Mayo Clinic Cancer Center

MC15C1 Randomized Scrambler Therapy vs TENS for the Treatment of Chemotherapy-Induced Peripheral Neuropathy

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*No waivers of eligibility per NCI

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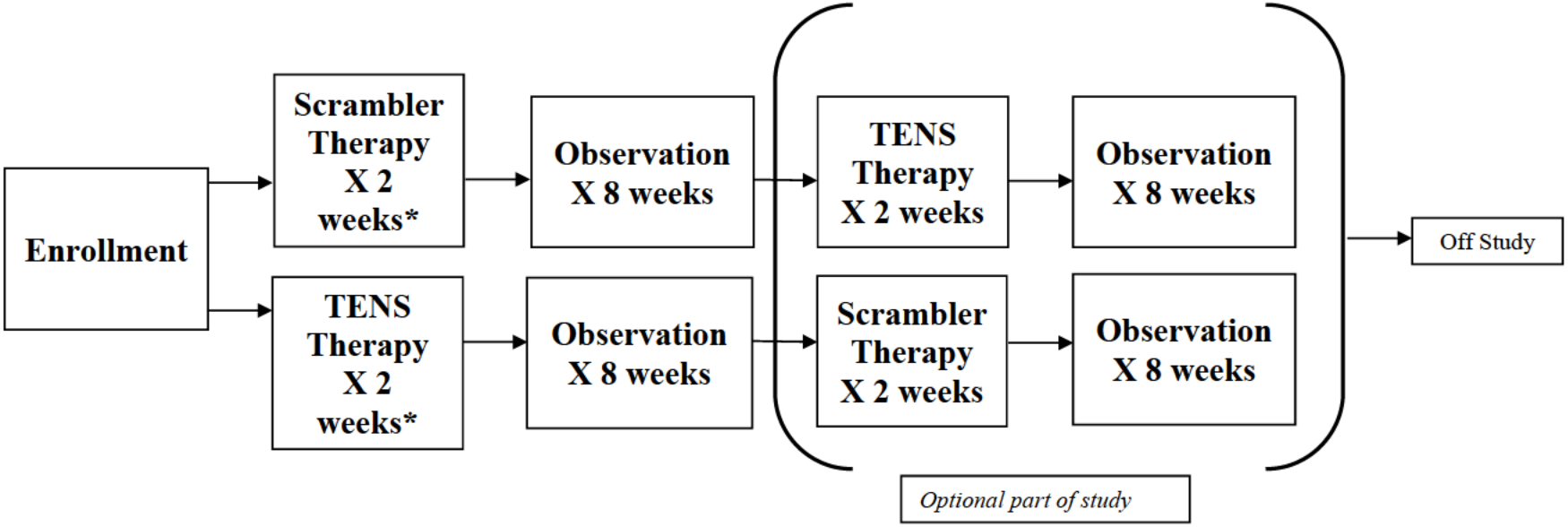
Schema



*Treatment period of primary interest

Unacceptable adverse Events
Patient refusal → **Off Study**

Therapy Cycles = Daily for 14 days
Observation cycles = Weekly

Generic name: Scrambler Therapy Mayo Abbreviation: NA Availability: Provided for study	Generic name: TENS Mayo Abbreviation: NA Availability: Provided for study

1.0 Background

1.1 Chronic Pain

Chronic pain is estimated to affect 100 million people in the U.S. alone, resulting in up to $635 billion in medical expenses and lost productivity each year (Simon 2012). It predisposes to psychiatric comorbidity, and its massive impact is highlighted by the fact that it is the most common cause of long-term disability in the U.S. (Stewart, Ricci et al. 2003).

In simplest terms, pain can be defined as a bodily sensation experienced during genuine, or perceived, tissue injury (Merskey and Bogduk 1994). In the acute setting, this sensation can serve a protective role by alerting an individual to avoid potentially harmful stimuli and protect a body part during healing. When pain fails to communicate biologically useful or accurate information, it is maladaptive and thereby becomes pathologic—pain becomes a disease in its own right. It is generally agreed that pain becomes "chronic" when it persists beyond the expected period of tissue injury and healing. The specific duration of symptoms required to qualify for a diagnosis of chronic pain is debatable, but usually this is considered to be three to six months (Merskey and Harold 1986).

The perception of noxious stimuli originates from nociceptors of the peripheral nervous system. Nociceptors recognize noxious stimuli in the form of thermal, mechanical, or chemical inputs. This stimulation leads to activation of primary sensory nerve fibers that transmit this information to the central nervous system, via a complex network of interneurons housed predominantly in the dorsal root ganglia, posterior horn of the spinal cord, brain stem, and thalamus. Ultimately, signals reach the forebrain for interpretation of the sensory experience. There are multiple mechanisms that underlie the dysregulation of this system in chronic pain. In the setting of injury, for example, inflammatory changes in the biochemical milieu surrounding peripheral nerves can result in hypersensitization of nociceptors, such that pain signals are communicated in the absence of appropriate stimuli (Woolf and Doubell 1994). Neurons surrounding damaged tissue have even shown the ability to develop spontaneous discharges that communicate pain information in the absence of external input (Zimmermann 2001). Similarly, spinal cord neurons in the central nervous system exposed to repetitive pain stimuli may undergo changes that result in transmission of action potentials with a reduced threshold of synaptic input (Ji, Kohno et al. 2003).

Currently, several treatment modalities exist for the management of chronic pain, including physical therapy, pharmacologic therapy, behavioral medicine, neuromodulation, minimally-invasive interventions, and surgery. Unfortunately, the heterogeneous nature of chronic pain syndromes and the lack of a functional understanding of chronic pain contribute to the absence of a clearly identifiable, appropriate management strategy for many patients. Nonetheless, pharmacologic measures are commonly prescribed as a component of chronic pain management. With many medications available, such as non-steroidal anti-inflammatory agents, anti-convulsants, anti-depressants, and opioids, it is exceedingly common for patients to use multiple agents to try to achieve reasonable pain control(Freynhagen and Bennett 2009).

Recognizing the limitations and hazards of polypharmacy, increasing emphasis has been placed on the non-pharmacologic options for management of persistent pain. A strategy combining psychological and physical medicine approaches can provide significant benefit for many of these patients (Allegrante 1996). Neuromodulatory techniques,

particularly since the commercial availability of wearable transcutaneous electrical nerve stimulation (TENS) units in the mid-1970s, gained popularity as an adjunct to both pharmacological and non-pharmacologic pain managements(Maurer 1974). TENS was developed based on the Gate Control Theory(Melzack and Wall 1965), which suggests the gate of transmission from nociceptive peripheral C fibers is typically closed, but opened in pain states, including pathologic pain. In line with the Gate Control Theory, TENS is specifically designed to stimulate myelinized Aβ fibers (tactile fibers) and avoid the stimulation of C fibers. It is thought that spinal cord stimulation, similar to TENS, also works through the Gate Control Theory mechanism stimulating myelinated fibers and has been used for chronic pain that has not responded to less invasive approaches. It has proven efficacy in such diverse pain syndromes as refractory angina, failed back syndrome, complex regional pain syndromes, and other conditions, with the ability to reduce pain intensity by over 50% (Marineo 2003; Sabato, Marineo et al. 2005; Abdi, Lakkimsetty et al. 2011; Ghatak, Nandi et al. 2011; Marineo, Iorno et al. 2011; Sparadeo F 2012; Campbell, Nimunkar et al. 2013; Coyne, Wan et al. 2013; Park, Sin et al. 2013; Deer, Mekhail et al. 2014; Moon, Kurihara et al. 2014; Pachman, Weisbrod et al. 2014; Sparadeo and D'Amato 2014). However, it is invasive, expensive, and not universally effective. While promising in theory, the scientific data supporting such methods remain limited without consistently-shown benefit, underscoring the need for novel therapeutic options (Cruccu, Aziz et al. 2007; Nnoaham and Kumbang 2008).

One thought is that while TENS devices have become more sophisticated and can deliver signals of varying frequencies, intensities, and morphologies, their nature is so stereotypical and non-physiologic that their effectiveness is limited, with patients experiencing rapid tachyphylaxis.

1.2 Chemotherapy-induced Peripheral Neuropathy (CIPN)

CIPN is a major and often dose-limiting side effect of antineoplastic agents including the taxanes (paclitaxel and docetaxel), platinums (carboplatin, cisplatin, oxaliplatin), vinca alkaloids (vincristine, vinblastine, and vinorelbine), proteosome inhibitors (bortezomib) and epithelones (such as ixabepilone). The incidence of chemotherapy-induced neurotoxicity ranges from 0 to 70% (commonly 30-40%) of patients receiving chemotherapy, related to the timing and cumulative dose. Unlike chronic diabetic nerve damage it is not caused by nutritional starvation but rapid damage to microtubules of the nerves. Pain is a common symptom, usually described as a burning, stinging dysesthesia. However, many patients also complain of numbness and tingling and being unable to do activities of daily living because of these symptoms.

Substantial data demonstrate that CIPN can remain as a prominent problem for months to years following the completion of chemotherapy (Hershman, Lacchetti et al. 2014).

Recent American Society of Clinical Oncology (ASCO) guidelines have reviewed the prevention and treatment of CIPN (Hershman, Lacchetti et al. 2014). Despite the review of 42 randomized prevention trials, none have been proven to be helpful. With regards to treatment, only duloxetine has been reasonably proven to be helpful, but only to a limited extent (Hershman, Lacchetti et al. 2014). Thus, better therapy is needed for this prominent clinical problem.

