Transcutaneous Electrical Nerve Stimulation (TENS) Therapy for Neuropathic Pain in NMOSD

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1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a chronic relapsing autoimmune disease of the central nervous system (CNS) that preferentially targets the optic nerves and spinal cord, leading to paralysis, blindness and death. NMOSD is a rare disease that affects approximately 4,000-8,000 (1-2:100,000 persons in the US) people in the United States, disproportionately affects non-Caucasians and females, and has a worldwide prevalence estimated to be 0.52 to 4.4/100,000. Pain is a severely disabling component of the disease with up to 91% of patients reporting central neuropathic pain (CNP) characterized by agonizing burning, shooting or tingling sensation in the face, arms, torso and legs. NMOSD lesions in the spinal cord are characteristically long and destructive, and pain is more prevalent in NMOSD than in most other neurological diseases. Research on the impact of persistent pain on quality of life (QoL) in NMOSD has found that those patients with CNP experience more depression, less enjoyment of life, and more difficulty with ambulation. Currently, there is no standard of care for CNP treatment and off-label use of medications typically used for diabetic peripheral neuropathy are often insufficient. NMOSD is a devastating disease and there remains a high unmet need for effective treatment of CNP.

Transcutaneous electrical nerve stimulation (TENS) therapy is a non-invasive pain modifying intervention that utilizes transcutaneous electrical stimulation of ascending (sensory) fibers with the intent of re-organizing maladaptive signaling pathways. This neuromodulatory therapy has been investigated for treatment of persistent peripheral neuropathic pain in several conditions including chemotherapy-induced neuropathy, post-herpetic neuralgia and post-surgical neuropathic pain with promising results. Patients report sustained relief after undergoing daily treatment sessions for 10 consecutive weekdays.

Recently we completed a sham-controlled trial using a TENS unit called Scrambler in NMOSD patients showing a meaningful reduction in neuropathic pain compared to controls. The Scrambler device must be operated in an office by a professional technician, thereby limiting its usefulness to the wider NMOSD population. The Quell transcutaneous electrical nerve stimulation device delivers varying electric pulses non-invasively to reduce pain. It is a small, wearable device that utilizes regularly-changing electric pulses to stimulate nerves such that the experience of pain is blocked. Because the Quell Flex is programmable remotely, a sham-controlled trial can be conducted while keeping the patient blinded to the trial arm.

For patients with NMOSD and other conditions that cause pain originating in the central nervous system, non-obtrusive, non-pharmacological devices might prove a viable alternative to pain medications. Pharmaceutical treatments for pain such as opioids have led to addiction and life-style changes with unacceptable side effects. Cost and side effects are concerns with other pharmacologic therapies for pain. In addition, in efforts to control pain, many patients are prescribed multiple medications, and then have to cope with the complexities and hazards of polypharmacy. Most importantly, none of the pharmaceutical treatments for pain in NMOSD have been proven effective in a trial.

If we could show among a significant patient cohort that a safe and effective at-home nonpharmacological pain therapy is available for patients with NMOSD, it would be life altering for a great many – not only those with NMOSD, but also with related neuroimmune disorders and other conditions with central neuropathic pain.

The goal of this project is to provide an effective, non-invasive treatment for neuropathic pain in NMOSD that can be safely employed at home. Many NMOSD patients have such chronic pain and/or disability that frequent visits to the clinic for therapy is difficult, if not impossible, in the best of times. Secondly, safe at-home treatments that offer continuous relief of pain (and potentially other co-occurring symptoms) can improve quality of life immensely during this, and likely future times of social distancing, when leaving home is dangerous, especially for a population on lifelong immune suppressants. Also, an at-home therapeutic option will save both time and money for patients.

2. Trial Scheme and Objectives

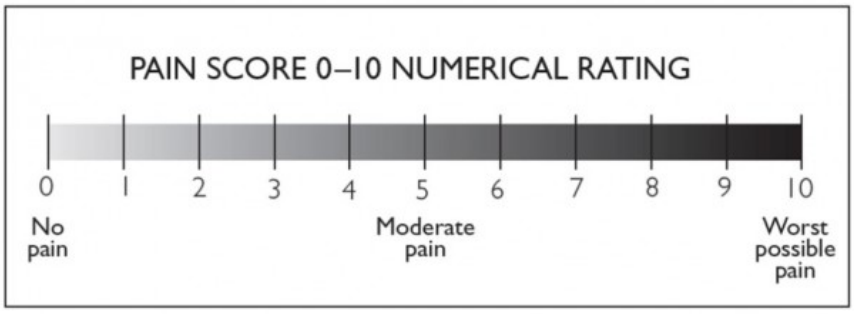
2.1. Scheme

Patients will be randomized 1:1 to receive treatment daily for 4 consecutive weeks versus sham, followed by an open-label phase for additional 4 consecutive weeks.

