method of brain stimulation that was developed in 1985 [36]. It is based on a time-varying magnetic field that generates an electric current inside the skull where it can be focused and restricted to small brain areas by appropriate stimulation coil geometry and size [37]. This current applied repetitively, repetitive TMS (rTMS), induces a cortical modulation that lasts beyond the time of stimulation [37]. Although tDCS has different mechanisms of action, it induces similar modulatory effects. Several animal studies in the 1960s showed that this technique changes brain activity reliably [38, 39]. tDCS is based on the application of a weak direct current to the scalp that flows between two relatively

large electrodes, the anode and cathode. The effects depend on polarity of stimulation: cathodal stimulation induces a decrease in cortical excitability, while anodal stimulation induces an increase in cortical excitability. Studies have shown that the efficacy of tDCS depends critically on parameters such as electrode position and current strength [38, 39]. In fact, application of tDCS for 13 min to the motor cortex can modulate cortical excitability for several hours [40, 41]. The most common protocol with tDCS is the M1-S0 montage for 20min. Moreover, 2mA is the most effective dose of stimulation, compared with 1mA, at the clinical and biological levels [42]. Doses are relatively confortable at 2mA, but can become less tolerable above that. The effects are also accumulative, been daily sessions for 1-2 weeks more reliable to achieve faster analgesia, which can be maintained with more sparse sessions later. Hence, our decision to have a more frequent sessions at the beginning of the trial. This approach follows other long-term studies with tDCS.

We have recently reported significant acute reductions in μ-opioid receptor (MOR) availability in pain-related regions during a single session of real tDCS in a postherpetic neuralgia patient [43]. The μ-opioid system is the most important mechanism involved in the regulation of nociceptive signals, and specific target of several opioid analgesics currently available for clinical use. The case report utilized [^{11}C]carfentanil, a selective MOR radiotracer, and the application of real tDCS was associated with significant changes in thermal pain thresholds. Those preliminary findings suggested that clinical outcomes observed with tDCS could be positively associated with activation of the MOR system, which has been similarly reported in placebo studies [44]. Furthermore, we have recently measured with MR spectroscopy that GABA, Glx, and NAA play an important role in the pathophysiology of chronic pain and its modulation by tDCS. Both the sham and active tDCS phases of a trial with fibromyalgia patients resulted in significant alterations in the brain metabolites for various pain-related structures in the brain, including the ones described in our previous PET study. In fact, baseline Glx levels in the anterior cingulate predicted response to treatment. These findings encourage further work to pursue targeted cortical therapy with tDCS for head and neck cancer induced pain, especially associated with the chemoradiotherapy.

Studies using tDCS have been performed on well over 100 patients, including healthy patients and patients with stroke [45], spinal cord injury [46], depression [47], multiple sclerosis [48], fibromyalgia [49], chronic migraines [50], and trigeminal neuropathic pain [43]. No significant adverse outcomes were seen.

The portable size, ease of application, and consistent cortical effects make tDCS a potentially powerful cancer therapy in the palliative clinical setting. One case report has demonstrated this benefit in pancreatic cancer, by relieving pain and decreasing rescue medication usage. [12] tDCS modulation has shown significant results in different types of chronic pain [51] and to be more effective in increasing pain tolerance than other forms of transcranial stimulation [52]. This may be explained by our forward analysis, which predicated significant electric current in neighboring inner cortical structures linked to chronic pain pathophysiology. This was later confirmed by our subsequent study where we applied the M1-tDCS during the neuroimaging session in multiple subjects. Our results confirm the activation of those pain-related structures, directly or indirectly, with concurrent analgesia. [43]

Lefaucheur et al [53] reviewed the literature for both rTMS and tDCS and found several studies that support the analgesic potential of this non-invasive therapy on acute, experimentally induced pain perception. [54] [55] [56] [57] [58] [59] [60] [61] It has been shown that stimulation using tDCS immediately affects the mu-opioid system [43] and that repetitive stimulation, in as few as 5 daily sessions, has significant pain improvement that then lasts for weeks after the end of treatment. [11, 62]

Previous studies have been reported that accumulative tDCS sessions are required to improve clinical outcomes. Recently, the remotely supervised tDCS (RS-tDCS) protocol was implemented to provide an extension of in-clinic tDCS sessions and to facilitate patients' compliance and retention during multiple visits [63-65]. Besides that, the RS-tDCS marks a major step in the tDCS field, mainly when lead to conditions that promote distinct deficits on the patients, such as multiple sclerosis and palliative care

patients [63-66]. Hence RS-tDCS may also be helpful to progress in clinical trials.
More recently, simultaneous tDCS/EEG evaluation of cortical mechanisms can elucidate valuable information regarding the immediate tDCS effects on the brain. Furthermore, an emerging technology has been used for brain imaging. Functional near-infrared spectroscopy (fNIRS) has become a reliable and objective tool to evaluate cortical activity of patients by measuring changes in blood oxygenation within different layers of tissue, similar to functional MRI (67, 68, 69). Interestingly, a recent study reported the use of concurrent EEG/fNIRS to clarify hemodynamic changes presenting clusters of infantile spasms. (70). Hence, in order to optimize our understanding of the central analgesic mechanisms of neuromodulation, our study will examine the human cortices responses through EEG and also fNIRS related to electrical stimulation on the brain to reduce odinophagia and pain due to mucositis. This will be performed in patients with locally advanced head and neck cancer undergoing definitive chemoradiotherapy or radiation therapy.

2. HYPOTHESES/OBJECTIVES

The goal of this randomized Phase II study is to investigate the effectiveness of tDCS as a novel pain relief modality for odynophagia due to mucositis in patients with locally advanced head and neck cancer undergoing definitive chemoradiotherapy or radiation therapy. The hypotheses and specific aims of this investigation are:

Primary Aim: To compare the effect of TDCS versus standard care on patient-reported odynophagia.
Hypothesis: tDCS will result in reduced patient-reported odynophagia at middle and final timepoints (10_{th}, and 20th sessions).

Secondary Aim 1: To compare the effect of tDCS versus standard care on weight loss during radiotherapy.
Hypothesis: tDCS will relieve odynophagia thereby improving oral intake and reducing weight loss during radiotherapy at middle and final time-points (10_{th}, and 20th sessions).

Secondary Aim 2: To compare the effect of tDCS versus standard care on narcotic pain medication requirements due to odynophagia and mucositis.
Hypothesis: tDCS will relieve odynophagia and mucositis pain thereby reducing narcotic pain medication use during radiotherapy at middle and final time-points (10_{th}, and 20th sessions).

Secondary Aim 3: To compare the effect of TDCS versus usual care on the need for feeding tube placement during radiotherapy.
Hypothesis: tDCS will relieve odynophagia thereby improving oral intake and reducing the need for feeding tube placement during radiotherapy.

Secondary Aim 4: To investigate whether tDCS neuromodulation alters the quality of odynophagia and mucositis pain during head and neck radiotherapy.
Hypothesis: tDCS will alter the quality of odynophagia and mucositis pain such that the pain is less noxious.

Secondary Aim 5: To compare the effect of tDCS on overall (unprovoked) mucositis pain compared with standard care.
Hypothesis: tDCS will reduce the intensity of unprovoked mucositis pain.

Secondary Aim 6: To compare changes in diet with tDCS during head and neck radiotherapy compared to standard care.
Hypothesis: tDCS will result in less significant diet changes.

Secondary Aim 7: To compare EEG changes with tDCS compared with standard care during head and neck radiotherapy.
Hypothesis: alpha amplitude will be significantly higher in response to active-tDCS and correlated with pain relief compared to standard care.

Secondary Aim 8: To compare fNIRS changes with tDCS compared with standard care during head and neck radiotherapy.
Hypothesis: cortical activity will be significantly higher in response to active-tDCS compared to standard care

3.0 ELIGIBILITY/EXCLUSION CRITERIA

Patient Standard of Care: Definitive treatment is usually over 7 weeks, delivering 2 Gy per day, 5 days a week, to a total of 7 weeks. Many of these patients receive concurrent chemotherapy, usually every Monday during the 7 week treatment time. Some of these patients can decrease the amount of Gy and weeks of the treatment. Patients receiving postoperative radiation therapy (RT) get 60 Gy to the high-risk tumor bed, with or without chemotherapy (chemo is delivered if positive margins or ECE). There are patients that have g-tubes placed prospectively. There is not a strict line that is used clinically, but they generally have already lost 5-10% body weight and are not eating anything.

The control group will consist of patients receiving the Standard of Care and no neuromodulation.

3.1 Eligibility criteria:

- 3.1.1 Patients with any AJCC stage head and neck malignancy scheduled for definitive chemoradiotherapy or radiation therapy, and who are capable of understanding and adhering to the protocol requirements.
- 3.1.2 Patients must be willing to comply with the study procedures and visits.
- 3.1.3 Patients aged 18-75 years old

3.2 Exclusion criteria:

- 3.2.1 Substantial dementia.
- 3.2.2 Patients are actively being treated for another cancer at the time of enrollment.
- 3.2.3 Any condition that would prevent use of tDCS including skull abnormality, implanted metal, implanted electronic device, seizure disorder, neurologic condition.
- 3.2.4 Use of an investigational drug or device within 30 days of study screening.

4.0 PRETREATMENT EVALUATION

4.1 History and Physical examination

4.1.1 Hospital Dentistry Evaluation – Performed as part of the normal protocol for these patients.

5.0 SUBJECT SCREENING, REGISTRATION PROCEDURES, AND REIMBURSEMENT
Patient registration for this trial will be centrally managed by the Headache & Orofacial Pain Effort Laboratory, Biologic & Materials Sciences, School of Dentistry.

A potential study subject who has been screened for the trial and who has signed the Informed Consent document will be initially documented by the Department of Radiation Oncology. After patient eligibility has been determined, a copy of the **completed** Eligibility Worksheet together with all the pertinent de-identified source documents will be collected and stored in the Headache & Orofacial Pain Effort Laboratory, Biologic & Materials Sciences, School of Dentistry.

The participants and/or his/her caregiver will receive, during the first week of tDCS session in-clinic, a proper training with a trained team member regarding remotely supervised tDCS using ElectraRx website (https://www.soterixmedical.com/electrarx/login) and provided with a study stimulation device and guidelines. After that, the participants will be able to do their stimulation sessions at home, if the subjects properly follow the steps to ensure correct electrode preparation and placement, low impedance and safe removal of the device.
During the remotely supervised tDCS session, the participants or his/her caregiver will have remote observation through videoconference and the ElectraRX webpage. Each remotely session the participant will fill out the steps through the ElectraRx website ahead the remotely session start and then will be provide a code that allow the participant to start the neuromodulation session. (Appendix C)

The participant will have choice to be treated either with at the clinic tDCS sessions or at home tDCS sessions via videoconference and can adjust the schedule of sessions (tDCS in clinic or RS-tDCS) at any moment during the study visits according to patient's decision.