1.3 Scrambler Therapy Development and Mechanisms

Giuseppe Marineo, a biophysicist who developed an interest in treating chronic pain, developed Scrambler Therapy and conducted basic and applied research related to it. This research produced a new chronic pain model and consequently its treatment. Marineo

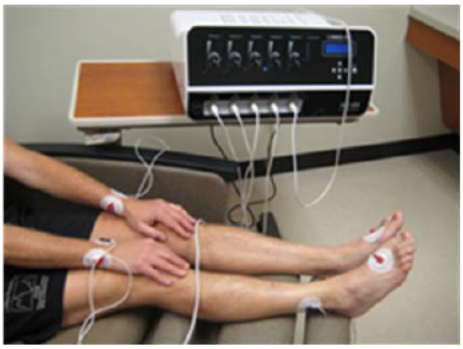


Figure 1: Scrambler machine.

claims that chronic pain is the consequence of a phenomenon produced by the persistence in time of pain pathway activation, a typical condition of neuropathies. This process results in a loss of the linearity in the cause/effect relation that characterizes physiological acute pain (which is protective) and creates a new type of non-linear behavior of the pain system, that tends to self-sustain an anomalous response to painful and non-painful stimuli. According to Marineo, the entire chronic pain process is therefore controlled and controllable by intervening on the information property, the variable that characterizes and mainly regulates every activity of the nervous system, and represents its natural cybernetic expression (Marineo 2003). In short, Scrambler therapy's active principle is information control that, in its different possible ways of origin, controls the modulation or re-modulation of the pain system, and its physiological or pathological responses, in line with plastic properties of the nervous system. More specifically, a Scrambler therapy unit (Figure 1) is composed of 5 artificial neurons that, through C fibers surface polymodal receptors, replace the endogenous pain information with a synthetic one of “non-pain” or “normal-self” that travels through the same pain pathways to the brain. Through plasticity within brain networks mediating the perception of pain, a series of treatments "retrain" the brain so that the area of concern is no longer considered painful. This functioning principle, like its neurophysiological target that uses the polymodal receptors of C fibers, replaces the chronic pain information, rather than attempting to block its ascending path. This makes for a theoretical model that is completely new, and radically different from TENS devices. While Scrambler therapy works through C fibers to retrain the peripheral sensation in the area being treated, it is a different mechanism than stimulating myelinated fibers through Gate Control Theory such as TENS and possibly spinal cord stimulation. An in-depth analysis on these differences is described in the International Patent PCT/IT2007/000647 and U.S. Patent No. 8,380,317. A comparison between TENS and Scrambler Therapy has not yet been done.

1.4 Scrambler Therapy Clinical Trials

To date, there are 17 trials/reports, including 4 primarily treating patients with CIPN, that are available for review (Table 1)(Marineo 2003; Sabato, Marineo et al. 2005; Smith, Coyne et al. 2010; Abdi, Lakkimsetty et al. 2011; Ghatak, Nandi et al. 2011; Marineo, Iorno et al. 2011; Ricci, Pirotti et al. 2011; Sparadeo F 2012; Campbell, Nimunkar et al. 2013; Coyne, Wan et al. 2013; Park, Sin et al. 2013; Moon, Kurihara et al. 2014; Pachman, Weisbrod et al. 2014; Sparadeo and D'Amato 2014; Starkweather, Coyne et al. 2015). Fifteen have been published as manuscripts(Marineo 2003; Sabato, Marineo et al. 2005; Ghatak, Nandi et al. 2011; Marineo, Iorno et al. 2011; Ricci, Pirotti et al. 2011; Sparadeo F 2012; Campbell, Nimunkar et al. 2013; Coyne, Wan et al. 2013; Park, Sin et al. 2013; Moon, Kurihara et al. 2014; Pachman, Weisbrod et al. 2014; Sparadeo and D'Amato 2014; Starkweather, Coyne et al. 2015), two only as abstracts (Abdi, Lakkimsetty et al. 2011; Campbell, Nimunkar et al. 2013).

Five reports deal with clinical practice experiences(Sparadeo F 2012; Ko, Lee et al. 2013; Park, Sin et al. 2013; Moon, Kurihara et al. 2014; Sparadeo and D'Amato 2014), nine are prospective single-arm clinical trials(Marineo 2003; Sabato, Marineo et al. 2005; Smith, Coyne et al. 2010; Abdi, Lakkimsetty et al. 2011; Ghatak, Nandi et al. 2011; Ricci, Pirotti et al. 2011; Coyne, Wan et al. 2013; Pachman, Weisbrod et al. 2014), one is a randomized open-label controlled trial(Marineo, Iorno et al. 2011), and two are randomized, blinded, placebo-controlled trials(Campbell, Nimunkar et al. 2013; Starkweather, Coyne et al. 2015).

Table 1

	Reports, by first author	Year	Pt #	Condition	Results	Trial type	Comments
1	Marineo (Marineo 2003)	2003	11	Drug-resistant visceral pain	Substantial pain reduction	Prospective trial	
2	Sabato (Sabato, Marineo et al. 2005)	2005	226	multiple chronic pain syndromes	80% of patients with greater than a 50% pain reduction	Prospective trial	
3	Smith (Smith, Coyne et al. 2010)	2010	18	Chemotherapy-induced neuropathy	Over 50% reduction in pain	Prospective trial	(16 evaluable)
4	Abdi (Abdi, Lakkimsetty et al. 2011)	2011	10	Back pain	28% reduction in pain.	Prospective trial	Abstract only
5	Marineo (Marineo, Iorno et al. 2011)	2011	52	post-herpetic neuralgia, spinal canal stenosis, and post-surgical neuropathic pain	Pain reduced more in Scrambler arm, than the control arm at 1 month and 3 months ((P<0.0001)	Randomized, controlled	Open label trial
6	Ricci (Ricci, Pirotti et al. 2011)	2012	82	Various cancer and non-cancer pains	Mean pain scores dropped from 6.2/10 prior to treatment to 1.6 just after completing 10 treatment days to 2.9, 2 weeks after finishing treatment.	Prospective trial	73 evaluable pts.
7	Ghatak (Ghatak, Nandi et al. 2011)	2011	8	Chronic low back pain	Pain score drop from 8.12 to 6.93; Drop in ODI from 49.88 to 18.44	Prospective trial	Open label
8	Sparadeo (Sparadeo F 2012)	2012	173	Chronic pain >6 months	Marked pain reduction	Clinical practice experience	91 provided 3-6 months f/u
9	Coyne (Coyne, Wan et al. 2013)	2013	39	Cancer pain syndromes, including Chemotherapy-induced neuropathy	Significant pain reduction with 10 treatment days that largely lasted for 3 months	Prospective trial	
10	Smith (Coyne, Wan et al. 2013)	2013	10	Post-herpetic neuralgia	95% pain reduction, that largely lasted for 3 months	Prospective trial data	Some pts were the same as in a previous trial [18]
11	Ko (Campbell, Nimunkar et al. 2013)	2013	3	Post-herpetic neuralgia	Marked pain reduction	Clinical practice experience	

	Reports, by first author	Year	Pt #	Condition	Results	Trial type	Comments
12	Park (Park, Sin et al. 2013)	2013	3	Cancer bone metastases	Marked pain reduction	Clinical practice experience	
13	Campbell (Campbell, Nimunkar et al. 2013)	2013	14	Chemotherapy-induced neuropathy	No differences between active and placebo arms	Prospective, double-blind, placebo-controlled trial	Abstract only
14	Pachman (Pachman, Weisbrod et al. 2014)	2014	37	Chemotherapy-induced neuropathy	Average pain decreased by 53% at end of treatment and benefit largely remained for 10 weeks after completion.	Prospective trial	Decrease in tingling and numbness, too.
15	Sparadeo (Sparadeo and D'Amato 2014)	2014	91	Variety of pain syndromes	Substantial pain reduction	Clinical practice experience	Consecutive patients; Some pts were the same as in a previous trial[30]
16	Moon (Moon, Kurihara et al. 2014)	2014	147	Variety of pain syndromes		Clinical practice experience	
17	Starkweather (Starkweather, Coyne et al. 2015)	2015	30	Low back pain	Significant improvements in active vs control group for: 1) worse pain and pain interference states; 2) pain sensitivity measures, and 3) differential mRNA expression of 17 pain genes	Prospective, double-blind, placebo-controlled trial	

The first trial was authored by the Scrambler therapy developer, Marineo, in 2003, and reported the results of the treatment of 11 patients with cancer-associated, drug-resistant, visceral pain(Marineo 2003). This manuscript noted that pain was quickly and markedly reduced in the studied patients, with 9 of 11 patients stopping the use of pharmacologic pain therapy altogether after the first five sessions, without any associated side effects. It noted that pain reduction continued until death, although some patients had recurrent pain which was successfully reduced with retreatment. Pain scores were decreased from approximately 8.5 out of 10, at study initiation, to approximately 0.5 out of 10, after 10 treatments (Figure 2). No adverse effects were reported.

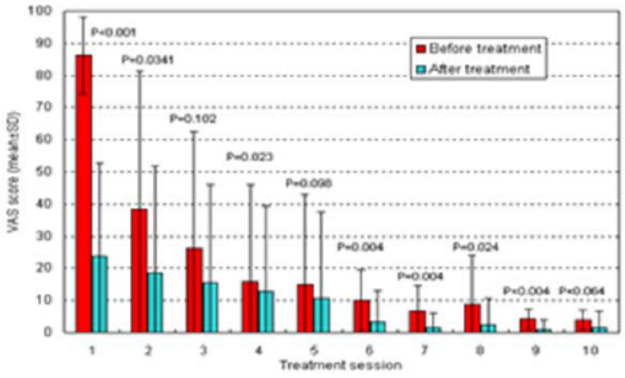


Figure 2. VAS pain before and after each treatment session.