2.2. Primary Objective

The primary objective is to determine the difference in the Numerical Pain Scale score between the baseline screening call and at week 4 in the treatment group compared with the same difference in the placebo or sham group.

The Numerical Pain Scale is an 11-point scale (0-10) that includes guides to assist in the



determination of the pain level.

2.3. Secondary

Six secondary objectives are intended to collect additional information about the potential benefit of QUELL FLEX:

A. The difference in pain scores at the end of the open label phase compared to the end of the initial blinded phase.
B. A change in the "worst" pain score in the treatment arm vs. the sham arm between the baseline screening call and week 4; and the change in the "worst" pain from baseline to week 8 for all subjects.
C. A change in the "average" pain score in the treatment arm vs. the sham arm between the baseline screening call and week 4; and the change in the "average" pain from baseline to week 8 for all subjects.
D. The number of patients who withdraw because of poor compliance. We expect a higher withdrawal and non-compliance rate in the sham group.
E. Quality of life surveys will be conducted before and after the treatment phase and at the end of the study to determine if the QUELL FLEX treatment impacts overall quality of life.
F. Reduction in pain medication use over the course of the study.

3. Hypotheses

3.1. Primary

- QUELL FLEX therapy reduces pain scores in NMO patients on the Numerical Pain Scale at the week 4 study visit compared to baseline/screening visit, and this reduction is significantly greater compared to the reduction due to sham treatment during the same time period. Power for this study is calculated based on our previous study using a TENS unit (Scrambler) in the same patient population.

3.2. Secondary

- QUELL FLEX therapy is an acceptable treatment measured by compliance and patient survey.
- Patients who were randomized initially to the sham arm will show a reduction in pain score after crossing over into the open label arm. In contrast, the patients in the treatment arm will not necessarily show additional benefit after rolling over in the open label arm.
- The “average” and “worst” pain scores will decline in the treatment arm and not necessarily in the sham arm.
- As pain is a primary driver of quality of life, quality of life will improve with treatment compared to sham.
- Patients for whom QUELL FLEX works well may choose to reduce their intake of pain medications.

4. Background and Rationale

4.1. Etiology and current treatment of central neuropathic pain in patients with neuromyelitis optica spectrum disorder

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disease of the central nervous system (CNS) that preferentially causes recurrent inflammatory attacks in the optic nerves and spinal cord, leading to blindness, paralysis and death. Despite these devastating consequences of the disease, patients have reported that pain is among the most prevalent and debilitating symptoms.

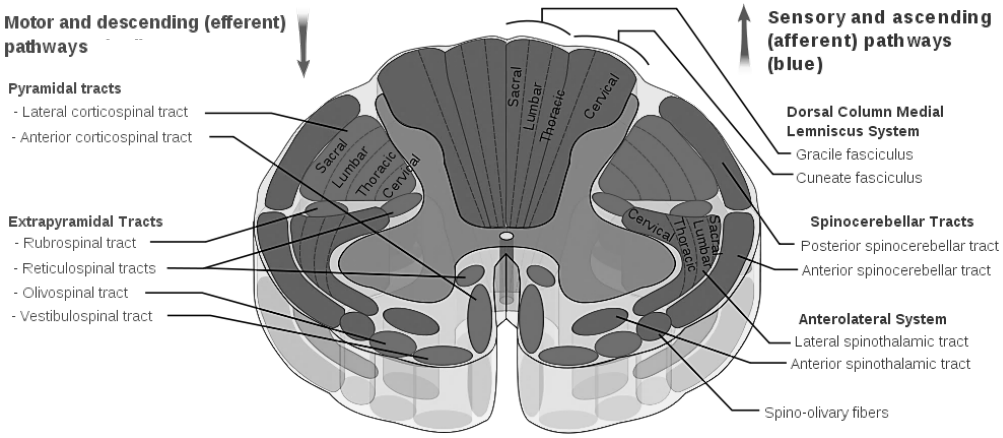


Figure 1. Cross-section of the spinal cord depicting spinal tracts. From:

In particular, central neuropathic pain (CNP) is pervasive, severe, intractable to treatment, and affects 62-91% of patients with NMOSD. CNP is described as agonizing burning, stabbing, shooting, tingling or squeezing sensation that is distressing, persistent and incapacitating. While the severity of CNP in NMOSD is not well-understood, its presence is a direct consequence of targeted immune-mediated destruction of the spinal cord and occurs at and below the spinal cord lesion level, and may be a result of damage to ascending sensory pathways where there is inadequate stimulation of peripheral sensory nerve endings. Ascending (sensory) pathways are nerves that go upward from the spinal cord toward the brain carrying sensory information from the body to the brain. In contrast, descending (motor) pathways are nerve pathways that go down the spinal cord and allow the brain to control movement of the body below the head (Figure 1). As a consequence of ongoing spontaneous activity arising in the periphery, surviving neurons develop increased background activity, enlarged receptive fields and increased responses to ascending nerve impulses, including normally harmless tactile stimulation.

4.2. TENS Therapy: potential application to central neuropathic pain

4.2.1. Rationale for nerve-based treatments

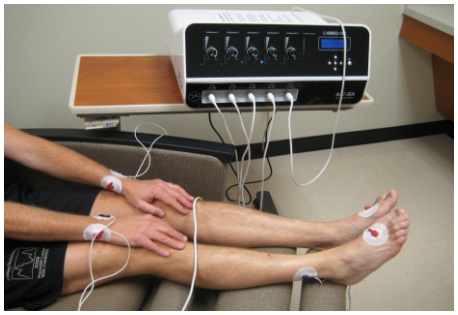


Figure 2. A picture of the machine with electrode placement. Permission from Thomas Smith, MD

Scrambler Therapy is a new, non-invasive technology with Food and Drug Administration (FDA) 510(k) approval, "Scrambler ST 5 TENS Device," (K081255) granted in February 2009. It uses cutaneous electrostimulation that simulates normal nerve action potentials. The impulses are transmitted via surface electrodes placed surrounding the pain area along the same nerve pathways, done by following the dermatomes and avoiding areas that hurt (Figure 2). The device synthesizes 16 different types of nerve action potentials similar to the endogenous kinds, strings them into sequences, and directly stimulates the nerves. These different waveforms are dynamically assembled into strings of information that are recognized by the CNS and replace pain with "no-pain" information. Neuroplasticity enables these new signals to replace the old, inappropriate amplification of pain signals. Scrambler therapy provides 16 continuously changing variable nonlinear waveforms, or a "scrambled" signal, thus making it different from transcutaneous electrical nerve stimulation (TENS), which provides an on-off, biphasic waveform. TENS is thought to block the pain signal rather than replace it with new information, which translates into often short-lived results that are not as practical for persistent pain. Data in Scrambler therapy, on the other hand, suggests that patients can have significantly reduced pain or be pain-free for up to 3 months following a series of treatments, and that follow-up treatments may require fewer sessions for continued relief, including limited data from randomized controlled trials. The exact mechanism by which Scrambler Therapy relieves pain is under investigation.

OH DEAR. THE ENDNOTES ARE ALL MESSED UP.

4.2.2. Data on Scrambler therapy

In 2018, the Johns Hopkins Neuromyelitis Optica Clinic conducted a sham-controlled randomized trial of Scrambler treatment over 10 consecutive days in 22 NMOSD patients to determine efficacy, acceptability, feasibility and duration of in-clinic therapy. We measured changes in pain with the numerical rating scale and analyzed change in pain levels and related symptoms at time of treatment and again at 30 and 60 days. The findings showed significant pain reduction and quality of life improvements, including reduction of anxiety and depression, up to 30 days. Scrambler has been used in other patients with central neuropathic pain including a brainstem lesion and transverse myelitis.

Because of the positive effects of Scrambler therapy on NMOSD patients, and because of the complications inherent in accessing said therapy, we became interested in following that study with one assessing portable devices using similar methodology.