The participants will be real-time supervised and instructed to abort the RS-tDCS session if reports significant discomfort or other adverse event, otherwise needs to discontinue a session, or if study staff determines that the session should be discontinued. In addition, the study will be made aware of the designated "stop criteria". If the stop criteria will be met at any time throughout the study, the session and/or ongoing study participation will be reviewed. (Figure 1.0)

Patients will not be compensated for their participation in the study. In cases of financial hardship and extended travel situations, funds may be available to reimburse patients for travel to visits that cannot be scheduled on days in which they have previously scheduled appointment at UMHS. The study team will determine this on a case-by-case basis.

Patients found to be ineligible for participation after being consented will be considered screen failures, and documented as such in the Screening and Enrollment Log. These patients will not have study identification number assigned to them, and will not receive study treatment.

Data Forms for Quality of Life and Toxicity Assessments will be completed once the patient has signed the consent form. When the patient is deemed eligible and enrolled, the data will be entered into the research database. In the event that the patient is deemed ineligible/screen failure, the data will not be used and the forms will be kept with the ICD in the study record.

Randomization will be conducted by the statistician as outlined in section 8.0

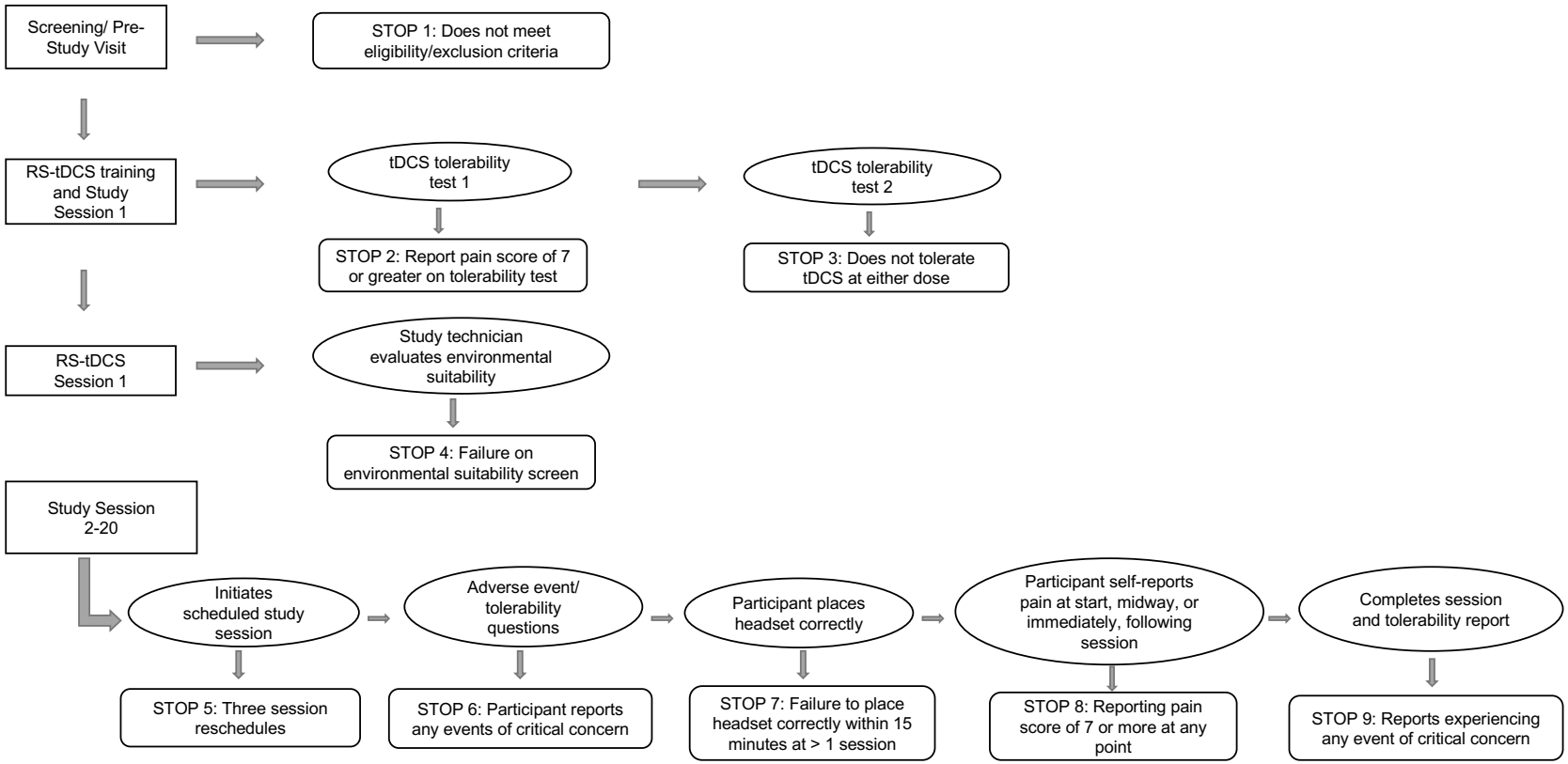

Figure 1.0 STOP CRITERIA. Transcranial direct current stimulations feasible for remotely supervised home delivery in multiple sclerosis. Adapted from: Kasschau, M.et al. Neuromodulation. 19: 824-831 (2016)

6.0 SCHEMA

Study Entry
Eligibility
↓
Pretreatment
Patient-reported odynophagia assessment
Weight measurement
Narcotic pain medication baseline assessment
Oral mucositis quality of life assessment
Diet assessment
Pain questionnaires
EEG
Hospital Dentistry Evaluation
↓
Randomization: Standard Care OR tDCS
↓
Initiation of Chemoradiotherapy/Radiation Thearpy
↓
During Chemoradiotherapy/Radiation Therapy
tDCS
- Week 2/3: daily (5x per week)
- Week 4/5: 3x per week
- Week 6/7: 2x per week

Patient-reported odynophagia assessment
Weight measurement
Narcotic pain medication assessment
Oral mucositis quality of life assessment
Diet assessment
Pain questionnaires
Nutritional assessment weekly by Cancer Center Nutrition, including feeding tube necessity assessment
EEG
fNIRS
Evaluation of oral mucositis
↓
After Chemoradiotherapy/Radiation Therapy: 1 week and 1 month follow-ups
Patient-reported odynophagia assessment
Weight measurement
Narcotic pain medication assessment
Oral mucositis quality of life assessment
Diet assessment
Pain questionnaires
Nutritional assessment weekly by Cancer Center Nutrition, including feeding tube necessity assessment
EEG

7.0 Study Design and Calendar

Patients will undergo the intervention on the day of their chemoradiotherapy/radiation therapy appointments, prior to receiving treatment when doing tDCS session in-clinic or after doing tDCS session at home. This will occur daily (5 days per week) during the second and third weeks of chemoradiotherapy/ radiation therapy, three times per week during the fourth and fifth weeks, and twice per week during the sixth and seventh week. If a stimulation appointment cannot occur on a scheduled day (i.e. extended chemotherapy, etc.) or is missed (i.e. weather, personal emergency), two stimulations will be given the day before or the following day. The first stimulation will occur in the morning and the second in the afternoon, depending on the patient's schedule.

Study Calendar

	Pre-Study	Chemoradiotherapy/Radiation Therapy Week							One week follow-up	One month post-treatment
		1	2	3	4	5	6	7		
tDCS in-clinic			Daily (M,T,W,T,F)			Last session on week		Last session on week		
Remotely supervised tDCS (at home)				Daily (M,T,W,T,F)	3 times per week	Twice per week	Twice per week	Once a week		
Patient-reported odynophagia assessment	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X
Narcotic pain medication assessment	X	X	X	X	X	X	X	X	X	X
H & N Quality of life assessment	X							X	X	X
Diet assessment	X	X	X	X	X	X	X	X	X	X
Nutritional (feeding tube) assessment	X	X	X	X	X	X	X	X	X	X
Pain Questionnaires	X	X	X	X	X	X	X	X	X	X
EEG	X		Twice (M and F)			Last session on week		Last session on week	X	X
fNIRS	X		First session			Last session a week		Last session		
Oral mucositis and quality of life assessment	X	X	X	X	X	X	X	X	X	X

Positive and Negative Affect Schedule (PANAS-X)		X	X	X	X	X	X	X	X	X

tDCS Procedure

Detailed step-by-step information of the tDCS/EEG and RS-tDCS procedure also provided in the following video-article: http://www.jove.com/video/50426/simultaneous-eeg-monitoring-during-transcranial-direct-current
https://www.jove.com/video/53542/a-protocol-for-use-remotely-supervised-transcranial-direct-current

1) **Materials:** check if all materials are available before starting the following steps:
   a) The cap has 27 holes representing EEG positions based on the 10/20 system. In our study we will use C3 or C5, depending on the location of the cancer, (motor cortex) and F4 (frontal cortex) for the tDCS stimulation.
   b) The electrodes have 2 different uses; they can be used for the EEG (six channels) and for tDCS (two channels for sponge-electrodes, the anode and the cathode).
   c) The variation of the tDCS electrodes size leads to a variation of focal effects. In this study, sponge-electrodes of 25 cm2 will be used.
   d) All the electrodes will be connected to the Control Box device through the wires. The device will be charged periodically using the Control Box Battery charger.
   e) The USB for Bluetooth connection will be needed to pair the Control Box to the laptop/computer (see below).

2) Skin Preparation
   a) We will inspect the skin for any pre-existing lesions – to avoid electrical stimulation/EEG recording over damaged skin or over skull lesions.
   b) To increase conductance, we will move hair away from the site of electrical stimulation/EEG registering and place plastic hair clips to keep hair away, clean the surface of the skin to remove any signs of lotion, dirt, grease, etc. and allow it to dry.

3) Head Measurements
   a) We will find and mark the localization of the Vertex or Cz, by measuring the distance of nasion to inion and marking halfway using a skin marker.