A second trial was published in 2005, with Marineo as a co-author (Sabato, Marineo et al. 2005). A total of 226 patients with neuropathic pain were treated, including patients with failed back surgery, brachial plexus neuropathy, and other chronic pain conditions. This trial, while also uncontrolled, was impressively large and found that 80% of subjects reported at least a 50% pain reduction and 10% experienced a reduction of 25-49%. Ten percent (10%) had no appreciable response. No adverse effects were reported.

Additional groups became involved in the clinical evaluation of this therapy, with the publication in 2010, of the first study that did not include Marineo as an author (Smith, Coyne et al. 2010). This was a pilot trial in 16 patients with chronic chemotherapy-induced peripheral neuropathy, conducted at the Virginia Commonwealth University. The findings from this study were in sync with the success seen with the previously reported trials. After 10 treatments, the average reported pain score dropped nearly 60%, with four patients achieving complete resolution of pain. Patients with recurrent pain were successfully retreated with 1-3 subsequent treatments.

The next trial, currently only available as an abstract, involved 10 patients with failed back surgery treated by an anesthesiology-trained pain physician(Abdi, Lakkimsetty et al. 2011). While it only noted a 28% mean pain reduction, there were patients on this trial who had substantial relief after multiple other therapies had failed to provide benefit. The author of this abstract (verbal communication, May 2015) notes that there are three reasons why his success rate might have been relatively low: 1) he had limited operator experience; 2) he included study subjects with multifactorial intractable pain despite intensive polypharmacy; and 3) treatment while adjuvant anticonvulsants were continued. Empiric observations have suggested less than optimal outcomes if these medications are not discontinued prior to treatment.

Marineo and colleagues published the first randomized controlled trial in 2011, which involved 52 patients with chronic neuropathic pain related to postsurgical causes, postherpetic neuralgia, or spinal cord stenosis(Marineo, Iorno et al. 2011). Scrambler Therapy was compared to a control arm that utilized standard pharmacologic guideline-based recommendations, including frequent phone calls to modify analgesics. The pain

reduction after finishing 10 days of treatment was 28% in the control group (pain scores dropped from 8.0 to 5.8 out of 10) compared to a 91% reduction with the Scrambler group (pain scores dropped from 8.1 to 0.7; $p < 0.0001$; Figure 3). Pain scores in the control arm were 5.7 and 5.9 at two and three months, respectively, as opposed to 1.4 and 2.0 in the Scrambler group ($p < 0.0001$). Pain drug consumption, including opioids, antidepressants, and anticonvulsants, decreased by 72% in the Scrambler group. Allodynia also was reduced in the Scrambler patients, from 77% at baseline to 15% at three months. Benefit was obtained relatively equally amongst patients of all of the three diagnostic categories.

The sixth trial involved 82 (73 evaluable) prospectively-treated patients, about half of whom had cancer-related pain(Ricci, Pirotti et al. 2011). Mean pain scores reduced from 6.2/10 before to 1.6/10 at the end of treatment; and were 2.9/10 one month after treatment was finished. Similar results were seen in patients with and without cancer. When patients were asked whether they would repeat this treatment, 97% (71/73) responded affirmatively.

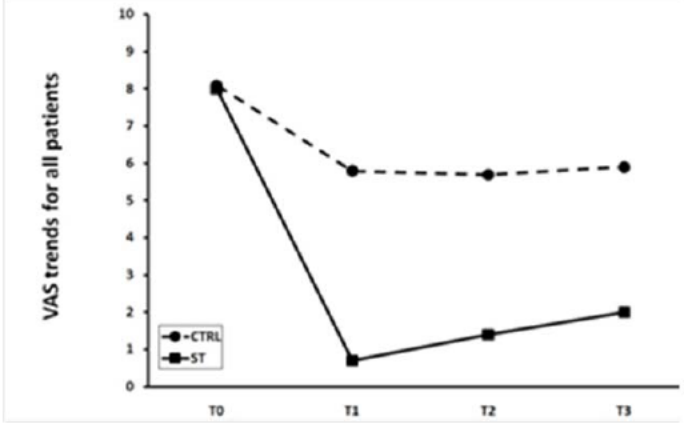


Figure 3: VAS pain over 3 months

The seventh trial was conducted in India, involving a cohort of eight patients treated with Scrambler therapy for chronic low back pain(Ghatak, Nandi et al. 2011). Patients were treated for six consecutive days; pain scores were recorded prior to initiation of treatment and after each session. The mean pain score was 8.12/10 at baseline, dropping to 6.93/10 after the first treatment. The mean pain score dropped to 3.63/10 by day six. The group also recorded the Oswestry Disability Scale (ODI) and found that mean score dropped from 49.88/100 to 18.44/100 by the end of the study, signifying an average drop from severe to minimal disability.

The eighth piece was another prospective trial that reported on a series of 39 patients with cancer pain syndromes, including 33 patients with chemotherapy-induced peripheral neuropathy(Coyne, Wan et al. 2013). Scrambler therapy was associated with significant positive changes from baseline for a large number of outcomes, including degree of pain, interference with normal activities, and sensory neuropathy symptoms. The benefit persisted up to three months.

A small IRB-approved prospective trial published in 2013 involved 10 patients with post-herpetic neuralgia, some of whom had been previously reported in another publication(Coyne, Wan et al. 2013). The study reported a 95% reduction in pain scores at one month, with sustained benefit observed at two and three month follow-up times.

In 2014, we published a Mayo prospective pilot trial experience involving the treatment of 37 patients with chemotherapy-induced peripheral neuropathy, noting about a 50% reduction in pain, tingling, and numbness (Figure 4)(Pachman, Weisbrod et al. 2014). There was an increase in Scrambler benefit over the course of the trial supporting that, despite initial operator training in the administration of Scrambler therapy; thus, a learning curve was evident in this trial. The last 25% of patients entered on this clinical trial did substantially better than did the first 25% of patients, likely a reflection of improved technique afforded by greater experience. The benefit largely was maintained for 10 weeks after the Scrambler therapy was stopped. In this trial, patients were asked on each treatment day and weekly for 10 weeks after finishing Scrambler therapy, whether they would recommend such treatment for other patients with similar problems. In response to this question, 83%, 1%, and 16% responded yes, no, and unsure, respectively.

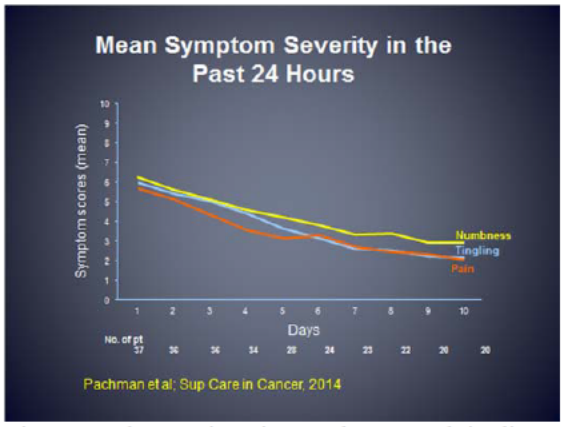


Figure 4: Changes in pain, numbness, and tingling during Scrambler therapy.

The first attempt to compare Scrambler therapy to a sham control was presented as an abstract at the 2013 Annual Meeting of the American Society of Clinical Oncology, involving 14 patients who were treated in a randomized, controlled, double-blind manner (Campbell, Nimunkar et al. 2013). Results have not been published as a manuscript. While the authors did note that the sham treatment from this particular trial was believable, in that most patients could not detect which of the two procedures was the true one, the authors did not observe any real improvements in neuropathy in the patients treated with the sham procedure versus Scrambler therapy. This may well have been because this group had little experience with Scrambler therapy prior to conducting their study and did not use the proper technique for applying this therapy. This finding fits with above-noted work that observed that there is a learning curve for the appropriate application of this therapy for treating chemotherapy neuropathy(Pachman, Weisbrod et al. 2014), which likely also applies to the treatment of other conditions. Additionally, the results of this trial support that there was not much of a placebo effect in this trial, as no benefit was noted in either trial arm. Paradoxically, this would support the argument that the positive results reported in other chemotherapy neuropathy Scrambler therapy trials are not just ascribable to a placebo effect.

The most recently reported trial was a double-blind, placebo-controlled, randomized clinical trial involving 30 patients with low back pain, was reported from Virginia Commonwealth University.(Starkweather, Coyne et al. 2015) These authors noted significant decreases in the Brief Pain Inventory back pain scores and pain interference scores ($P \leq 0.05$). They also noted improvements in pain sensitivity, participants' thresholds for pain from a noxious stimulus in the initially painful area. Of note, the group randomized to Scrambler therapy had substantial decreases in 10 serum mRNAs associated with nerve pain such as Nerve Growth Factor (NGF) and Glial Derived Nerve Factor (GDNF), compared to no decreases in the sham group, understanding that these mRNAs have not yet been established correlates for pain.

Turning to the clinical practice experiences, as opposed to the prospective trials, two case series, published in 2013, each included three patients with cancer pain or post-herpetic pain (Campbell, Nimunkar et al. 2013; Park, Sin et al. 2013). Both of these reports came from different authors in Korea and both reported positive benefits in the patients who were treated.

Sparadeo et al. reported their clinical practice experience regarding 91 of their initial 173 patients, representing all of those for whom they had collected data. These patients had a variety of pain syndromes, including complex regional pain syndrome (CRPS), spine pain, neuralgias (such as post-herpetic or post-chemotherapy), and multi-focal pain problems(Sparadeo F 2012). As part of their practice, with these 91 patients, they collected visual pain scores before and after each treatment for all of them and Brief Pain Inventory (BPI) questionnaires prior to treatment initiation in a subset of them, at three and six month follow-ups. The mean pain score prior to the first treatment was 7.2/10 and it was 3.0/10 on the 10^{th} day, prior to that day's treatment. Relatively similar results were seen for the different pain syndromes. BPI scores at three to six months of follow-up were reported to be improved by more than 50%.