4.2.3. Data on Quell Relief

In a study for Quell TENS on back pain, the following results were reported:

"After six weeks, those in the Experimental group reported lower "worst" pain scores and less overall interference than those in the Control group ($p<0.025$). After three months those assigned to the Experimental group (hfTENS device) reported significantly less pain (worst, least, average, now) than those in the Control condition ($p<0.01$; Table 3). Pre-post comparisons on average pain intensity on the BPI showed significant groups differences (Experimental=1.24; Control=-0.03; $t=2.74$; $p<0.01$) with 31.0% of the Experimental group showing ≥2.0 differences vs. 12.9% among the Control group. Those in the Experimental group also reported less overall pain-related interference (general activity, mood, walking ability, work, relation with others, sleep, and enjoyment of life) compared with the Control group ($p<0.025$). Also, subjects assigned to use the hfTENS reported reduced pain catastrophizing scores compared with the Controls ($p<0.025$). No differences were noted between groups on the self-report questionnaires assessing disability (PDI) and anxiety and depression (HADS). Both groups demonstrated a reduction in the use of prescription pain medication, but no differences were found between groups."

5. Patient Population

5.1. Inclusion Criteria

5.1.1. Men and women 18 years of age or older diagnosed with NMOSD per the 2015 NMOSD criteria

5.1.2. Patients must be positive for the aquaporin-4 antibody in serum

5.1.3. Presence of persistent neuropathic pain (≥3 months) rated at a level of 4 or higher on the Numerical Pain Scale

5.1.4. Patients must be stable in their disease, such that they have had no spinal cord relapses within 6 months prior to enrollment

5.1.5. Patients must be on a stable medication regimen that may include anti-epileptic, antidepressant, or non-steroidal anti-inflammatory medications, with no adjustments to the regimen within 30 days of enrollment

5.1.6. Pain must be localized to a spinal cord lesion

5.1.7. Patient understands the study regimen, its requirements, risks, and discomforts, and is able and willing to sign an informed consent form

5.1.8. Patients must own and be able to operate an iOS or Android smartphone with internet connection

5.2. Exclusion Criteria

5.2.1. Patients who are cognitively or mentally incompetent

5.2.2. Patients whose primary complaint is numbness/tingling

5.2.3. Any of the following: pregnant women, nursing women, women of childbearing potential or their sexual partners who are unwilling to employ adequate contraception

(condoms, diaphragm, birth control pills, injections, intrauterine device [IUD], surgical sterilization, subcutaneous implants, abstinence, etc.).

5.2.4. Use of an investigational agent for pain control concurrently or within the past 30 days

5.2.5. History of an allergic reaction or previous intolerance to transcutaneous electronic nerve stimulation or to latex

5.2.6. Patients with implantable drug delivery systems, e.g. Medtronic Synchromed.

5.2.7. Patients with heart stents or metal implants such as pacemakers, automatic defibrillators, cochlear implants, aneurysm clips, vena cava clips and skull plates (Metal implants for orthopedic repair, e.g. pins, clips, plates, cages, joint replacements are allowed)

5.2.8. Patients with a known history of myocardial infarction or ischemic heart disease within the past six months

5.2.9. Patient who have had surgery to treat a pain-related condition in the last 6 months

5.2.10. Prior celiac plexus block, or other neurolytic pain control treatment, within 1 month

5.2.11. Other identified causes of painful parasthesias existing prior to chemotherapy (e.g., carpal tunnel syndrome, B12 deficiency, AIDS, monoclonal gammopathy, diabetes, heavy metal poisoning amyloidosis, syphilis, hyperthyroidism or hypothyroidism, inherited neuropathy, etc.) that might be responsible for the patient's current neuropathic symptoms

5.2.12. Skin conditions such as open sores that would prevent proper application of the electrodes

5.2.13. Patients with an ongoing concomitant central neurologic disorder or history of epilepsy, brain damage, or symptomatic brain metastases

5.2.14. Other medical or other condition(s) that in the opinion of the investigators might compromise the objectives of the study

5.2.15. Pain is primarily due to prior spinal fusion procedure or pain is in an area where there was previously a spinal fusion procedure

5.2.16. History of an allergic reaction or previous intolerance to hydrogel adhesive used in TENS devices

5.2.17. Patients with implantable spinal cord stimulators

5.3. Inclusion of Women and Minorities

This interventional clinical trial will involve the recruitment of 46 participants with central neuropathic pain resulting from neuromyelitis optica spectrum disorder (NMOSD). There are no restrictions related to sex, race or ethnicity for trial inclusion. NMOSD disproportionately affects women and minorities. Given that the ratio by sex of those diagnosed with NMOSD is 6.5-9 females for every 1 male, the expectation is that at least 80% of participants will be women.