4) Electrodes Positioning in the Cap
   a) We will put saline solution on the tDCS sponge-electrodes. The sponge-electrodes will be soaked with saline solution before wearing the head cap. It is important to periodically refill the sponge-electrode with saline solution.
   b) The EEG and the tDCS electrodes will be fixed in the cap before the subject is physically wearing it.
   c) For further details on general tDCS electrodes preparation and positioning please check the following link: (http://www.jove.com/details.php?id=2744)

5) Wearing the Cap and Fixing the Control Box on it
   a) We will make sure the subject is seated comfortably.
   b) We will place the cap in a way that the Vertex (measured on the head) matches the Cz point on the cap.
   c) We will fill the EEG electrodes with gel using a curved syringe.
   d) We will Connect EEG and tDCS electrodes to the Control Box wires. The Control Box will be fixed to the posterior part of the cap. We use channels 1 and 2 for stimulation and the remaining ones for EEG recording. The anodal tDCS contralateral to the pain set up will be displayed: anode = M1;

cathode = Supraorbital contralateral. For this montage, connect the anode (red sponge-electrode) to the C3 or C5 and the cathode (black sponge-electrode) to F4.

e) We will put the reference electrodes to one of the mastoids making sure they do not touch one another and attached them to the wires (CMS, Common Mode Sense and DRL, Driven Right Leg) from the Control Box.

6) Stimulation and Recording Set Up

a) In order to configure parameters of stimulation and check recording, the software will be installed according to the manufacturer's instruction.
b) Press "STIMULATION" in the horizontal bar on upper screen.
c) Select the option "EDIT" in the upper screen and choose "tDCS" or "sham".
d) Choose the total duration of the electrical stimulation, in this study 20 min and at intensity of 2mA.
e) We will configure tDCS and EEG channels according to the experimental approach. The reference electrodes are labeled as DRL and CMS. Label the active stimulation electrode as "anode" or "cathode" and its reference as "return".
f) In the bar menu located in the lower part of the screen choose the duration of the ramp down and ramp up period for 30 sec. During this step we will also select the duration of pre- and post EEG recordings. The EEG recording is not dependent on the stimulation and will be programmed to start 5min before, during tDCS, and 2min after the end of the tDCS.
g) To check electrode impedance we will press "STIMULATION" in the upper part of the screen and then "MOUNT" in the left side of the screen and then "START IMPEDANCE CHECK"

7) Start the Device

a) The subject will be placed in a relaxed and comfortable position during the procedure.
b) Press "LAUNCH" in the lower part of the screen.
c) Check if the vertical gray bar is moving forward before, during and after the tDCS.
d) Re-check electrode impedances.
e) Press "Abort" to suspend the stimulation at any moment, if needed.

8) Record EEG Data

a) We will press "EEG" in the upper screen to check if the EEG signals are visible and without any artifacts. The signals will be filtered from in order to clarify the EEG traces.
b) EEG recording will start automatically as soon as the icon LAUNCH is pressed.

Assessment Measures

Patient-reported odynophagia assessment

A Visual Analog Scale (VAS) will be used to assess patient-reported odynophagia at weekly Radiation Oncology on-treatment visits (OTVs). The VAS is a traditional pain assessment tool that has been used and validated widely in both clinical and research settings, including studies of oral mucositis pain.[31,71-73] This simple tool offers a straightforward method that can be completed quickly by the patient. Baseline pain will be established at the enrollment visit, and Area Under the Curve above this baseline will be calculated from the weekly OTV assessments.

Oral Mucositis Assessment:
The WHO scale will be used for grading Oral Mucositis and including both visual and functional assessments (Table 1.0)[1]. Assessments will be made prior to treatment, weekly during treatment, one week and one month post treatment.

Grade	Description	Additional Guidance
0	none	None
1	Soreness, erythema	May include buccal scalloping with or without erytherma. Patient can swallow a solid diet.
2	Erythema, ulcers, ability to eat solid foods	Must include ulcer +/- erythema. Patient can swallow a solid diet.
3	Ulcers, requiring liquid diet	Must include ulcer +/- extensive erythema. Patient can swallow a liquid diet but not a solid diet.
4	Alimentation not possible	If total parenteral nutrition is started for reasons other than mucositis, a determination of the patient's ability to swallow must be made using the above criteria.

Adapted from: Miller, AB, Hoogstraten B, Straquet M et al, Reporting results of cancer treatment. Cancer 47: 207-214, 1981.

Weight
Patient weight will be measured regularly as an objective measure of nutritional status, and has been used in numerous head and neck radiotherapy trials, including oral mucositis mitigation trials.[4, 6, 23, 74,75] Weekly weight measurement is standard practice in the Radiation Oncology clinic, and therefore no additional infrastructure is needed to collect this data. The Area Under the Curve (AUC) of weight, using the baseline weight at the enrollment visit as baseline, will be compared between the groups.

Narcotic pain medication requirement
Narcotic pain medications are often required to relieve oral mucositis pain and odynophagia. As such, the level of narcotic pain medication required offers a somewhat objective proxy measure of the level of oral mucositis pain and odynophagia that is often used in head and neck cancer trials.[19,76-78] Narcotic pain medications will be managed by the Medical Oncology service that is blinded to the randomization assignment. At weekly on-treatment visits with Radiation Oncology, the amount of narcotic pain medicine used over the previous week will be recorded. Amounts will be converted to milligram oral morphine equivalents for comparison among various narcotic medications. If the patient has chronic narcotic use due to other conditions that preceded the head and neck cancer diagnosis, the researchers will attempt to determine the pre-cancer usual amount of narcotic pain medication. The weekly amounts of narcotic pain medications during treatment will be used to calculate the AUC, with a

baseline of zero or the pre-cancer baseline amount. The AUCs will then be compared between the two groups.

Feeding tube placement
Severe nutritional deficiency during chemoradiotherapy/radiation therapy due to severe odynophagia requires placement of a feeding tube, and therefore offers another objective measure of odynophagia that has been used in many head and neck cancer trials.[4-6, 33,77] The number of patients in each group requiring feeding tube placement will be recorded. Nutritional assessment and determination of need for feeding tube placement will be conducted by the Medical Oncology service, which is a usual part of our multidisciplinary practice. The Medical Oncology service will also be blinded to the intervention randomization.

Oral Mucositis Quality of Life
Numerous tools have been developed to assess the overall quality of life related to oral mucositis pain due to chemoradiotherapy/radiation therapy. The Oral Mucositis Weekly Questionnaire for Head and Neck Cancer (OMWQ-HN) has been validated for this purpose, and has been used in several trials.[29, 79,80] The OMWQ-HN will be administered weekly including pre-study and one month post-treatment. Individual and overall scales will be compared between the tDCS and Standard Care patient groups. Photographs may be taken at middle, end, and follow-up appointments. These photographs will be used in "adjunct" with the OMWQ-HN to examine objective and subjective pain as reported by the patient. The physician will interpret oral mucositis, as graded using the scale above, clinically, and without any use of the photographs.
A multicenter, longitudinal study to assess the validity, reliability, and feasibility of the OMWQ-HN was performed by Epstein et al 2007, and found the questionnaire to be valid, reliable, and feasible.

Diet
Severe odynophagia during chemoradiotherapy/radiation therapy prompts changes in diet that contribute to nutritional deficiency. Diet changes can be assessed quickly with simple categorization of the patients' diet, such as full/unrestricted, minimally restricted, soft, liquid, and minimal or no oral intake.[2] This simple assessment will be considered on an ordinal scale as levels of restriction and will be performed at the enrollment visit, the weekly Radiation Oncology OTVs during chemoradiotherapy/radiation therapy, and 1 month after treatment completion, as is standard practice in the Radiation Oncology clinic. The AUC will be calculated against the baseline diet level at the enrollment visit, and will be compared between the tDCS and Standard Care patient groups. A score at each follow up time point based on number of levels changed from baseline will also be analyzed. For example a patient who was at baseline only eating soft foods but during treatment was assessed as minimal or no intake will be scored -2 during treatment; at one month follow-up, if that patient is assessed fully/unrestricted their score at that time-point will be +2.

H & N Quality of Life
Numerous tools have been developed to assess the overall quality of life related to pain due to chemoradiotherapy/radiation therapy. The Head and Neck Quality of Life Weekly Questionnaire and University of Washington QOL Questionnaire have been validated for this purpose, and have been used in several trials. [53, 54] The Washington QOL is one of the most frequently reported health-related QOL questionnaires in head and neck cancer. Laraway et al 2010, published a structured review and found 19 papers discussing the development and validation of this questionnaire. [81]

The H&N QOL and UW QOL will be administered during the pre-treatment session, one week and one month post-treatment. Individual and overall scales will be compared between the tDCS and Standard Care patient groups.

EEG

EEG evaluation of cortical mechanisms can elucidate valuable information regarding the immediate tDCS effects on the brain. EEG recording will be taken at the pre-study visit, the first stimulation visit, last stimulation on first week of tDCS session, and the fifth and seventh week of treatment (both on the last session on week), as well as the follow-up appointment.

fNIRS

fNIRS is an important tool for clinical monitoring of tissue oxygenation and measurement of cortical activity, thereby appear that an advancement in brain imaging. (80) fNIRS will taken at the pre-study visit, first stimulation visit, at the fifth week of treatment and the last stimulation visit.