In a second manuscript, Sparadeo and D'Amato (Sparadeo and D'Amato 2014) analyzed the pre- and post-treatment data of 95 individuals (some of whom had been reported in the previous publication) entering their Scrambler therapy program for treatment of chronic neuropathic pain, divided into two groups: Complex Regional Pain Syndrome and Chronic Spine-Based Pain. All patients were weaned from opioids and anticonvulsants being used for pain control. The data analysis revealed that 70% of the entire sample was still reporting significant improvement three to six months following treatment. The two studied groups had similar levels of pain and degrees of lifestyle impact. Additionally, the 3-6 month successes were similar in the two treatment groups.

1.5 Does Scrambler Therapy Actually Work?

Arguments against Scrambler therapy certainly exist, with critics attributing much of the benefit to a placebo effect. Some of the positive endorsements in social media and on the internet are only anecdotal. Additionally, the developer of Scrambler therapy participated in the initial clinical trials, and this could be perceived as a potential conflict of interest even though it is scientifically desirable and logical to expect that the same person who invented this therapy, would be one to report the results. Additionally, there are no large, placebo-controlled, double-blinded clinical trials to estimate the effectiveness of Scrambler therapy.

On the other hand, while some reports (Marineo 2003; Sabato, Marineo et al. 2005; Marineo, Iorno et al. 2011; Coyne, Wan et al. 2013) involved the inventor of the Scrambler device, these positive findings have been independently replicated by diverse groups (Smith, Coyne et al. 2010; Abdi, Lakkimsetty et al. 2011; Ghatak, Nandi et al. 2011; Ricci, Pirotti et al. 2011; Sparadeo F 2012; Campbell, Nimunkar et al. 2013; Coyne, Wan et al. 2013; Park, Sin et al. 2013; Moon, Kurihara et al. 2014; Pachman, Weisbrod et al. 2014; Sparadeo and D'Amato 2014; Starkweather, Coyne et al. 2015) in nearly all of the reported studies, involving over 700 patients in total. In some cases, the benefit achieved has been substantial, with some patients achieving complete pain resolution and substantially reduced dependence on pharmacologic therapy. There has been only one report of a negative experience [(Campbell, Nimunkar et al. 2013)]. This was from one small, placebo-controlled trial in patients with chemotherapy-induced peripheral neuropathy. This was published only as an abstract, did not show much of a reduction in either study arm (arguing against a placebo effect), and it is worth noting that

the group did not have much experience using Scrambler therapy prior to conducting this trial. This raises concerns regarding the validity of this trial as data have demonstrated an extended learning curve with the provision of Scrambler therapy, particularly for chemotherapy-induced neuropathy (Pachman, Weisbrod et al. 2014).

1.6 Additional Research is Needed

Additional work is needed to better understand the mechanism of Scrambler therapy and to conduct larger randomized clinical trials investigating the efficacy of Scrambler therapy in a number of chronic pain states. Randomized, sham-controlled double-blinded trials, involving patients with a variety of chronic pain syndromes, would strengthen the conclusions from initial studies. The data compiled, to date, support the feasibility and value of such an undertaking. However, there is significant controversy amongst those who treat patients with Scrambler therapy as to whether a blinded placebo control is realistic. Part of the process of correct treatment is placing the electrodes properly and getting feedback from the patient that the pain has been markedly improved. If that is not achieved, the leads should be reapplied in a different area and the process repeated until there is success in replacing the patient's perception of pain with the characteristic pleasant sensation from the Scrambler's electric stimuli, and markedly improving the initial pain. It is, thus, argued by some that the nature of the treatment technique makes placebo control impractical, just as in certain surgical procedures (e.g. laparoscopic versus open colectomy(2004). Thus, it could be argued that trials should be randomized and compared to other potential treatments, rather than a placebo. An example of such a trial was discussed above where Scrambler therapy was compared to guideline-based drug therapy (Marineo, Iorno et al. 2011).

The possibility of variability in treatment outcomes being attributed to differences in how and where electrodes are applied suggest that the next phase of research more objectively evaluate fidelity to intervention in terms of electrode placement over repeated sessions. We suspect that there is a group learning phenomenon in how electrodes are placed serially, such that teams delivering the intervention may get better at delivering the intervention over time. In order for larger scale trials with more heterogeneous teams to eventually implement a trial of scrambler therapy, we need to gather more information about fidelity to the intervention through direct observation with video technology.

1.7 Rationale for using TENS as a control

TENS (Transcutaneous electrical nerve stimulation) therapy, first developed in 1974, has been utilized for treatment of neuropathic pain from a variety of causes.

TENS is commonly done using a small unit, operated by a battery, with 2-4 leads that can be applied to the skin via sticky attachment pads. They are usually available for patients to use at home, following some relatively simple instructions.

A few small studies have explored TENS units for treatment of diabetic neuropathy. Whereas these small studies have not demonstrated convincing evidence of benefit on their own, a meta-analysis suggests that TENS may provide some benefit for diabetic neuropathy.(Jin, Xu et al. 2010; Pieber, Herceg et al. 2010) Nonetheless, it is generally agreed that larger, placebo-controlled clinical trials are necessary to delineate whether TENS is helpful for diabetic neuropathy.

To our knowledge, there are no good studies available looking at TENS therapy for treatment of chemotherapy-induced peripheral neuropathy.

There are potential pros and cons for evaluating TENS as a sham control. The advantages are that it has similarities to the Scrambler machine. For example, wires are placed on the skin in a similar manner and an electrostimulation sensation is felt by patients in a similar manner. The major disadvantage of using TENS as a control is that it, potentially, may actually help chemotherapy-induced peripheral neuropathy.

1.8 mRNA Information

Starkweather et al described mRNA gene expression changes in patients who received real versus sham Scrambler therapy. Starkweather et al treated 15 patients with real ST and 15 with sham ST for persistent low back pain, and observed in the ST group a significant downregulation in the serum mRNAs for 17 pain genes such BDKRB1 and NGF at the 3 week mark, many of which code for proteins and receptors that mediate inflammation and nociceptive signaling. (Table 1.71) (Starkweather, Coyne et al. 2015). We will also obtain a white blood count (WBC) collected as CBC with differential, as this count will help to illustrate that there were reasonable numbers of WBCs to obtain the RNA for testing.

Table 1.71. Differential Gene Expression in the Calmare Group at 3 Weeks Post-Treatment

Gene	Fold Regulation[a]	p value
BDKRB1	-2.468	0.0069
CACNA1B	-1.518	0.0091
CHRNA4	-1.924	0.0053
GDNF -2.141	-2.141	0.0036
GRM1 -1.715	-1.715	0.0033
NGF	-2.599	0.0040
NTRK1	-1.980	0.0035
OPRD1	-1.812	0.0049
PENK	-1.850	0.0042
PLA2G1B	-1.816	0.0020

[a]Difference from sham treatment group.

1.9a fMRI Discussion

1.9a1 Functional neuroimaging

Functional neuroimaging, specifically functional MRI (fMRI), produces characteristic patterns during pain activity (Peyron, Laurent et al. 2000). Though the CNS circuit of transduction of pain is relatively well-defined (involving relay of a signal from dorsal root ganglia to dorsal horn, thalamus, and ultimately cortex), it has been postulated that evaluating brain conditions, in terms of functional connectivity, will be of high yield, given the alterations that occur during pain states (Borsook, Becerra et al. 2011). An elegant example of this has been shown with the use of fMRI in complex regional pain syndrome (CRPS), which provided evidence of change in CNS circuitry, as it relates to pain processing (Lebel, Becerra et al. 2008). fMRI has also been used in a similar manner to evaluate CNS processing in migraineurs, both during and between attacks, with presently defined brainstem, sub-cortical, and cortical changes(Sprenger and Borsook 2012). More recently, fMRI has been used at Mayo in a study led by Dr. Fred Cutrer (Mayo Department of Neurology) to define alterations in functional differences in patients with chronic daily migraine headache versus patients who have reverted from chronic to episodic migraine.

The preliminary findings from these studies have been encouraging.

1.9a2 fMRI use in this study

Drawing on its use in neuro-imaging of other pain states, we see opportunity to characterize changes in CNS processing of patients with chronic pain conditions receiving ST. This approach would not only enable reporting of objective data, but also potentially elucidate the mechanism of ST, which currently remains hypothetical. Of note, unpublished data presented in Korea showed dramatic improvement of the fMRI in patients treated with Scrambler Therapy, lasting at least 3 months. (Kong Sung Taik. Scientific Validation on Scrambler Therapy - Case Result of Resting-State fMRI. International Symposium: New Paradigm in Pain Management, September 27, 2014, Seoul)

The fMRI sequences will be analyzed and interpreted with assistance of investigator David Borsook MD PhD, a neurologist and Chair in Pain Systems Neuroscience at Boston Children's Hospital, and his colleague, Lino Becerra PhD. Both of these individuals are experts in the use of functional imaging in pain conditions.

Brain system adaptations in responders (greater than 50% pain or tingling reduction) vs. non-responders data will be provided from this work.

1.9b Sensation Changes

Our clinical experience with patients receiving Scrambler therapy has supported that patients develop improved normal sensation in areas treated with Scrambler therpy. This includes improved feeling and proprioception. Thus, we plan to look at quatitative sensory testing (QST) in a subset of patients on this trial. Dr Peter Dyck and colleagues at Mayo have world-renowned expertise in this area. We will, in an exploratory manner, obtain touch pressure and heat pain testing on both the dorsal foot and the lateral leg in 10 patients per study arm, before Scrambler/TENS therapy and on the last couple days of ScramblerTENS therapy.