5.4. Inclusion of Children

This study includes women and men with central neuropathic pain caused by neuromyelitis optica spectrum disorder (NMOSD) who are of age 18 years or older. Because previous trials have involved those aged 18 and older, children under the age of 18 will not be included. Most patients are diagnosed with NMOSD in their 30's and 40's, and it is the expectation that this will impact recruitment very little.

6. Study Design and Treatment Plan

6.1. Summary

Building on the recent successful phase II study using Scrambler TENS among NMOSD patients, we propose bringing a non-invasive neuromodulation technology to a larger NMOSD population with the important distinction that we will study self-administered take-home QUELL FLEX units on this cohort of patients for the reasons outlined above.

6.2. Recruitment

We plan to recruit 46 consecutive patients with NMOSD (23 per arm) with a diagnosis of NMOSD based on the 2015 international consensus diagnostic criteria and the presence of neuropathic pain. Trial information will be made available through clinicaltrials.gov.

6.3. Determination of Eligibility

Eligibility for participation will be reviewed and confirmed by a member of the study staff. Upon successful eligibility, the patient will be eligible for registration into the study, at which time a study-specific subject ID/number will be assigned.

For patients who reach the study team from outside of the Mass General NMO Clinic, a member of the patient's care team will be consulted to confirm that s/he believes that the participant is appropriate for protocol participation.

Study intervention cannot begin until the patient is successfully registered and consented.

6.4 Randomization and Blinding

Randomization would be done in blocks of 4 (e.g. 2 placebo and 2 treatment assignments) assigned at random at the beginning of the study for each 4 patients enrolled in the study consecutively. This ensures that it is not possible to predict the arm assignment of patients as we unblind them in groups of 4 at the conclusion of each patient's participation in the study.

Blinding keys, including the arm assignment of the patient, will be sealed in envelopes and not opened until unblinding occurs for the 4-patient-block.

6.5. Methods and Intervention

6.5.1. QUELL FLEX Transcutaneous Electrical Nerve Stimulation Therapy

The locations of symptoms will be assessed remotely by telemedicine and remote MRI review. If patient has pain areas referable to more than one lesion, treatment will be done on the area that is most bothersome to the patient.

6.5.1.1. Treatment Days

1. Prior to initiation of Quell therapy, patients will be asked to rate their pain on the Numerical Pain Scale and will complete a Short Form-36 Health Inventory (SF-36).
2. All training on the use of the device will be conducted remotely through Zoom.

3. Patients will be shipped a QUELL FLEX device. It will either be a functional QUELL FLEX device for the treatment arm or a non-functional QUELL FLEX device in the sham arm. All of the lights, charging equipment, and app connectivity will be the same. The only difference is that the non-functional sham devices will administer an electrical current for only 2 minutes each at the top of a treatment hour, at 30 minutes and at 58 minutes, as opposed to for the full hour when the device is engaged.
4. Patients will be informed that we are conducting a number of different treatment paradigms – some of them have high frequency waves that are not perceptible, and some have lower frequency waves that may be transiently perceptible. In addition, we will re-inform them there is a sham arm.
5. The electrodes will be placed on patients on the back in the dermatome of the most painful area. The intensity of the stimulus is increased until the patient can first feel some sensation associated with the electrodes. Script: "Tell me when you feel something."
6. Stimulation intensity will be increased until a maximum threshold is tolerated without being painful.
7. Once the intensity is at its maximum setting, the study coordinator will evaluate the level of pain. If the patient feels a constant burn, single sting or feeling of discomfort, the electrodes will be repositioned. The exact electrode positioning will depend on the delimitation of the surface pain area, and analgesic response of the patient.
8. Once satisfactory electrode placement and stimulus intensity is determined, therapy is maintained for at least an hour per day for 4 weeks (both treatment and sham groups).
9. Patients will report pain scores weekly throughout experimental period while on a zoom call with the trial researcher. Patients will again complete all measurement tools and pain ranking at end of treatment.
10. At the conclusion of the 4-week experimental arm, all patients will be shipped a new QUELL FLEX device for use in the 4-week open label phase. This one will be functional. The experimental QUELL FLEX devices will be returned in the same shipping box to the study team. Study staff will administer the SF-36 Quality of Life questionnaire.
11. In the 4-week open label phase, patients will continue to use the device with the electrodes in the same position. Weekly pain scores will be documented as before as well as the SF-36 Quality of Life questionnaire at the conclusion of the 4-week open label period.
12. At the conclusion of the 4-week open label period for the 4-patient block, blinding will be unsealed and reported to the patients. They will then have the opportunity to keep the functional QUELL FLEX if they wish.
13. Four and eight weeks after the completion of the open label phase, patients will be called for a wellness check and asked to rate their pain again.
14. Adverse Events will be monitored and documented weekly.