Pain Questionnaires

Patients will complete 3 forms regarding their current pain levels immediately before and after stimulation: the McGill Short Form, the HOPE Pain Assessment, and the GeoPain App. These forms will be used to assess patient pain both during treatments and from beginning to end of the tDCS stimulation. The McGill Short Form was shown to be valid with the following articles: Pain. 1987 Aug;30(2):191-7; The short-form McGill Pain Questionnaire. Melzack R. The HOPE Pain Assessment was shown to be valid using DaSilva AFM, Granziera C, Tuch D, Snyder J, Hadjikhani N. “Interictal Alterations of the Trigeminal Somatosensory Pathway and PAG in Migraine”. Neuroreport – March; 2007, 18: 301-305. DaSilva AFM, Granziera C, Snyder J, Hadjikhani N. “Thickening in the Somatosensory Cortex of Migraine Patients”. Neurology – Nov 20, 2007; 69(21):1990-5. Granziera C *, DaSilva AFM*, Snyder J, Tuch DS, Hadjikhani N. “Anatomical Alterations of the Visual Motion Processing Network in Migraine with and without Aura”. * Equal contribution. PLoS Medicine, 2006 Oct 17;3(10). Sceintific Abstract: DaSilva AFM, Loder E, Sorensen AG, Hadjikhani, N. Development of a Craniofacial Pain Map for use in Neuroimaging Studies, 11th International Headache Society Congress, Rome, Italy, 2003.The PainTrek App is a free and interactive mobile application developed by our laboratory (H.O.P.E.) and the 3DLab at the University of Michigan. It allows our researchers to track, display and analyze facial pain information acquired from the patients during our research protocol (www.youtube.com/watch?v=CP8tvz2nmpY). PainTrek was awarded first prize in the last University of Michigan Mobile App Challenge, and it is now available in the Apple App Store for patients to download and use for free. The app changed the name to GeoPain and can record and analyze headache and facial pain intensity, pain area, percentage dermatomes affected, descriptors ratings, signs, symptoms, and so forth. No identifying information is stored on the iPad. The participant can also fill out through the internet using Soterix platform integrated with GeoPain. All information is deidentified. DosSantos MF, Martikainen IK, Nascimento TD, Love T, DeBoer M, Maslowski E, Monteiro AA, Vincent MB, Zubieta JK, DaSilva AF. "Reduced Basal Ganglia μ-Opioid Receptor Availability in Trigeminal Neuropathic Pain: A Pilot Study". Mol Pain. 2012 Sep 24;8:74. DaSilva AF*, Nascimento TD*, Love T*, DosSantos MF, Martikainen IK, Cummiford CM, DeBoer M, Maslowski E, Smith YR, Zubieta JK, “3D-Neuronavigation In Vivo Through a Patient's Brain During a Spontaneous Migraine Headache”. JVisExp.2014 Jun 2;(88) PMID:24962460 *Equal contribution. DaSilva AF, Nascimento T, DosSantos M; Lucas S; Van Holsbeeck H, DeBoer M, Maslowski E, Love T, Martikainen I, Koeppe R, Smith Y, Zubieta, JK. “μ-Opioid activation in the prefrontal cortex in migraine attacks – brief report I." Ann of Clin and Transl Neurol. 2014 1(6): 439-444.

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In addition, patients will also complete a tDCS Side Effects assessment after each stimulation. This assessment will objectively gauge any adverse events the patient undergoes as a direct result of the stimulation. This assessment has been used multiple studies by our lab.

Positive and Negative Affect Schedule (PANAS-X)
Patient mood will be measured using the Positive and Negative Affect Schedule (Watson D, Clark LA, Tellegen A: Development and validation of brief measures of positive and negative affect: the PANAS scales. Journal of personality and social psychology 1988, 54:1063-70) (Nemanick RC, Jr., Munz DC: Measuring the poles of negative and positive mood using the Positive Affect Negative Affect Schedule and Activation Deactivation Adjective Check List. Psychological reports 1994, 74:195-9) —a scale that consists of sixty words describing different feelings and emotions to assess both positive affect (PA) and negative affect (NA). The PANAS-X scale has high reliability and validity, is strongly correlated with commonly used state affect measures and current psychiatric symptomology, and many studies indicate the scale is sensitive to short-term mood fluctuation (Watson D, Clark LA, Tellegen A: Development and validation of brief measures of positive and negative affect: the PANAS scales. Journal of personality and social psychology 1988, 54:1063-70). Patients will complete this questionnaire at week 1, to establish a baseline, before and after each stimulation session (or once a week for patients in the standard care group), and at one-week and one-month follow-up. Mood changes throughout the study and before and after each stimulation will be analyzed, in addition to comparing the results between the tDCS and Standard Care patient groups.

8.0 STATISTICAL CONSIDERATIONS

Allocation
Participants who successfully complete baseline testing are then allocated into one of the two intervention groups: active tDCS or Standard care, using a minimization scheme for age (<60 vs. >60) and gender.[82] The minimization scheme ensures balance between treatment groups over these prognostic variables.

Data analysis
Subjects who are missing more than 2 odynophagia VAS timepoints will not be included in this primary analysis. Comparison of odynophagia between the 2 treatment groups (primary aim and hypothesis) will be performed with a simple 2 sample t-test comparing the AUCs from the VAS. If necessary, a log or other transformation will be applied to the endpoints before statistical tests performed. We will perform both intent-to-treat (ITT) and per-protocol analyses, and the degree of compliance will be summarized at each study week.

Analysis for the secondary and exploratory aims will be performed in a similar manner using two sample comparisons (t-tests for continuous or chi-square for categorical variables) between the treatment groups for Oral Mucositis assessments, weight, narcotic pain medication requirements, OMWQHN, HNQOL, UW QOL, feeding tube requirement, and diet.

Treatment groups should be similar at baseline with respect to potential confounding variables due to the randomization, eligibility and exclusion criteria, therefore no covariate adjustment is planned in the analysis comparing treatment groups. Descriptive statistics will however be used to compare the 2.

Sample size justification

Over a two year period, 40 patients will be randomized into active tDCS group (n=20) or standard care group (n=20). Based on previous experience with impaired populations, we may have attrition as high as 25%, leaving 16 participants in each group for analyses of 1 month post-treatment data. With a total sample of 32 patients, and a between group standard deviation of 1.5, there is 79% power to detect a mean absolute difference of 25%. This power calculation is based on a 2-sided t-test at .05 level. Regardless of whether this trial achieves statistical significance, a larger study will be needed to confirm any findings. Such a trial will be run only if the results of the present study are sufficiently promising. The present trial will provide reasonable estimates of effect size and between subject variability to use in designing and powering a larger randomized Phase III trial.

Timeline

Sessions will occur daily for the initial two weeks, every other day the following two weeks, and two days per week during the last two weeks. Processing and analytic model development will be ongoing so that results will be available soon after completion of the study.

Criteria for Discontinuation

Patients unwilling or unable to complete more than 75% of study assessments, or who miss more than 1 session in the first two weeks. (those enrolled and unable to meet this requirement will be taken out of study and replaced).

Study strengths

This study brings together expertise in HNCa treatment with expertise in tDCCS central pain neuromodulation and assessments of participants with an active medical condition under treatment. The intervention is directed at relieving odynophagia, a major driver of anorexia, malnutrition, and QoL, in HNCa. The outcomes are commonly performed and readily analyzable.

Study limitations

Patients undergoing HNCa treatment are likely to experience fatigue due to the disease, treatment side-effects, and the numerous treatment appointments, and therefore may have difficulty complying with all study interventions and assessments.

Future plans

Findings from the pilot, including operational and effect size issues, will be used as the basis for external funding for a large randomized Phase III study.

Significance of the study

Odynophagia is a major driver of definitive chemoradiotherapy/radiation therapy morbidity in HNCa. Significant relief of odynophagia is expected to reduce narcotic pain medication requirements, which also carry significant side-effect morbidity. In the ideal setting, odynophagia relief with tDCS would improve nutritional oral intake enough to reduce weight loss and the need for feeding tube placement. Based on these effects, relief of odynophagia with tDCS would have a major impact in HNCa.

9.0 REPORTING ADVERSE EVENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. Data on adverse events will be collected from the time of the initial investigational intervention administration through the end of the study calendar. Serious Adverse Events (SAEs) will continue to be followed until resolution or clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Mild or benign adverse side effects, such as a mild headache, have been reported in a small number of patients. It has been demonstrated that no significant side effects in cognitive changes have been reported including by NIH researchers, and they can be avoided if the safety guidelines are followed ([39]). Patients will be closely monitored, and any adverse outcomes will be managed appropriately and reported immediately to the PI.

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE. The definitions of AEs and SAEs are given below. It is the responsibility of the principal investigator to ensure that all staff involved in the trial is familiar with the content of this section.

Any medical condition or laboratory abnormality with an onset date before intervention administration is considered to be pre-existing in nature. Any known pre-existing conditions that are ongoing at time of study entry should be considered medical history.

All adverse events occurring from the initial investigational intervention administration through the end of the study calendar must be recorded as an adverse event in the patient's source documents regardless of frequency, severity (grade) or assessed relationship to the investigational intervention. In addition to new events, any increase in the frequency or severity (i.e., toxicity grade) of a pre-existing condition that occurs after the patient begins the investigational intervention is also considered an adverse event.

All adverse events specified in the Case Report Form Completion Guidelines will be recorded in the study database (Microsoft Excel).

9.1 Definitions

Adverse event

Adverse event means any untoward medical occurrence associated with the use of a medical treatment or procedure regardless of whether or not considered related to the medical treatment or procedure. An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the medical treatment or procedure, without any judgment about causality.

Unexpected

An adverse event is considered "unexpected" if specificity or severity that has been observed is not described in the protocol, informed consent document or published medical literature.

Serious Adverse Event
An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor (UNIVERSITY OF MICHIGAN), it results in any of the following outcomes:

- o Death
- o A life-threatening adverse event
- o Inpatient hospitalization or prolongation of existing hospitalization
- o A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- o A congenital anomaly/birth defect.
- o Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Previously planned (prior to signing the informed consent form) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study. Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. 14
Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs. However, if the preexisting condition worsened during the course of the study, it should be reported as an SAE.

Life-threatening
An adverse event is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

9.2 Adverse Event Characteristics

CTCAE term
Adverse events [83] will use the descriptions and grading scales found in the revised National Cancer Institute [12] Common Toxicity Criteria for Adverse Events (CTCAE). A copy of the CTCAE version 3.0 can be downloaded from the CTEP home page: http://ctep.info.nih.gov/reporting/ctc.html

Attribution of the AE
The investigator is responsible for assignment of attribution.

Definite – The AE is clearly related to the investigational intervention.
Probable – The AE is likely related to the investigational -intervention.
Possible – The AE may be related to the investigational -intervention.
Unlikely – The AE is doubtfully related to the investigational -intervention.
Unrelated – The AE is clearly NOT related to the investigational -intervention.

9.3 Reporting Procedures

Serious adverse Events (SAEs) that are unexpected and definitely, probably or possibly related to protocol therapy should be reported to the Principal Investigator within 48 hours of awareness of the event.

Principal Investigator: Alexandre DaSilva, DDS, DMedSc
Phone: 734-763-5280
Fax: 734-647-4130
E-mail: adasilva@umich.edu

Follow-up information must also be reported within 48 hours of receipt of the information.
SAEs and/or unanticipated problems will also be reported concurrently to the IRBMED within 48 hours of awareness of the event.

9.3.1 Exceptions to SAE Reporting

The following adverse events are excluded from SAE reporting:

- Hospitalization secondary to expected cancer morbidity
- Admission for palliative care or pain management
- Planned hospitalizations for surgical procedures either related or unrelated to the patient's cancer.