1.9c Audiovisual recording rationale

As Scrambler therapy is operator dependent and there is a learning curve with providing it, obtaining audiovisual recording of the treatment sessions should be helpful. This recording may allow us to ask for outside input for individual treatments that are being performed. It may also allow us to provide examples of successful treatment of individual patients. Of course, patient confidentiality issues need to be kept in mind.

We are proposing to include video recording of intervention delivery into the routine delivery of the intervention. Using established direction/observation protocols developed with local clinical communication research experts, we will consent patients to be video recorded.

Dr Jon Tilburt, a co-investigator on this protocol, has extensive expertise with regard to patient communication topics, which have included audiovisual recording sessions of patient encounters. After the trial is completed this recordings may be used to conduct a structured "fidelity to treatment" analysis in which two independent raters score the recorded intervention delivery for fidelity to protocol a priori criteria based on scientific expert criteria. If we do this, raters will be blind to the final clinical outcomes of participants, although they would hear patients' thoughts while they were getting the treatments.

2.0 Goals

2.1 Goal 1 Efficacy

Evaluate the efficacy of Scrambler therapy compared to TENS therapy for pain and/or tingling related to CIPN.

Hypothesis 1: Scrambler therapy will improve pain related to chemotherapy induced neuropathy more than TENS therapy.

2.2 Goal 2 Tolerability

Evaluate the tolerability of Scrambler therapy and compare it to TENS therapy, in this population.

Hypothesis 2: Scrambler therapy will be well tolerated and there will be no substantial differences in side effects between the Scrambler and TENS treatment groups.

2.3 Goal 3 Efficacy

Evaluate whether Scrambler therapy, compared to TENS therapy, can decrease the use of pain medication for CIPN.

Hypothesis 3: Pain medication and morphine oral equivalent dose (MOED) daily amounts will decrease more in the group receiving Scrambler therapy, compared to those who received TENS therapy.

2.4 Goal 4 mRNA

Explore whether mRNA gene expression before and after scrambler therapy shows similar findings to what Starkweather et al observed.

Hypothesis 4: Scrambler therapy will be associated with mRNA gene expression modifications as was previously reported by Starkweather et al.

2.5 Goal 5 fMRI

Utilizing high-field MRI, to define alterations in functional differences (using resting state BOLD measures to measure differences in functional connectivity) in treated with the Scrambler device in the setting of chemotherapy induced peripheral neuropathy pain. In the same subjects, we will utilize high-field MRI to measure morphometric changes in specific cortical (cingulate, S1 and hippocampus) and subcortical regions (basal ganglia).

Hypothesis 5: Scrambler therapy will be associated with fMRI changes

2.6 Goal 6 Quantitative Sensory Testing

Explore whether Scrambler therapy will alter sensation.

Hypothesis 6: Scrambler therapy will be associated with improved sensation, as detected by quantitative sensory testing.

3.0 Patient Eligibility

3.1 Inclusion criteria

3.11 Age ≥18 years.

3.12 Pain or symptoms of CIPN of ≥3 months duration, for which the patient wants intervention.
NOTE: Neurotoxic chemotherapy must have been completed ≥3 months prior to registration and there must be no further planned neurotoxic chemotherapy for >5 months after registration.

3.13 Patients have to relate that tingling or pain was at least a four out of ten problem ≤7 days prior to registration, on a 0-10 scale where zero was no problem and ten was the worst possible problem.
NOTE: The patient is expected to have tingling or pain of at least 4/10 at the time of the first treatment (Appendix II: A or B).

3.14 ECOG Performance Status (PS) = 0, 1, or 2.

ECOG Performance Status*	
	ECOG Performance Status
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

*As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5 649-655, 1982.

3.15 Life expectancy ≥6 months.

3.16 Ability to complete questionnaire(s) by themselves or with assistance.

3.17 Ability to provide informed written consent.

3.18 Case review by the study chair, or designate, as a case where treatment should be tried.

3.2 Exclusion Criteria

3.21 Any of the following because this study involves an investigational device whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:
- Pregnant women
- Nursing women
- Women of childbearing potential who are unwilling to employ adequate contraception

3.22 Existing operational implantable drug delivery systems, e.g. Medtronic

Synchromed.

3.23 Existing implantable medical electronic devices, life-supporting medical devices, and medical monitoring devices.
Note: Metal implants for orthopedic repair, e.g. pins, clips, plates, cages, joint replacements are allowed, as are central venous access devices.

3.24 History of myocardial infarction or ischemic heart disease within the past six months.

3.25 History of epilepsy, brain damage, use of anticonvulsants for seizure prevention, concurrently using ketamine, symptomatic brain metastases.

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

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

3.28 Currently receiving gabapentin or pregabalin and not willing to be weaned off of these medications prior to Scrambler therapy initiation.
Note: It is OK to continue these medications in patients who are receiving TENS. (See Appendix I).

3.29a History of peripheral neuropathy prior to receiving neurotoxic chemotherapy.

3.29b Prior treatment with Scrambler therapy.

4.0 Test Schedule

Use for first treatment period; repeat for second treatment period

Tests and procedures	Active Monitoring Phase				
	≤30 days prior to registration	Day 1, Prior to therapy	Daily for 14 consecutive days beginning on Day 1 of active therapy	Last day of assigned therapy (±1 day)	Weekly for 8 weeks
History and exam, PS[1], Eligibility questions[2] (Appendix II: A or B)	X				
Pregnancy test[3]		X			
Declaration of most problematic site (upper versus lower extremities) and most problematic symptom (tingling versus pain): Appendix III	X				
Pain/tingling questionnaire regarding the prior week (Appendix IV: A or B)		X[4]			
Patient Questionnaire: Before each treatment (Appendix V: A or B)		X[5]	X[5]		
Patient Questionnaire: After each treatment (Appendix VI: A or B)			X[5]		
EORTC CIPN 20 (Appendix VII)		X		X[6]	X
Patient Questionnaire: Analgesic Use (Appendix VIII)		X	X		X
Patient Questionnaire After each therapy and during weekly follow-up: Global Impression of Change and Patient Preference (Appendix IX: A or B)			X[7]		X[7]
Daily Treatment Log and Adverse Assessment (Appendix X)			X		
Individual Patient Dermatome Map-Electrode Placement (Appendix XI) Scrambler only			X		
Audiovisual recordings[R]			X[8]		
Weekly follow-up patient questionnaire (Appendix XII:A or B)					X[9]
Written patient summary (if the patient is willing to provide)[R]					X[10]
Research Blood draw for CBC/diff and mRNA[11,R]		X		X	
fMRI[12,R]		X		X	
Quantitative Sensory Testing[13,R]		X		X	

Tests and procedures	Active Monitoring Phase				
	≤30 days prior to registration	Day 1, Prior to therapy	Daily for 14 consecutive days beginning on Day 1 of active therapy	Last day of assigned therapy (±1 day)	Weekly for 8 weeks
Study Coordinator/Nurse phone call to discuss therapy and any concerns, record any adverse events that are reported and to remind the patient to complete questionnaires and mail them			X[14]		X

Footnotes:

1. PS must be done ≤7 days prior to registration.
2. Appendix II A or B, as labeled depending on neuropathy area type. (This evaluation is used for eligibility.)
3. For women of childbearing potential only. Must be done prior to first Scrambler therapy (or the first day of the second treatment period, if Scrambler therapy is crossover).
   NOTE: This testing is not needed for TENS therapy.
4. Appendix IV A or B, as labeled depending on neuropathy area to be treated
5. Beginning on Day 1 of active treatment and continuing for 14 consecutive days, complete Appendix V daily pre/post therapy. If no therapy is received on a day during this timeframe, complete once daily. To be filled out only for primarily treated area. For post-therapy questionnaires VIA and VIB.
6. Prior to the last therapy.
7. Appendix IX A or B, as labeled depending on pain or neuropathy area to be treated.
8. If patient provides written consent for AV recording. Recording may be done on any day.
9. Appendix XII A or B, as labeled depending on pain or neuropathy area to be treated.
10. To be completed any time after completion of active treatment.
11. Optional use in selected patients: Blood draws are completed at Baseline (prior to treatment) and on the last planned day or two of treatment (e.g., Day 9 or 10, if 10 treatments are given but sooner if earlier treatment completion is planned) (±2 days). Ideally, do prior to treatment. See Section 14.0.
12. fMRI: Optional use in selected patients, do at baseline and on approximately the last day of the initial treatment (±1 day).
13. Quantitative sensory testing: Optional use in selected patients, do at baseline and then the last day of the initial treatment (±3 days) on 10 patients from each cohort. Do prior to treatment.
14. For TENS patients only: Study Coordinator or Nurse to call on Treatment Day 2 and once on Treatment Day 8-10 to assess toxicities and remind the patient to complete daily questionnaires and mail them back.

R Research funded

5.0 Stratification Factors

5.1 Gender: Male vs female.

5.2 Causative drug: Paclitaxel-regimen vs oxaliplatin-regimen vs other/combination.

5.3 Primary problematic area: Upper vs lower extremity.

5.4 Primary problematic symptom: Pain vs tingling.

6.0 Registration/Randomization Procedures

6.1 Registration Procedures

6.11 To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at ([redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page [redacted] and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office [redacted]. If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.12 Correlative Research

An optional correlative research component is part of this study, there will be an option to select if the patient is to be registered onto this component (see Sections 7.0 and 14.0).