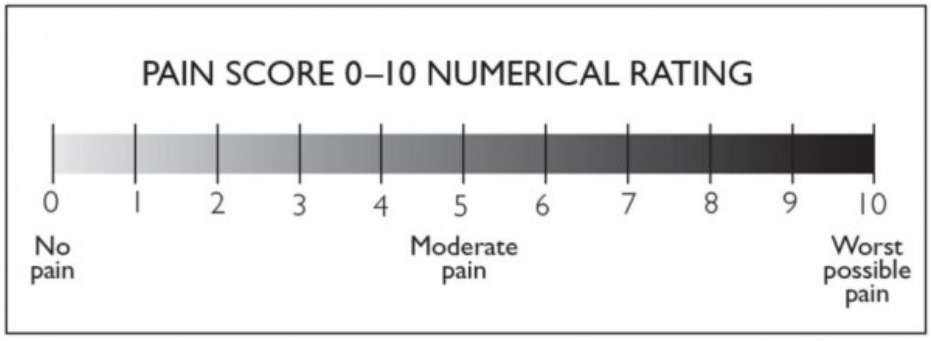
6.5.1.2. Treatment follow-up:

Patients will be contacted by Zoom weekly during the experimental and open-label phases to check in on them, and will be asked weekly to report their pain score. At the conclusion of the experimental phase and at the end of the study, patients will be asked again to complete the Short Form-36 Health Inventory (SF-36).

Patient-Reported Outcomes

6.6.1. General

The numerical pain scale will be administered verbally during each study visit.



Study staff will ask both average and worst pain experienced in the week prior to each study visit, using the same Numerical Rating Scale. Additionally, she will ask if and for how long relief lasted after QUELL FLEX use on average over the week.

6.6.2. Measurement tools: description and rationale for use

The Numerical Pain Scale used to collect input prior to initiation, and at end of treatment, has been validated in dozens of persistent pain conditions and is the most widely used tool in both Scrambler therapy and NMOSD research to date. SF-36 is a patient-reported survey of overall patient health-related quality of life and has been widely used for QoL assessment in chronic conditions, including in NMOSD research.

NOTE: Please see questionnaires in Appendix A.

6.7. Concomitant and Supportive Therapy

The concomitant medications and therapies deemed necessary for the supportive care and safety of the subject are allowed, provided their use is documented in the medical records.

The use of other concurrent investigational drugs or devices for management of pain is not allowed unless approved by the Principal Investigator.

6.8. Discontinuation and Withdrawal of Subjects

All patients who initiate protocol intervention will be included in the overall evaluation of tolerability and acceptability (intent-to-treat analysis). All reasons for discontinuation of therapy will be clearly documented in the record.

Unless the subject refuses, follow-up will continue for the planned duration following the study intervention.

6.8.1. Discontinuation of Intervention

The reasons for discontinuation of protocol treatment include:

- Non-compliance with the study protocol; including, but not limited to not using the device more than 75% of the study duration.
- Unacceptable major reaction to electrical stimulation or other major adverse events
- Intercurrent illness or condition that would, in the judgment of the treating investigator, affect assessment of clinical status to a significant degree or require discontinuation of study intervention.
- At subject's own request. Note: The reason for discontinuation from the study must be documented. The patients will be included in the overall evaluation of tolerability and acceptability (intent-to-treat analysis) if any protocol intervention was administered prior to withdrawal.
- Study is closed or cancelled for any reason.

6.8.2. Withdrawal from Study

The reasons for withdrawal from the study include:

- Subject withdraws consent for follow-up.
- Subject is lost to follow-up.
- Study is terminated for any reason.