10.0 STUDY MONITORING

10.1 Data and Safety Monitoring Procedures

The principal investigator, co-investigator(s), data manager and study coordinator and other members of the study staff involved in the conduct of the trial will hold quarterly meetings to discuss matters related to:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (Serious Adverse Event & Adverse Event reporting)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

These meetings are to be documented by the data manager or study coordinator using the Protocol Specific Data and Safety Monitoring Report (DSMR), signed by the site principal investigator or co-investigator, and submitted quarterly to the Rogel Cancer Center Data and Safety Monitoring Committee.

Similarly, protocol deviations are to be documented using the Notice of Protocol Deviation Form and requires the signatures of both the data manager or study coordinator and the principal investigator or co-investigator. These reports will be collected by the Headache & Orofacial Pain Effort Laboratory, Biologic and Materials Sciences, School of Dentistry, and on a quarterly basis with a Protocol Specific Data and Safety Monitoring Report. The Headache & Orofacial Pain Effort Laboratory, Biologic and Materials Sciences, School of Dentistry will provide the Data and Safety Monitoring Reports to the Data Safety Monitoring Committee.

10.2 Clinical Monitoring Procedures

Clinical studies coordinated by The University of Michigan Rogel Cancer Center must be conducted in accordance with the ethical principles that are consistent with Good Clinical Practices (GCP) and in compliance with other applicable regulatory requirements.

Additionally, patients receiving tDCS will fill out a "tDCS Side Effects" Questionnaire after each session they received the treatment, including on remotely supervised tDCS session. This data will be used to assess patient safety and any adverse events per the patient. This questionnaire was developed by a neuromodulation group at Harvard University and used by several other centers. Our team has conducted several tDCS trials, most of them combined with neuroimaging, including fibromyalgia, migraine, neuropathic pain, and temporomandibular disorders. We've had no report of significant side effects or incidents with any of our patients and healthy controls. However, in case of any incident, we will report it to IRB immediately.

10.3 Data Monitoring and Confidentiality

Subjects will provide information in a secluded area. This information will then be kept in confidential locked offices, including cabinet or storage units and secured laptops, within the Molecular and Behavioral Neuroscience Institute. Data will not be provided to a repository. Individual identifiable sensitive data will no be accessed, collected, used, maintained, or disclosed in this study.

No information will be generated that, if revealed, will place the subjects at risk of personal safety, liability, employability, or reputation.

At the conclusion of the study, the data will be retained at the MBNI for record keeping purposes. They will be retained for at least 2 years in locked cabinets in a locked office or storage room. These areas will only be accessible by study team members, who frequently monitor.

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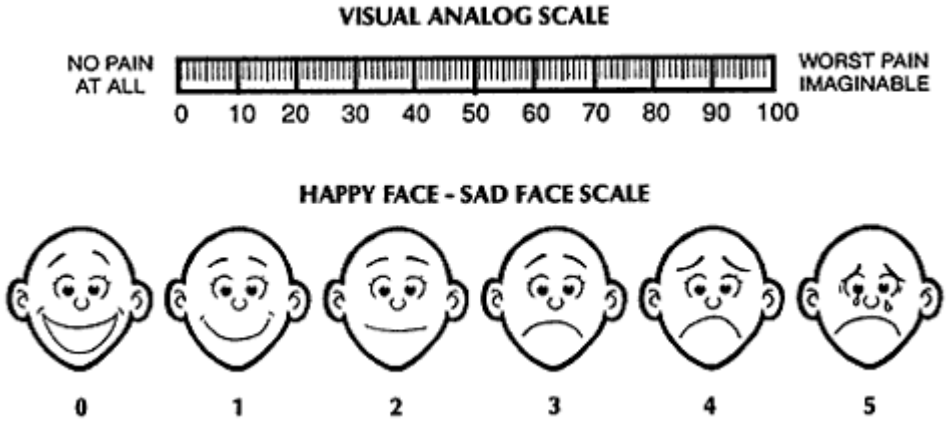
12.0 APPENDICES

Appendix A: Visual Analog Scale



Source: hospiceworld.org

Appendix B: Questionnaires

Oral Mucositis Weekly Questionnaire for Head and Neck cancer (OMWQ-HN)

HUM00078942

Patient ID: _____

Week: _____

Date: _____

Oral Mucositis Weekly Questionnaire

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. ALL of the questions are regarding your health over the *PAST WEEK*.

1. How would you rate your overall physical condition during the *past week*?

   1 2 3 4 5 6 7

   Very Poor Excellent

2. How would you rate your overall quality of life during the *past week*?

   1 2 3 4 5 6 7

   Very Poor Excellent

3. How much MOUTH AND THROAT SORENESS did you experience in the *past week*?

   0 1 2 3 4 5

   No Soreness Extreme Soreness

If you answers "0" for question 3, you may stop the questionnaire now. If you marked >0 (1-5), please continue the questionnaire:

4. How much did MOUTH AND THROAT SORENESS limit you in each of the following activities during the *past week*?
   A. Sleeping
      0 1 2 3 4 5
      Not Limited Unable to do
   B. Swallowing
      0 1 2 3 4 5
      Not Limited Unable to do
   C. Drinking
      0 1 2 3 4 5
      Not Limited Unable to do
   D. Eating
      0 1 2 3 4 5
      Not Limited Unable to do
   E. Talking
      0 1 2 3 4 5
      Not Limited Unable to do
   F. Brushing your teeth
      0 1 2 3 4 5
      Not Limited Unable to do

5. On a scale from 0-10, how would you rate your OVERAL MOUTH AND THROAT SORENESS during the *past week*?

0	1	2	3	4	5	6	7	8	9	10
no pain or soreness										**the worst pain or soreness imaginable or possible**

6. On a scale from 0-10, what number best describes the MOUTH PAIN that you have experienced in the *past week*?

0	1	2	3	4	5	6	7	8	9	10
no pain or soreness										**the worst pain or soreness imaginable or possible**

7. On a scale from 0-10, what number best describes the THROAT PAIN that you have experienced in the *past week*?

0	1	2	3	4	5	6	7	8	9	10
no pain or soreness										**the worst pain or soreness imaginable or possible**

University of Washington Quality of Life Questionnaire (UW-QoL)

Study #_____
Initials_____
Date of questionnaire_____

Each of the following items lists different numbered statements. Think about what each statement says, then place a circle around the one statement that most closely describes how you have been feeling during the ***past*** week, including today. Please circle only ***one*** statement for each item.

I. PAIN (General)

A. General
10 I have no pain.
20 There is mild pain not needing medication.
30 I have moderate pain--requires regular medication (codeine or non-narcotic).
40 I have severe pain controlled only by narcotics.
50 I have severe pain not controlled by narcotics.

B. Mouth
10 I have no pain in my mouth.
20 I have mild pain but it is not affecting my eating.
30 I have moderate pain which is affecting my eating.
40 I have severe pain and need medication in order to eat.
50 I have severe pain and cannot eat even with the medication.

C. Throat
10 I have no pain in my throat.
20 I have mild pain but it is not affecting my eating.
30 I have moderate pain which is affecting my eating.
40 I have severe pain and need medication in order to eat.
50 I have severe pain and cannot eat even with the medication.

II. DISFIGUREMENT

10 There is no change in my appearance.
20 The change in my appearance is minor.
30 My appearance bothers me but I remain active.
40 I feel significantly disfigured and limit my activities due to my appearance.
50 I cannot be with people due to my appearance.

III. ACTIVITY

10 I am as active as I have ever been.
20 There are times when I can't keep up with my old pace, but not often.
30 I am often tired and I have slowed down my activities although I still get out.
40 I don't go out because I don't have the strength.

50 I am usually in a bed or chair and don't leave home.

IV. RECREATION/ENTERTAINMENT

10 There are no limitations to recreation at home and away from home.
20 There are a few things I can't do but I still get out and enjoy life.
30 There are many times when I wish I could get out more but I'm not up to it.
40 There are severe limitations to what I can do, mostly I stay home and watch T.V.
50 I can't do anything enjoyable.

V. EMPLOYMENT

10 I work full time.
20 I have a part time but permanent job.
30 I only have occasional employment.
40 I am unemployed.
50 I am retired (circle one below)
51 not related to cancer treatment
52 due to cancer treatment

VI. EATING

A. Chewing
10 I can chew as well as ever.
20 I have slight difficulty chewing solid foods.
30 I have moderate difficulty chewing solid foods.
40 I can only chew soft foods.
50 I cannot chew soft foods.

B. Swallowing
10 I swallow normally
20 I cannot swallow certain solid foods.
30 I can only swallow soft foods.
40 I can only swallow liquid foods.
50 I cannot swallow.

VII. SALIVA

A. Amount
10 I have a normal amount of saliva
20 I have a mild loss of saliva
30 I have a moderate loss of saliva.
40 I have a severe loss of saliva.
50 I have no saliva.

B. Consistency

10 My saliva has normal consistency.
20 My saliva is slightly thicker.
30 My saliva is moderately thicker.
40 My saliva is extremely thicker.
50 I have saliva that dries in my mouth and/or on my lips.

VIII. TASTE

10 I can taste food normally.
20 I can taste most foods normally.
30 I can taste some foods normally.
40 I can taste few foods normally.
50 I cannot taste any foods normally.

IX. SPEECH

10 My speech is the same as always.
20 I have difficulty with saying some words, but can be understood over the phone.
30 I have moderate difficulty saying some words, and cannot use the phone.
40 Only family and/or friends can understand me.
50 I cannot be understood.

X. MUCUS OR PHLEGM

A. Amount

10 I have a normal amount of mucus.
20 I have a mild amount of mucus
30 I have a moderate amount of mucus.
40 I have a severe amount of mucus.
50 I have no mucus.