- Patient has/has not given permission to give his/her blood sample for research testing
- Patient has/has not given permission to have functional MRI testing (fMRI) for research testing
- Patient has/has not given permission to have Quantitative Sensory Testing (QSART) for research testing
- Patient has/has not given permission to have audiovisual recording for research testing

At the time of registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her sample(s) for future research of cancer at Mayo.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.
- Patient has/has not given permission for MCCC to give his/her sample(s) to researchers at other institutions.

6.2 IRB approval

Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office (fax: [redacted]. If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.3 Verification

Prior to accepting the registration, registration application will verify the following:

- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.4 Treatment location requirements

Treatment on this protocol must commence at Mayo Clinic Rochester under the supervision of a medical oncologist, pain specialist, or associated allied health personnel.

6.5 Start of treatment

Treatment cannot begin prior to registration and must begin ≤50 days after registration.

6.6 Booklets

Patient questionnaire booklet is available on site; copies are not acceptable for these submissions.

6.7 Randomization Procedures

6.71 The factors defined in Section 5.0, together with the registering membership, will be used as stratification factors.

6.72 After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups.

- Scrambler Therapy
- TENS Therapy

6.8 Optional continuation - Treatment Crossover

6.81 Patient may enter crossover treatment once original 2 weeks of treatment and 8 weeks of observation are complete.

6.82 Complete Optional Crossover Continuation form.

7.0 Protocol Treatment

7.1 Treatment Schedule for Scrambler arm

7.11 **Day 1- Initial treatment**

7.111 The locations of symptoms will be assessed.

7.112 Pretreatment questionnaires completed

7.113 Placement of electrodes and treatment

A decision will be made by the treating person as to where electrodes should be placed, keeping in mind that the general principal regarding Scrambler Therapy is that the cutaneous EKG electrode patches, or channels, are applied above and below the area of pain/tingling if possible. The placement of the electrode pair of each channel follow the "geometry" of the pain, which in CIPN normally extends in vertical arrangement. See appendix XIII for principles of this treatment.

More specifically, the treatment is carried out using surface electrodes, two for each channel (maximum 5) of the device, depending on need. Choosing where to apply the electrodes is important. As basic technique, the electrodes should never be applied directly on the painful area, but, ideally, should be 2-3 fingerbreadths proximal, distal, or lateral to the pain.

Treatment should be started and over about 10-30 seconds, the intensity should be increased to the maximal level that is tolerated. In doing so, the operator will ask the patient to let it be known when they feel any stimulation, then when they note any stinging feeling and then when any stinging is too uncomfortable. The goal is to have the patient at the highest tolerable setting while helping the baseline tinging and/or pain and to be below any substantial discomfort under the electrodes.

The patient should then be asked whether he/she has any residual pain/tingling in the area of focus. The goal is to reduce all pain to zero. If there is residual pain, then the operator can choose to increase intensity if possible, relocate the electrodes of the initial channel, or, if there is substantial improvement with the initial channel and pain is outside the area of the initial channel, another channel can be used to treat the residual pain/tingling area, again striving for a complete resolution of the discomfort.

If a patient develops pain or a burning sensation with any of the electrodes, then the treatment should be interrupted and the electrode should be moved farther away from the pain source. For the electrodes that were moved, the intensity should start again as described above.

7.12 **Subsequent days of Scrambler Therapy**

7.121 Treatment will be administered using the above outlined principles of the recommended scrambler for 30 minutes of application time, on up to 10 consecutive weekdays as long as the patient has numbness/pain/tingling rating of more than 0 at the time they come in for treatment. This is

because without pain, there is no guidance to the provider about electrode placement. Subsequent treatments can rapidly be titrated up to the highest intensity tolerated during the previous treatment. Up to three days may be skipped to allow for weekends and holidays, if needed. Treatment must start on a Monday, Tuesday, or Wednesday; with the goal being 3 consecutive days of treatment before break (e.g. treatment cannot start Wednesday before Thanksgiving holiday weekend). The total of 10 treatments must be scheduled to be able to be completed within 16 calendar days).

7.122 The electrode placement may be modified on subsequent days, depending on how a patient responds to treatment.

7.2 Treatment Schedule for TENS arm

7.21 TENS Treatment Procedure

7.211 The patient will be given a new TENS machine that they will be able to keep. This unit will include a set of directions for use of this machine.

7.212 The study nurse will explain how to use the TENS machine, including a hands on learning session.

7.213 Written instructions will also be provided to the patient (Appendix XIV)

7.214 The patient will be instructed to use the TENS machine for 30 minutes per day, for 14 days, to address the area deemed most problematic (upper or lower extremities) of CIPN.

7.215 If the patient has questions during their 2 week treatment, they can call the study nurse.

7.216 The patient may also use the TENS on other areas of involvement (e.g. if their lower extremities are the main focus of the study, they may also treat their upper extremities).

7.3 Optional Substudies

7.31 **Functional MRI (fMRI)**

We plan to do fMRI on a subset of 12 patients, before Scrambler therapy and on the last planned day or two of treatment (±1 day).

We will use the same approach have been used in the past for imaging experiments (Lebel, Becerra et al. 2008; Upadhyay, Knudsen et al. 2008; Upadhyay, Maleki et al. 2010). Subjects will be scanned on a HDxt 3.0T - 60cm TRM,Spectro (GE). During the MR session, subjects will be placed in the magnet for the experimental procedure and attached to various physiological monitoring apparatuses. During the experimental procedure, a series of standard anatomical images will be acquired. Once the anatomical images are completed, subjects will also undergo RSN (10 min), and DTI (10 min) imaging. The total estimated time the subject will be inside the magnet is 60 minutes. The imaging details are described below.

Anatomical Scans: We will use an established approach for imaging experiments. Subjects will be scanned on a 3.0T - 60cm TRM, Spectro (GE).). We will acquire anatomical images using a magnetization prepared rapid gradient echo (MPRAGE) sequence (128 1.33mm-thick slices with an in-plane resolution of 1 mm (256x256)).

Resting State Scans (RSN): We will first obtain magnitude and phase images to unwarp functional scans; slice location, number, and thickness will be the same as those used in functional scans consisting of 41 slices with isotropic voxels (3mm) and 64x64 in-plane resolution. Then for RSN, we will generate images with a Gradient Echo EPI sequence (TR/TE = 2.5/30ms); 120 volumes will be collected per functional scan.

Diffusion Tensor Imaging (DTI): We will collect all DTI data using a single, shot-twice refocused echo planar pulse sequence at a 1.75 x 1.75 x 2.5 mm^3 resolution. We will collect 8 single, non-diffusion weighted (b = 0 sec/mm2) volumes and 72, diffusion-weighted volumes with different gradient orientation at b = 1000 sec/mm^2 (TR = 7900 msec, TE = 92 msec, 5/8 partial Fourier, 3-fold SENSE acceleration). Fifty axial slices are sufficient to cover the entire cerebral cortex.

7.32 mRNA blood testing

mRNA blood testing will be done on a subset of 12 patients. Blood draws for CBC with differential and mRNA are completed at Baseline (prior to treatment) and on the last day or two of treatment (e.g., Day 9 or 10, if 10 treatments are given but sooner if earlier treatment completion is planned; ideally collected prior to treatment) (±2 days).

For details on collection and processing see Section 14.0.

7.33 Audiovisual recording

For patients receiving Scrambler therapy who agree to participate in the audio-visual recording portion of this current trial, the established procedures are outlined below:

- An audio-video recording device will be placed in the treatment room prior to starting Scrambler Therapy. The device runs during the treatment and then is turned off.
- A study assistant will upload video files to a secure server the day of each recording.
- Files will be named “StudyID_Date” (MC15C1_3-2-2016) and placed in an “Original Recordings” folder.
- Files will be converted to Audacity and WAV formats.
- Recordings will be removed from the recorders following overnight backup on the specified research server.
- Audio-video recording files will be deidentified (e.g. removal of names) using Audacity editing software.
- After recordings have been de-identified, they will be converted to .WAV file type and stored for future review.

7.34 Quantitative Sensory Testing (QST)

We will do QST before Scrambler/TENS therapy and on the last day (±3 days)of Scrambler/TENS therapy. We will only do this testing on patients that have lower extremity neuropathy as their major symptom (as opposed to upper

extremity neuropathy). We will obtain touch pressure and heat pain testing on both the dorsal foot and the lateral leg in 10 patients per study arm.

This testing will be ordered as a clinical test and paid for by research dollars. Note: [redacted] is our contact person for ordering this test and the IRB number should be noted when ordering it.

7.4 Optional Crossover Continuation

7.41 Patients electing to crossover to the opposite treatment arm will be expected to complete an additional 2 weeks of treatment and 8 weeks of observation.

7.42 Substudies will not be offered for patients on crossover/continuation except by permission of PI.

8.0 Dosage Modification Based on Adverse Events

If a patient develops any substantial toxicity from the treatment (not expected), then treatment with either TENS or Scrambler therapty should be stopped.

9.0 Ancillary Treatment/Supportive Care

9.1 Full supportive care

Patients should, otherwise receive appropriate supportive care for their pain as clinically indicated.

9.2 Gabapentinoid use

Patients should not receive gabapentinoids (e.g. Neurontin®, Lyrica®) during treatment with Scrambler therapy. If patients are on gabapentinoids at the time of registration and are randomized to Scrambler therapy, they must be weaned off prior to receiving Scrambler therapy.

9.3 Other pain treatment

Other pain treatments are allowed if the pain is not satisfactorily controlled. All pain treatments and pain-related medications will be recorded.

9.4 Investigational agents

Concurrent use of investigational agents is not permitted unless preapproved by PI.