7. Table 3: Patient Event Calendar

Phase	**Baseline Screening/Consent**	**Experimental (Weeks)**				**Open Label (Weeks)**				**Follow-up (weeks)**	
Time Point (days)	Within 2 weeks	1	2	3	4	5	6	7	8	12	16
Exam/Tests *	Consent, MRI review, Q#	AE and weekly pain score assessment, Q				AE and weekly pain score assessment, Q				AE and pain score assessment	AE and pain score assessment
#Q: Questionnaire (SF-36)											

8. Adverse Events

In over 4000 patients treated and reported to the FDA for approval, published and in-press studies, no significant adverse events have been reported with Scrambler and related TENS units.

8.1. General

Adverse events will be monitored and documented weekly and at termination of final treatment. Any serious adverse events or study violations will be immediately reported to the Primary Investigator and Partners Institutional Review Board (IRB). Study deviations and other adverse events will additionally be reported to the PI immediately, and to the IRB within the IRB's specified time frame. Given that the device has been cleared for marketing for the proposed use,[28] no Investigational Device Exemption is needed through the FDA.

Even though this trial includes a blinded experimental phase, given the low risk of adverse events imposed by the trial, it does not rise to the level of requiring a data safety monitoring board.

Information about all intervention-related adverse events, including those volunteered by the subject, discovered by investigator/study personnel questioning, or detected through physical examination, or other means, will be collected, followed, and reported appropriately.

8.2 Reporting Procedures

All intervention-related adverse events will be captured on the appropriate source documents or in a designated database.

The same applies to any adverse event classified as a "serious adverse event;" these will also only be reported if intervention-/study-related.

Any unexpected intervention-related adverse events and serious adverse events will be reported to the IRB per current institutional standards. If an adverse event requires modification of the informed consent, these modifications will be provided to the IRB with the report of the adverse event. If an adverse event requires modification to the study protocol, these modifications will be provided to the IRB as soon as is possible.

9. Safety Monitoring

9.1. Data Management

All information will be collected by study staff through zoom conversations with patients. She will maintain all responses on computer programs using only de-identified patient numbers.

All study data will be reviewed for completeness and accuracy by the Principal Investigator.

9.2.Monitoring

Each week, patients will communicate with the study coordinator to check in and report adverse effects. At the start of the study, at the end of the experimental phase and at the conclusion of the study, quality of life surveys will be conducted by Zoom. Four and eight weeks after the study is completed, patients will be contacted to report their pain scores.

10. Administrative Procedures

10.1. Protocol Amendments

Any changes to the protocol will be made in the form of an amendment and must be approved by the IRB before implementation. The Principal Investigator (or his designee) is responsible for the coordination and development of all protocol amendments.

10.2. Informed Consent

Human subjects will be recruited through the Mass General NMOSD Clinic. This clinical trial will be posted through clinicaltrials.org and on The NMO Clinic's Facebook page. Those patients who seek participation from outside of the Massachusetts General Brigham network are eligible to be screened. On-line consent forms will be provided to interested patients after an initial intake phone call. The consent form RedCap (or other approved IRB platform) link will be emailed to the patient and then discussed with the study coordinator over a Zoom call. The Principal Investigator or the study coordinator will explain to each patient the nature of the study, its purpose, procedures involved, expected duration, potential risks and benefits. Each patient will be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment. This informed consent will be given by means of an on-line statement and has been approved by the IRB. No patient will enter the study before her informed consent has been obtained. In accordance with the Health Insurance Portability and Accountability Act (HIPAA), the informed consent document (or a separate document to be given in conjunction with the consent document) will include a participant authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history. The PI or study coordinator will file the signed consent forms.

10.3. Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and Good Clinical Practice, as described in:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice.

10.4. Regulatory Authorities

10.4.1. Institutional Review Board

Information regarding study conduct and progress will be reported to the Institutional Review Board (IRB) per the current institutional standards.

11. Statistical Plan

11.1.Acceptability

Counts and percentages will be used to assess acceptability based on adherence to treatment schedule. We will report the number and percent of patients in each group who are able to complete all treatments. A chi-square test for independence of group by dichotomous outcome will be performed to assess differences between the two groups. In the event that the expected frequencies are < 5, Fisher's exact test will be performed. While no serious adverse events have been reported with use of Scrambler or other TENS therapies in the NMOSD patient population, the numbers and percent observed for each group will be reported.