B. Consistency

10 My mucus has normal consistency
20 My mucus is slightly thicker
30 My mucus is moderately thicker
40 My mucus is extremely thicker
50 I have no mucus

Comments:_____
_____

Patient Name _____ Reg No. _____
Hospital _____

Date of Questionnaire _____

Below are several questions that will help describe the dryness in your mouth and how that dryness affects your daily life. Please encircle the number that corresponds to your condition during the last week in each of the following questions:

1. Rate the discomfort of our dentures due to dryness (if you do not wear dentures please check _____)

0 1 2 3 4 5 6 7 8 9 10
Comfortable Extreme discomfort

2. Rate the difficulty you experience in speaking due to dryness of your mouth and tongue:

0 1 2 3 4 5 6 7 8 9 10
Easy Extremely Difficult

3. Rate the difficulty you experience in chewing food due to dryness:

0 1 2 3 4 5 6 7 8 9 10
Easy Extremely Difficult

4. Rate the difficulty you experience in swallowing food due to dryness:

0 1 2 3 4 5 6 7 8 9 10
Easy Extremely Difficult

5. Rate the dryness your mouth feels when eating a meal:

0 1 2 3 4 5 6 7 8 9 10
No Dryness Extremely Dryness

6. Rate the dryness in your mouth while not eating or chewing:

0 1 2 3 4 5 6 7 8 9 10
No Dryness Extremely Dryness

7. Rate the frequency of sipping liquids to aid in swallowing food:

0 1 2 3 4 5 6 7 8 9 10

None required Extremely Frequent

8. Rate the frequency of fluid intake required for oral comfort when not eating:

0 1 2 3 4 5 6 7 8 9 10

None required Extremely Frequent

9. Rate the frequency of sleeping problems due to dryness:

0 1 2 3 4 5 6 7 8 9 10

None Extremely Frequent

10. Does your mouth feel dry when eating a meal? Yes / No

11. Are you thirsty? Yes / No

12. Does the amount of saliva in your mouth seem to be:

_____ Too little
_____ Too much
_____ Don't notice it

13. Do you have difficulties swallowing any food? Yes / No

14. Do you sip liquids to aid in swallowing dry food? Yes / No

15. Have you smoked in the last week? Yes / No

If yes, how many packs? _____

16. Do you drink alcohol more than twice a week? Yes / No

17. Do you have any medical problem/disease for which you take medication? Yes /No

Which pills/medication do you take?

_____
_____
_____
_____

Head and Neck Quality of Life Questionnaire

INSTRUCTIONS: This survey is designed to assess how much you are bothered by your Head and Neck condition and/or treatment. Please answer every question by marking one box. If you are unsure about how to answer, please give the best answer you can.

1. As a result of your head and neck condition or treatment, over the past FOUR WEEKS how much have you been BOTHERED by your…

	Not at all	Slightly	Moderately	A lot	Extremely
A. Ability to talk to other people	☐	☐	☐		☐
B. Ability to talk on the phone	☐	☐	☐		☐

2. As a result of your head and neck condition or treatment, over the past FOUR WEEKS how much have you been BOTHERED by problems with…

	Not at all	Slightly	Moderately	A lot	Extremely
A. Volume of your voice	☐	☐	☐		☐
B. Clarity of your voice	☐	☐	☐		☐
C. Difficulty opening your mouth	☐	☐	☐		☐
D. Dryness in your mouth while eating	☐	☐	☐		☐

2 (continued). As a result of your head and neck condition or treatment, over the past FOUR WEEKS how much have you been BOTHERED by problems with…

	Not at all	Slightly	Moderately	A lot	Extremely
E. Chewing food (for example, pain, difficulty opening or closing your mouth moving food in your mouth, or teeth or denture problems)	☐	☐	☐		☐
F. Swallowing liquids	☐	☐	☐		☐
G. Swallowing soft foods and/or solids	☐	☐	☐		☐
H. Your ability to taste food (For example, loss of taste, and/or loss of appetite due to poor taste)	☐	☐	☐		☐
I. Pain, burning, and/or discomfort in your mouth, jaw, or throat	☐	☐	☐		☐
J. Shoulder or neck pain	☐	☐	☐		☐

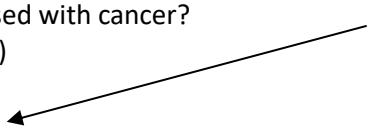
3. Over the past FOUR WEEKS, how often did you take pain medication?...

Never	Rarely	Sometimes	Frequently	Always
☐	☐	☐	☐	☐

4. Over the past FOUR WEEKS how much have you been bothered by…

	Not at all	Slightly	Moderately	A lot	Extremely
A. Concerns or worries about Your appearance related to your head and neck condition or treatment	☐	☐	☐	☐	☐
B. Emotional problems related to your head and neck condition or treatment	☐	☐	☐	☐	☐
C. Embarrassment about your symptoms	☐	☐	☐	☐	☐
D. Frustration about your condition	☐	☐	☐	☐	☐
E. Financial worries due to medical problems	☐	☐	☐	☐	☐
F. Worries that your condition will get worse	☐	☐	☐	☐	☐
G. Physical problems related to your head and neck condition	☐	☐	☐	☐	☐

5. Were you working (employed) prior to being diagnosed with cancer? Yes ☐ No ☐ If no, got to question 6 (next page) _____



5A. If yes, did your doctor declare you unable to work due to your head and neck condition or treatment? Yes ☐ No ☐

6. Have there been other problems related to your head and neck condition that were not mentioned? If so, please write them in the space below and tell us how much this problem has bothered you. (For instance, if your treatment included surgical transfer of tissue from a donor site to the head and neck, does the donor site bother you)

	Not at all	Slightly	Moderately	A lot	Extremely
A. _____	☐	☐	☐	☐	☐
B. _____	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐

C. _____

7. For the past FOUR WEEKS, please rate your OVERALL amount of disturbance or BOTHER as a result of your head And neck cancer condition? ☐ ☐ ☐ ☐

8. Overall how satisfied are you with your Head and Neck cancer care at this Hospital? ☐ ☐ ☐ ☐

9. Overall how would you rate your response to treatment?

Poor	Fair	Good	Very Good	Excellent
☐	☐	☐	☐	☐

---

10. Approximately how long did it take you to answer this questionnaire?
_____ Minutes

	Not at all	Slightly	Moderately	A lot	Extremely
11.How difficult was it to complete this questionnaire?	☐	☐	☐	☐	☐

tDCS Side Effects Questionnaire – Session_____

Patient Initials: Date:

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):			

SHORT-FORM McGILL PAIN QUESTIONNAIRE

RONALD MELZACK

PATIENT'S NAME: _____ **DATE:** _____

	NONE	MILD	MODERATE	SEVERE
THROBBING	0) _____	1) _____	2) _____	3) _____
SHOOTING	0) _____	1) _____	2) _____	3) _____
STABBING	0) _____	1) _____	2) _____	3) _____
SHARP	0) _____	1) _____	2) _____	3) _____
CRAMPING	0) _____	1) _____	2) _____	3) _____
GNAWING	0) _____	1) _____	2) _____	3) _____
HOT-BURNING	0) _____	1) _____	2) _____	3) _____
ACHING	0) _____	1) _____	2) _____	3) _____
HEAVY	0) _____	1) _____	2) _____	3) _____
TENDER	0) _____	1) _____	2) _____	3) _____
SPLITTING	0) _____	1) _____	2) _____	3) _____
TIRING-EXHAUSTING	0) _____	1) _____	2) _____	3) _____
SICKENING	0) _____	1) _____	2) _____	3) _____
FEARFUL	0) _____	1) _____	2) _____	3) _____
PUNISHING-CRUEL	0) _____	1) _____	2) _____	3) _____

NO PAIN |——————————————————————| WORST POSSIBLE PAIN

P P I

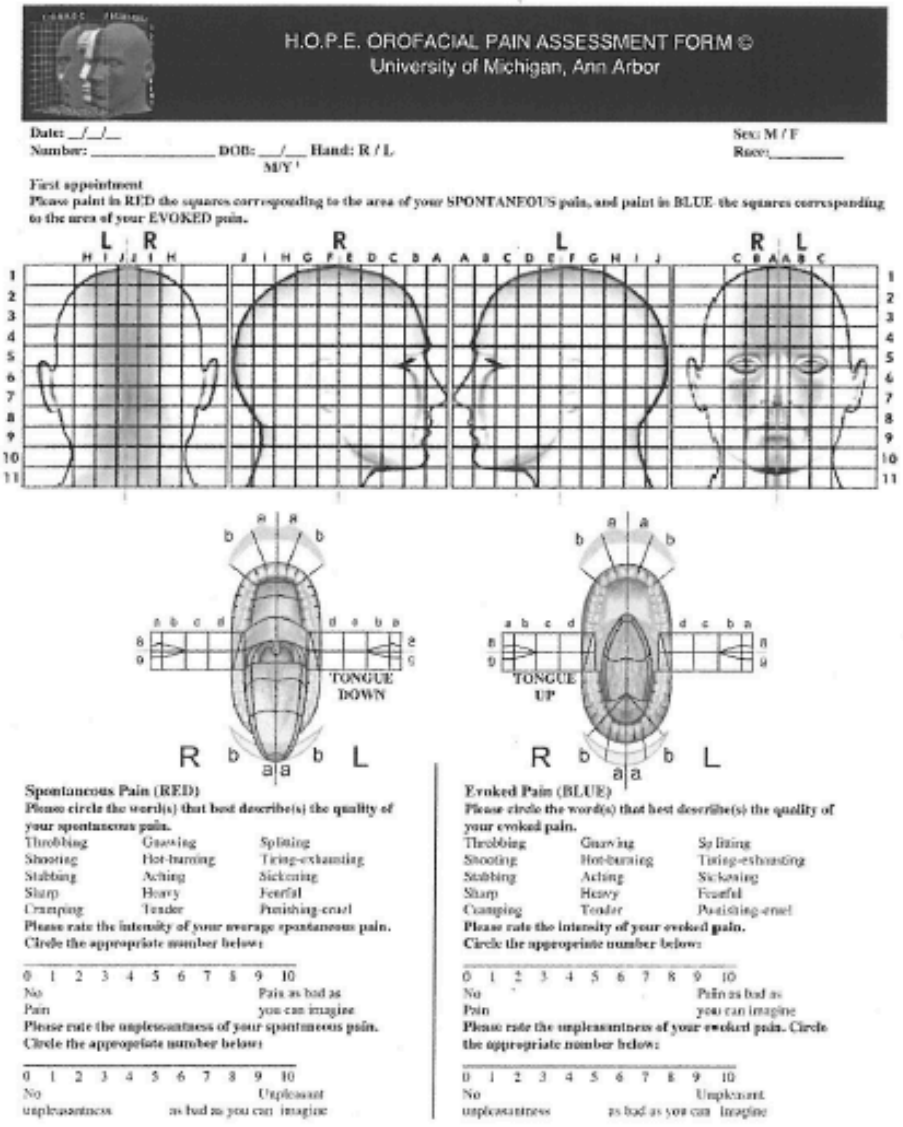
0	NO PAIN	_____
1	MILD	_____
2	DISCOMFORTING	_____
3	DISTRESSING	_____
4	HORRIBLE	_____
5	EXCRUCIATING	_____

HOPE Pain Assessment Form

Subject ID _____ Raters Initials_____

Time _____ Date_____

H.O.P.E questionnaire



H.O.P.E. OROFACIAL PAIN ASSESSMENT FORM ©
University of Michigan, Ann Arbor

Date: __/__/__ Sex: M / F
Number: _____ DOB: __/__ Hand: R / L Race:_____
M/Y

First appointment
Please paint in RED the squares corresponding to the area of your SPONTANEOUS pain, and paint in BLUE the squares corresponding to the area of your EVOKED pain.