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using a copy of the CTCAE v4.0. Next, determine whether the event is expected or unexpected (refer to Sections 10.12 and if the adverse event is related to the medical treatment or procedure (see Section 10.13). With this information, determine whether an adverse event should be reported as an expedited report (see Section 10.2) or as part of the routinely reported clinical data. Important: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.3).

Expedited and routine reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.2 and 10.3. All expedited AE reports must also be sent to the local Institutional Review Board (IRB) according to local IRB's policies and procedures.

10.12 Expected vs. Unexpected

- The determination of whether an AE is expected is based on adverse event information provided in Section 10.3 of the protocol.
- Unexpected AEs are those not listed in the adverse event information provided in Section 10.3 of the protocol.

10.13 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:
Definite - The adverse event *is clearly related* to the investigational agent(s).
Probable - The adverse event *is likely related* to the investigational agent(s).
Possible - The adverse event *may be related* to the investigational agent(s).
Unlikely - The adverse event *is doubtfully related* to the investigational agent(s).
Unrelated - The adverse event *is clearly NOT related* to the investigational agent(s)

10.2 Expedited Adverse Event Reporting Requirements

	Grade 4 or 5 Unexpected with Attribution of Possible, Probable, or Definite	Increased Incidence of an Expected AE[1]
FDA Form 3500 (MedWatch) within 10 working days[2]	X	X

1. An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AEs is reported in the package insert or the literature, including AEs resulting from a drug overdose.
2. Submit form to the FDA, MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, by fax at 1-800-332-0178 or online at http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm.

Mayo Clinic Cancer Center (MCCC) Institutions: Attach copies to the Mayo Cancer Center SAE Reporting Form:

[redacted]

The MCCC Regulatory Affairs Unit (RAU) Risk Information Specialist will determine and complete IRB reporting. The RAU will submit to the MCCC SAE Coordinator.

10.3 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading: NONE.

10.31 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.3:

10.311 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.312 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.313 Grade 5 AEs (Deaths)

10.3131 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.3132 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

11.0 Measurement of Effect?

11.1 Primary means of assessment

Patient reported outcome data, as illustrated in the appendices will be the primary means of assessment.

11.2 Adverse Event Assessment

Adverse events will be evaluated by using CTCAE criteria based on patient reporting and nurse observation and/or assessment.

11.3 mRNA

mRNA results will be correlated with outcomes. See Section 14.0.

11.4 Functional MRIs (fMRI)

fMRI results will be correlated with outcomes. See Appendix XV.

12.0 Descriptive Factors

12.1 Age *(years)*: <70 vs. ≥70
12.2 Duration of pain or neuropathy symptoms in months at baseline: 3 to 6 vs. >6.

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Ineligible

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry.

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted.
- If the patient never received treatment, on-study material must be submitted.

13.2 Major violation

A patient is deemed a *major violation*, if protocol requirements regarding treatment in Cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted.

13.3 Cancel

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given.

14.0 Body Fluid Biospecimens

In a subset of patients, blood will be obtained to look at mRNA gene expression in patients before and after Scrambler and TENS therapy

14.1 Summary Table of Research Blood and Body Fluid Specimens to be Collected for this Protocol*

Correlative Study (Section for more information)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Baseline Prior to Tx	Last Day of Tx ±2 days	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
mRNA gene expression (Section 14.2)	Optional	Whole Blood	EDTA (lavender)	6 mL (1)	X	X	No	Ambient
CBC with differential for correlation with mRNA	Optional	Whole Blood	EDTA (lavender)	3 mL (1)	X	X	Yes**	Ambient

*NOTE: Collection is only at Mayo Clinic in Rochester, MN

**Process through clinical lab so results are in medical record

14.2 Collection and Processing

14.21 mRNA gene expression

The samples will be obtained prior to the first Scrambler therapy and on the last day (±2 days) of Scrambler therapy.

14.3 Shipping and Handling

14.31 Kits will not be used.

14.32 After collection, blood will be taken directly to Dr Andreas Beutler's laboratory on Guggenheim 13 for processing.

14.4 Background and Methodology

14.41 **mRNA Gene Expression**

We, through Dr Andreas Beutler's lab, will obtain RNA expression levels that will be directly comparable to the originally reported assay, i.e., relative changes such as before and after treatment. This result will be expressed as a "fold change", such as saying "after scrambler the expression levels of gene X was increased 2-fold and Y was diminished to 0.7-fold." That calculation will be made relative to a reference gene that is assumed to be stable.

We will do RNA quantification genome-wide. The panel will then represented by genes of interest and a dozen reference genes, out of ca. 11,000-15,000 genes for which reliable expression levels will be available.

Via this process, we will look at all of the interesting-appearing genes from the Starkweather et al manuscript. This method will allow us to, hopefully, confirm that the gene changes were in line with that previously reported.

15.0 Drug Information – Not applicable

16.0 Statistical Considerations and Methodology

16.1 Primary Endpoint

The primary endpoint of this study is the proportion of patients who achieve at least 50% reduction in pain or tingling scores from baseline after two weeks of therapy.

16.2 Study Design

This is a prospective randomized study to explore the efficacy of Scrambler therapy compared to TENS therapy for the treatment of chemotherapy induced peripheral neuropathy. Patients will be randomized at a 1:1 ratio to receive either scrambler therapy or TENS therapy for two weeks and will be observed for eight weeks following treatment. The primary outcome is the reduction in pain or tingling scores after 2 weeks of scrambler therapy or TENS therapy.

At the end of the eight-week observational period, patients are allowed to cross over to receive the other therapy for two weeks and will, again, be followed for an additional eight weeks. Outcomes of this second period of treatment are for exploratory purposes only. There will be no fMRI, quantitative sensory testing, or mRNA gene expression done in this second period.

16.3 Analysis Plan

16.31 Primary endpoint

Evaluate the efficacy of Scrambler therapy compared to TENS therapy for pain and/or tingling related to CIPN.

The main efficacy endpoint is defined as achieving 50% reduction in pain or tingling from baseline. At enrollment, patients will be asked to select either pain or tingling as their primary symptom of concern. Allowing the patients to select their main symptom (pain or tingling) is reasonable since the scores and the patterns of reduction were similar for pain and tingling after Scrambler therapy as shown by Pachman et al.(Pachman, Weisbrod et al. 2014)

Descriptive statistics (mean, sd, median, range) of pain and tingling scores and changes pre- and post-treatment scores will be summarized and the percentage of pain and tingling reduction from baseline will be calculated for each timepoint, separately by treatment arm. Longitudinal plots of scores by arm will be provided. The frequency and percentages of patients who achieved more than 50% reduction in pain and/or tingling scores after 2 weeks of therapy (scores from the last treatment day compared to the pre-treatment data, using the question related to average symptom [pain or tingling, whichever the patient chose when entering the study] over the previous 24 hours) and after 8 weeks of observation (scores from Week 8 form) from baseline (scores from Day 1 pre-treatment form) will be summarized by treatment arm and will be compared between arms using a Chi-square test (or Fisher-exact test as appropriate).

16.32 Secondary efficacy endpoints

Perceived treatment efficacy from the Subjective Global Impression of Change instrument (Appendix IXA and B) will be summarized (median and range for impression of change and frequency for preference) by arm and compared

(Wicoxon rank-sum test for impression of change and Chi-square test for preference) between treatment arms.

EORTC CIPN20 scores and changes in scores will be summarized (mean, sd, median, range) at each time point by arm and will be compared between arms using two-sample t-tests.

16.33 Goal: Evaluate the tolerability of Scrambler therapy and compare it to TENS therapy, in this population.

Frequency and type of toxicities occurred during therapy will be summarized by treatment arm and compared between arms using Fisher-exact test.

16.34 Goal: Evaluate whether Scrambler therapy, compared to TENS therapy, can decrease the use of pain medication for CIPN.

Type and frequency of analgesic used will be summarized by treatment arms and will be compared using Fisher-exact test.

16.35 Goal: Explore whether mRNA gene expression changes are similar to that previously reported by Starkweather et al.

In a descriptive manner, the gene expression will be compared to what was previously reported.

16.36 Goal: Explore whether Scrambler therapy will change fMRI.

Changes in fMRI following Scrambler therapy will be described in the subset of patients selected for this component of the study.

16.37 Descriptive statistics will be used for the data from Quantitative Sensory Testing.

16.4 Accrual and Duration of Study

We plan to accrue 50 patients on this trial. Given our previous experience with requests for Scrambler Therapy, we estimate an accrual rate of 3 patients per month so that we expect to complete accrual within 1.5 years. With a maximum total time of treatment and observation of 5 months, the expected total duration of the study is 2 years.

16.5 Sample size

The sample size of 50 patients (25 per arm) in this prospective randomized study is mostly determined by feasibility. This study is not designed as a confirmatory study, hence, not powered as such. The primary purpose of this study is to estimate the effect of scrambler therapy for the treatment of CIPN which will inform hypothesis formulation for future studies. If the data from this study suggest a clinically non-ignorable effect of scrambler therapy compared to TENS therapy, we will plan for a larger study to confirm its benefit. However, if the data from this trial show a very large difference in changed pain scores between the two arms, such that the primary endpoint is positive with a p-value of less than 0.05, we will interpret this outcome as evidence that Scrambler therapy is better than TENS therapy, or vice-versa, depending on which arm is doing better.

More than 45% of patients in Pachman et al.'s study experienced treatment effect (50% or more reduction in symptom scores) after 2 weeks of scrambler therapy(Pachman, Weisbrod et al. 2014). This estimate includes patients who were enrolled early in the trial who did not respond to the treatment as well as the later cohort, potentially due to the study team's inexperience in the beginning of the trial. With the current level of experience, we expect a much higher percentage of reduction in patients' symptom scores after scrambler therapy in this trial. The likelihood of detecting an improvement of 30% or more after scrambler therapy compared to TENS is high with a sample size of 25

patients per arm. Table 16.51 shows the minimum detectable improvement with at least 80% power at a one-sided.05 significance level for various plausible scenarios with 25 patients per arm.