11.2. **Efficacy**

Change in pain score will be calculated by subtracting the patient's week 4 score from his or her baseline value prior to treatment initiation. Change in scores will be summarized using means and standard deviations provided the resulting distribution is symmetric, otherwise medians and interquartile ranges will be used. Provided the resulting distribution of pain scores is roughly normal, we will use a two-sample t-test to compare the QUELL FLEX and sham groups. Previous studies suggest that the average pain value at baseline is at least 4 on the 0-10 numerical rating scale with a standard deviation of the original pain value expected to fall in the range of 1-1.5 in this patient population. As such, a conservative estimate of the standard deviation would be approximately 20%. With 19 patients in each arm and under these assumptions, we will have the ability to detect a change of 2.0 points in the QUELL FLEX group with power of 0.90. If the change score distribution is highly skewed, Wilcoxon's signed rank test will be utilized instead.

To account for ~20% dropout rate, we will add 4 subjects to each arm for a total of 23 subjects per arm. We included a dropout rate of ~20% based on previous studies with this device. We will run a sensitivity analysis to determine if the drop-out rate in either arm had an impact on the trial results

A 20% reduction in pain has been previously determined to be a clinically meaningful improvement, we will report the number and percent of patients from each group who achieve this benchmark.

11.3.Quality of Life

As a sub-aim, we will investigate whether a decrease in pain impacts QoL (SF-36) over time by correlating the change in pain scores to the change in each variable between initiation of

treatment through the use of single variable regression. As an additional exploratory analysis we will categorize patients as having improved pain (> 20% point change on NPS scale) or not. We will then test for a relationship between improved pain and QoL, with the hypothesis that patients with less pain will be less likely to experience anxiety and depressive symptoms.

11.4.Reporting and Exclusions

Patients who sign a consent form, but do not initiate protocol intervention for any reason (e.g., patients who are screen failures), will be replaced and will not count towards our accrual goal.

12. APPENDIX A

SF-36 QUESTIONNAIRE

Name:_____ **Ref. Dr:**_____ **Date:** _____

ID#: _____ **Age:** _____ **Gender: M / F**

Please answer the 36 questions of the **Health Survey** completely, honestly, and without interruptions.

GENERAL HEALTH:
In general, would you say your health is:
Excellent Very Good Good Fair Poor

Compared to one year ago, how would you rate your health in general now?
Much better now than one year ago
Somewhat better now than one year ago
About the same
Somewhat worse now than one year ago
Much worse than one year ago

LIMITATIONS OF ACTIVITIES:
The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.
Yes, Limited a lot Yes, Limited a Little No, Not Limited at all

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Lifting or carrying groceries
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Climbing several flights of stairs
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Climbing one flight of stairs
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Bending, kneeling, or stooping
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Walking more than a mile
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Walking several blocks
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Walking one block
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Bathing or dressing yourself
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

PHYSICAL HEALTH PROBLEMS:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Cut down the amount of time you spent on work or other activities
Yes No

Accomplished less than you would like
Yes No

Were limited in the kind of work or other activities
Yes No

Had difficulty performing the work or other activities (for example, it took extra effort)
Yes No

EMOTIONAL HEALTH PROBLEMS:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Cut down the amount of time you spent on work or other activities
Yes No

Accomplished less than you would like
Yes No

Didn't do work or other activities as carefully as usual
Yes No

SOCIAL ACTIVITIES:
Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all Slightly Moderately Severe Very Severe

PAIN:
How much bodily pain have you had during the past 4 weeks?

None Very Mild Mild Moderate Severe Very Severe

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all A little bit Moderately Quite a bit Extremely

ENERGY AND EMOTIONS:
These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

Did you feel full of pep?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a very nervous person?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt so down in the dumps that nothing could cheer you up?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt calm and peaceful?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you have a lot of energy?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt downhearted and blue?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel worn out?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a happy person?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel tired?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

SOCIAL ACTIVITIES:
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

- All of the time
- Most of the time
- Some of the time
- A little bit of the time
- None of the Time

GENERAL HEALTH:
How true or false is each of the following statements for you?

I seem to get sick a little easier than other people
Definitely true | Mostly true | Don't know | Mostly false | Definitely false

I am as healthy as anybody I know
Definitely true | Mostly true | Don't know | Mostly false | Definitely false

I expect my health to get worse
Definitely true | Mostly true | Don't know | Mostly false | Definitely false

My health is excellent
Definitely true | Mostly true | Don't know | Mostly false | Definitely false

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