TONGUE DOWN

TONGUE UP

Spontaneous Pain (RED)
Please circle the word(s) that best describe(s) the quality of your spontaneous pain.

Throbbing	Gnawing	Splitting
Shooting	Hot-burning	Tiring-exhausting
Stabbing	Aching	Sickening
Sharp	Heavy	Fearful
Cramping	Tender	Punishing-cruel

Please rate the intensity of your average spontaneous pain.
Circle the appropriate number below:

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

Please rate the unpleasantness of your spontaneous pain.
Circle the appropriate number below:

0 1 2 3 4 5 6 7 8 9 10
No unpleasantness — Unpleasant as bad as you can imagine

Evoked Pain (BLUE)
Please circle the word(s) that best describe(s) the quality of your evoked pain.

Throbbing	Gnawing	Splitting
Shooting	Hot-burning	Tiring-exhausting
Stabbing	Aching	Sickening
Sharp	Heavy	Fearful
Cramping	Tender	Punishing-cruel

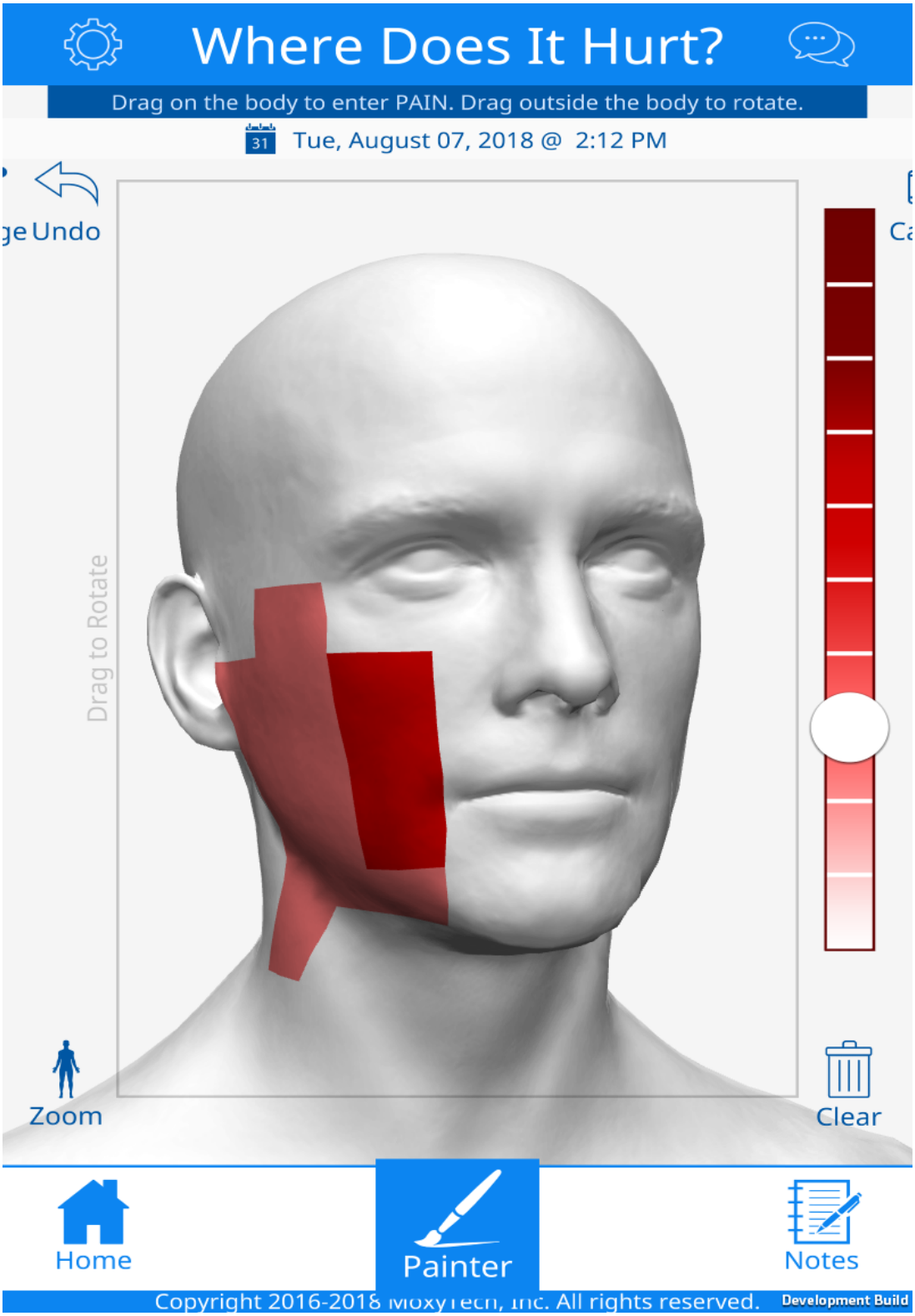
Please rate the intensity of your evoked pain.
Circle the appropriate number below:

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

Please rate the unpleasantness of your evoked pain. Circle the appropriate number below:

0 1 2 3 4 5 6 7 8 9 10
No unpleasantness — Unpleasant as bad as you can imagine

GeoPain App on iPad



Subject ID: _____

Date: _____

Positive and Negative Affect Schedule (PANAS-X)

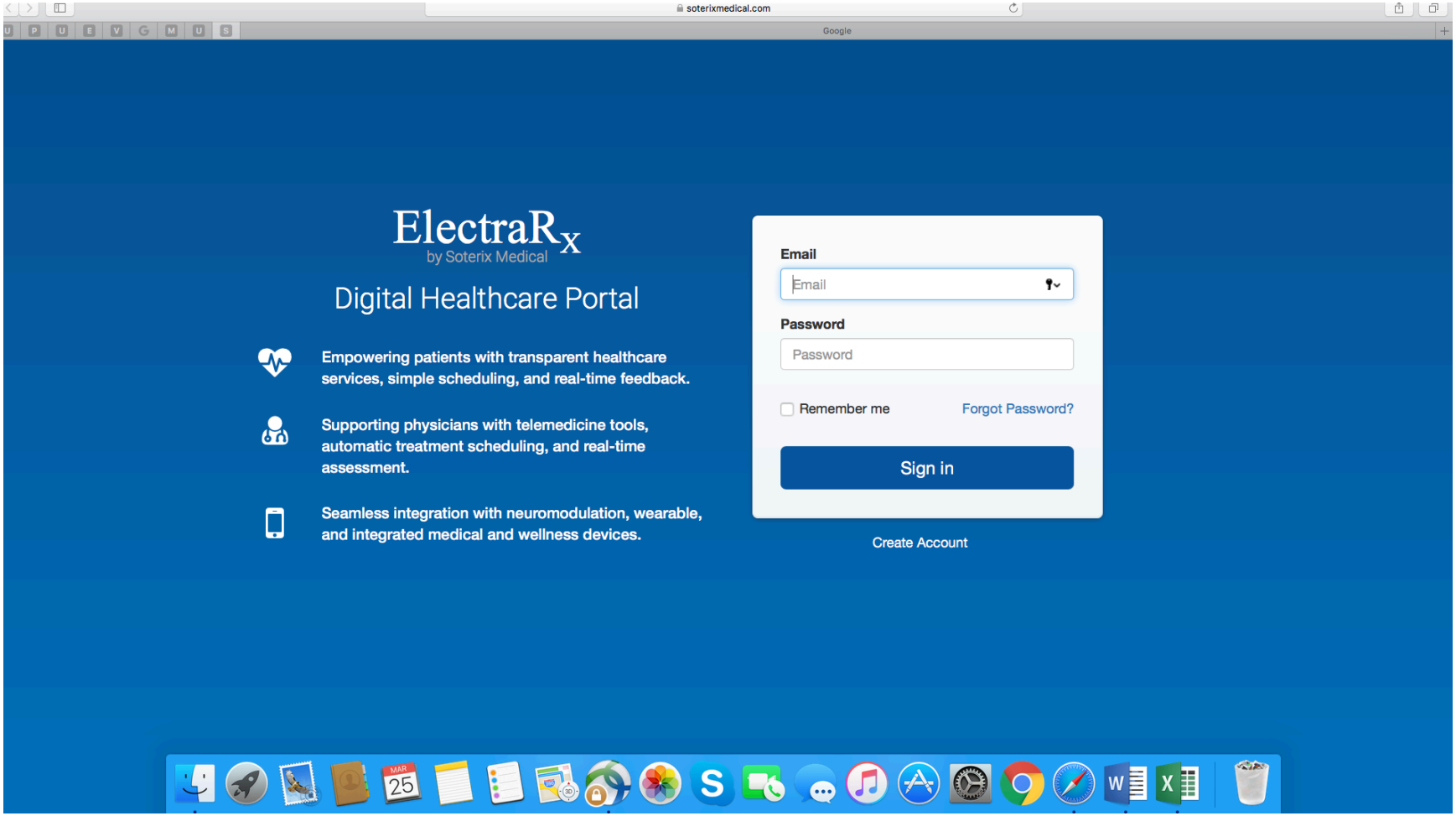
This scale consists of a number of words and phrases that describe different feelings and emotions. Read each item and then mark the appropriate answer in the space next to that word. Indicate to what extent you feel this way AT THIS MOMENT. Use the following scale to record your answers.

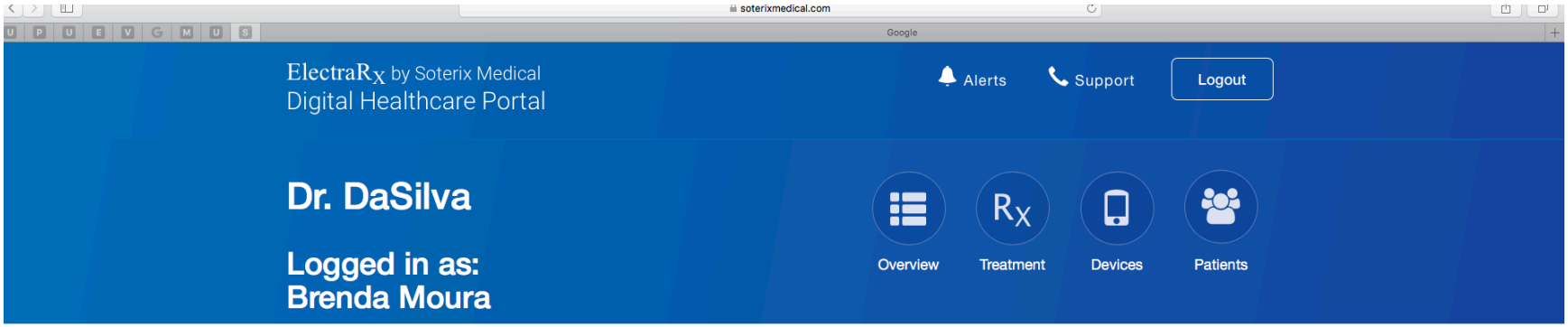
1	**2**	**3**	**4**	**5**
Very slightly/not at all	**A little**	**Moderately**	**Quite a bit**	**Extremely**

1. _____cheerful	16. _____sad	31. _____active	46. _____angry at self
2. _____disgusted	17. _____calm	32. _____guilty	47. _____enthusiastic
3. _____attentive	18. _____afraid	33. _____joyful	48. _____downhearted
4. _____bashful	19. _____tired	34. _____nervous	49. _____sheepish
5. _____sluggish	20. _____amazed	35. _____lonely	50. _____distressed
6. _____daring	21. _____shaky	36. _____sleepy	51. _____blameworthy
7. _____surprised	22. _____happy	37. _____excited	52. _____determined
8. _____strong	23. _____timid	38. _____hostile	53. _____frightened
9. _____scornful	24. _____alone	39. _____proud	54. _____astonished
10. _____relaxed	25. _____alert	40. _____jittery	55. _____interested
11. _____irritable	26. _____upset	41. _____lively	56. _____loathing
12. _____delighted	27. _____angry	42. _____ashamed	57. _____confident
13. _____inspired	28. _____bold	43. _____at ease	58. _____energetic
14. _____fearless	29. _____blue	44. _____scared	59. _____concentrating
15. _____disgusted with self	30. _____shy	45. _____drowsy	60. _____dissatisfied with self

Watson, D., & Clark, L. A. (1994). *The PANAS-X: Manual for the Positive and Negative Affect Schedule-Expanded Form.* Ames: The University of Iowa.

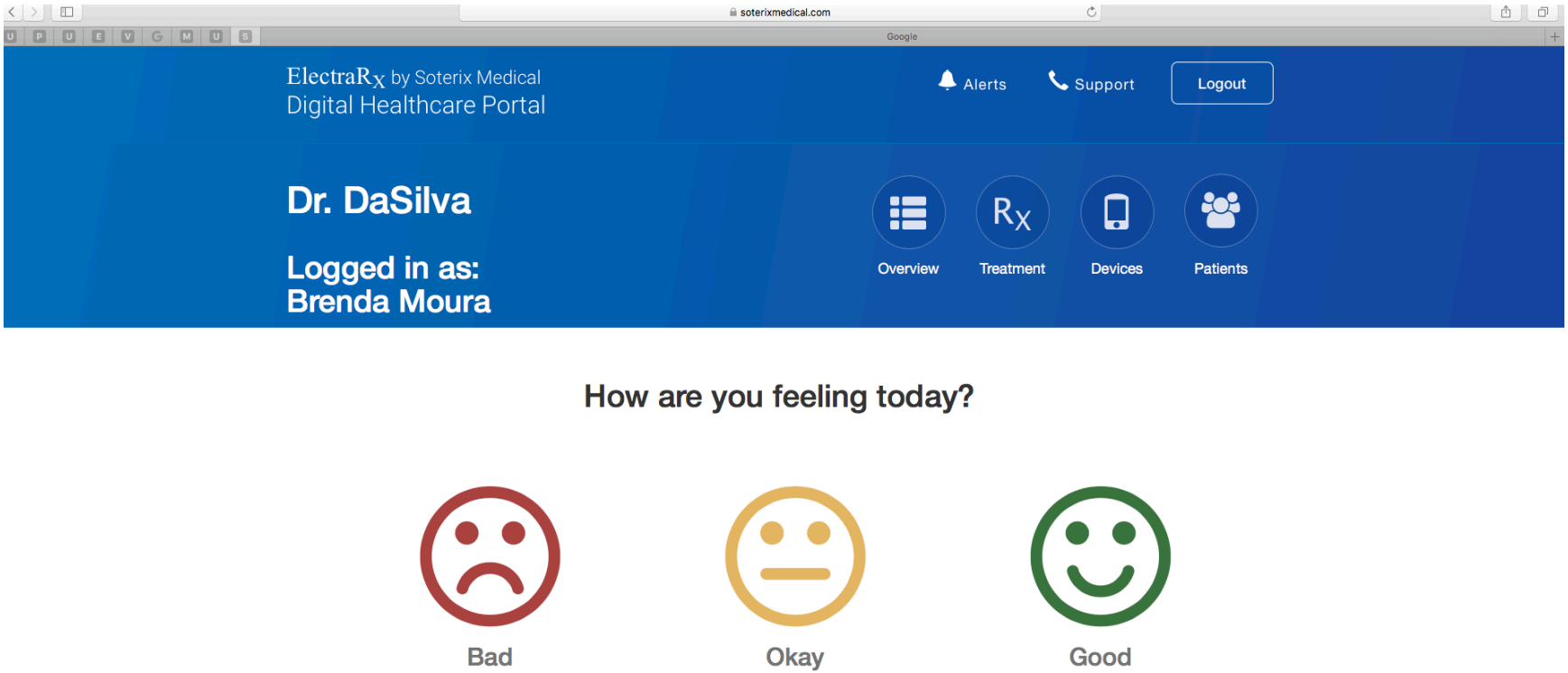
Appendix C: Screenshot Remotely tDCS website set-up

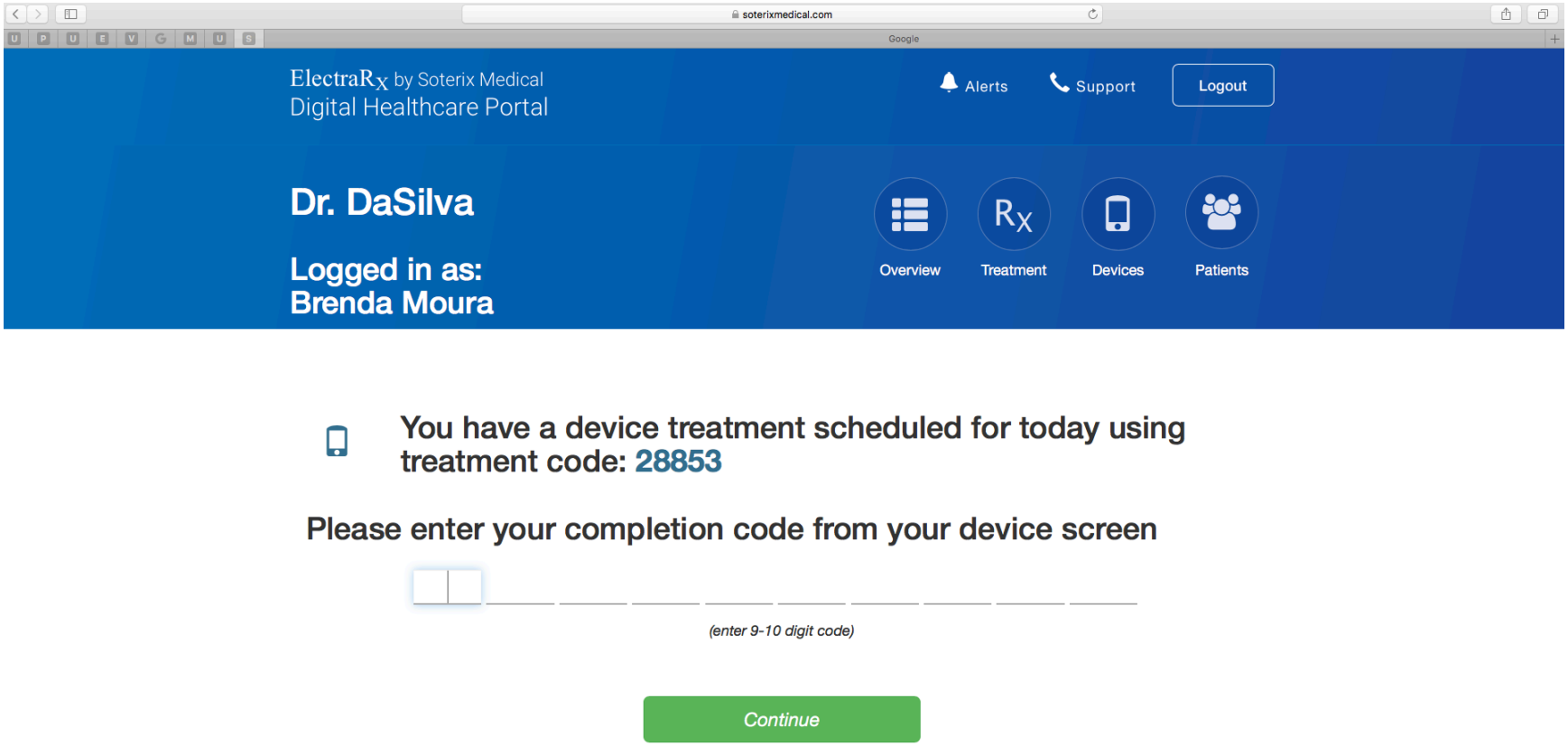




Hello Brenda, Dr. DaSilva at University of Michigan School of Dentistry has prescribed you
CanPain week 3

Continue


soterixmedical.com
Google
ElectraRx by Soterix Medical
Digital Healthcare Portal
Alerts
Support
Logout
Dr. DaSilva
Logged in as:
Brenda Moura
Overview
Treatment
Devices
Patients
How are you feeling today?
Bad
Okay
Good


soterixmedical.com
Google
ElectraRx by Soterix Medical
Digital Healthcare Portal
Alerts
Support
Logout
Dr. DaSilva
Logged in as:
Brenda Moura
Overview
Treatment
Devices
Patients
You have a device treatment scheduled for today using treatment code: 28853
Please enter your completion code from your device screen
(enter 9-10 digit code)
Continue