Table 16.51. Minimum Detectable Improvement with 80% power at a one-sided 0.05 significance level

Proportion of patients achieving 50% or more reduction in symptom scores from baseline		Minimum Detectable improvement	Power (%)
TENS	Scramber		
.05	.32	.27	80
.10	.40	.30	80
.20	.54	.34	81
.30	.65	.35	81
.40	.75	.35	82

16.6 Missing Data

Missing data are expected to be low in this prospective study, however, every attempt will be made to follow-up with patients to complete questionnaires. Patients will not be replaced if the data of primary endpoint are missing, instead, we will record and summarize the pattern of missing data. Exploratory analysis using simple imputation and/or multiple imputation maybe performed as appropriate. We plan to use last values carried forward for the initial 14 day daily data.

16.7 Data and Safety Monitoring

The study chair(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.8 Adverse Event Stopping Rules

16.81 The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

16.82 Adverse events will be monitored separately by arm. Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as “possible”, “probable”, or “definite”) that satisfy either of the following:

- if 3 or more patients in the first 10 treated patients experience a grade 3 or higher adverse event.
- if after the first 10 patients have been treated, 30 % of all patients experience a grade 3 or higher adverse event.

• if any grade 5 adverse events are observed that are related to study treatment.

16.83 If accrual is temporarily suspended, the study will be reviewed to determin whether accrual should continue or be permanently closed.

16.84 We note that we will review Grade 4 and 5 adverse events deemed “unrelated” or “unlikely to be related”, to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.9 Gender and minority accrual considerations

This study is open to patients from all races. Historical data indicate that no more than 10% of patients will be ethnic minorities. Subset analysis along ethnic subpopulations will hence have a lack of power to draw substantive conclusions but will provide some data for future meta-analytic procedures and hypotheses generation.

	Sex/Gender (%)			
Ethnic Category	**Females**	**Males**	**Unknown**	**Total**
Hispanic or Latino	0	1	0	1
Not Hispanic or Latino	30	19	0	49
Ethnic Category: Total of all subjects	30	20	0	50
Racial Category				
American Indian or Alaskan Native	1	0	0	1
Asian	1	1	0	2
Black or African American	1	2	0	3
Native Hawaiian or other Pacific Islander	0	1	0	1
White	27	16	0	43
Racial Category: Total of all subjects*	30	20	0	50

Ethnic Categories: **Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."
Not Hispanic or Latino

Racial Categories: **American Indian or Alaskan Native –** a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)
Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."
Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens - Not applicable

18.0 Records and Data Collection Procedures

18.1 Submission Timetables

18.11 Initial Material(s)

Case Report Form (CRF)	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
On-Study	≤2 weeks after registration
Research Submission (see Sections 4.0 and 14.0)	
End of (ALL) Active Treatment/Cancel Notification	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy
Patient Questionnaire	≤2 weeks after registration - Patient questionnaire booklet **must** be used; copies are not acceptable for this submission
Booklet Compliance	≤2 weeks after registration - This form **must** be completed only if the booklet(s) contains absolutely **NO** patient provided assessment information

18.12 Test Schedule Material(s)

	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)		
CRF	At each evaluation during treatment	Observation	At end of treatment
Adverse Event	X	X	
Research Submission (see Sections 4.0 and 14.0)	X	X	
End of Initial Treatment			X
Optional Crossover Continuation		X	
Patient Questionnaire [1]	X	X	X
Booklet Compliance [2]	X	X	X
End of (ALL) Active Treatment/Cancel Notification			X
ADR/AER (see Section 10.0)	At each occurrence		

1. Patient questionnaire booklet **must** be used; copies are not acceptable for this submission.
2. This form must be completed **only** if the booklet contains absolutely **NO** patient provided assessment information.

19.0 Budget

19.1 Costs charged to patient: routine clinical care.

19.2 Scrambler therapy and TENS units will be provided *gratis*.

19.3 Additional tests will be provided *gratis* including: fMRI, Quantitative Sensory Testing, and mRNA gene expression labs. Audiovisual recording will not be charged to the patient.

19.31 mRNA budget details

19.311 Blood draw and processing charges including CBC with differential: Included as part of CRTU.

19.312 Processing charges

- [redacted]

19.313 Analysis charges:

- [redacted]

19.32 fMRI associated budget detail

Budget: Harvard Team

[redacted]

19.33 Quanitative Sensory Testing Budget

[redacted]

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Appendix I Patient instruction sheet for tapering gabapentin and pregabalin

Tapering of gabapentin or pregabalin will preferably occur over two weeks. Lower doses may be tapered over one week to accommodate patient availability with approval of Dr. Loprinzi. During first week of taper, drug will be reduced approximately 25% for 3-4 days, then an additional 25% so that the drug has been reduced by approximately 50% by the end of the first taper week. Drug will continue to be reduced during the second week every few days until the final dose is taken the evening prior to treatment. Patient provider or Dr Loprinzi will need to be contacted if different doses of pills are needed. Patients will be instructed on potential symptoms of withdrawal and be asked to contact study staff if symptoms are experienced, as the taper may need to be adjusted. The decision of which dose to begin tapering (morning, noon, evening) will be decided between patient and study staff.

Patient Form

Gabapentin/Pregabalin (circle one)	mg	mg	mg	mg
Day/Date				
1= / /	pills	pills	pills	pills
2=__/__/__	__pills	__pills	__pills	__pills
3= / /	pills	pills	pills	pills
4= / /	pills	pills	pills	pills
5=__/__/__	__pills	__pills	__pills	__pills
6= / /	pills	pills	pills	pills
7= / /	pills	pills	pills	pills
8=__/__/__	__pills	__pills	__pills	__pills
9= / /	pills	pills	pills	pills
10= / /	pills	pills	pills	pills
11= / /	pills	pills	pills	pills
12=__/__/__	__pills	__pills	__pills	__pills
13= / /	pills	pills	pills	pills
14= / /	pills	pills	pills	pills
Day 1 of Treatment	0 pills	0 pills	0 pills	0 pills

Potential symptoms of gabapentin withdrawal may include nausea, insomnia, restlessness, agitation, anxiety, disorientation, confusion, light sensitivity, sweating, headaches, palpitations, chest pain, and flu-like symptoms.

Appendix IIA Peripheral Neuropathy Questionnaire for Upper Extremity Neuropathy

(Used for Eligibility)

Initials_____
Study #_____
Date_____
Day_____

How much of a problem has **pain** in your fingers or hands been **in the past week**?

0	1	2	3	4	5	6	7	8	9	10
No pain in fingers and/or hands										**Pain in fingers and/or hands as bad as you can imagine**

How much of a problem has **tingling** in your fingers or hands been **in the past week**?

0	1	2	3	4	5	6	7	8	9	10
No tingling in fingers and/or hands										**Tingling in fingers and/or hands as bad as you can imagine**

Appendix IIB Peripheral Neuropathy Questionnaire for Lower Extremity Neuropathy

(Used for Eligibility)

Initials_____
Study #_____
Date_____
Day_____

How much of a problem has **pain** in your toes or feet been **in the past week**?

0	1	2	3	4	5	6	7	8	9	10
No pain in toes and/or feet										**Pain in toes and/or feet as bad as you can imagine**

How much of a problem has **tingling** in your toes or feet been **in the past week**?

0	1	2	3	4	5	6	7	8	9	10
No tingling in toes and/or feet										**Tingling in toes and/or feet as bad as you can imagine**

Appendix III Declaration of most problematic site and symptom

Most problematic symptom:

___ Pain

___Tingling

Initials_____
Study #_____
Date_____
Day_____

Most problematic site:

___Upper extremities

___ Lower extremities

Appendix IVA Peripheral Neuropathy Questionnaire for Upper Extremity Neuropathy

Initials_____
Study #_____
Date_____
Day_____

Everyone has aches and pain at some time. We are interested in your experience of numbness, tingling and pain that you have developed related to chemotherapy.

How much of a problem has **pain** in your fingers or hands been **in the past week**?

0	1	2	3	4	5	6	7	8	9	10
No pain in fingers and/or hands										**Pain in fingers and/or hands as bad as you can imagine**

How much of a problem has **tingling** in your fingers or hands been **in the past week**?

0	1	2	3	4	5	6	7	8	9	10
No tingling in fingers and/or hands										**Tingling in fingers and/or hands as bad as you can imagine**

How much of a problem has **numbness** in your fingers or hands been **in the past week**?

0	1	2	3	4	5	6	7	8	9	10
No numbness in fingers and/or hands										**Numbness in fingers and/or hands as bad as you can imagine**

Appendix IVB Peripheral Neuropathy Questionnaire for Lower Extremity Neuropathy

Initials_____
Study #_____
Date_____
Dav

Everyone has aches and pain at some time. We are interested in your experience of numbness, tingling and pain that you have developed related to chemotherapy.

How much of a problem has **pain** in your toes or feet been **in the past week**?

0	1	2	3	4	5	6	7	8	9	10
No pain in toes and/or feet										**Pain in toes and/or feet as bad as you can imagine**

How much of a problem has **tingling** in your toes or feet been **in the past week**?

0	1	2	3	4	5	6	7	8	9	10
No tingling in toes and/or feet										**Tingling in toes and/or feet as bad as you can imagine**

How much of a problem has **numbness** in your toes or feet been **in the past week**?

0	1	2	3	4	5	6	7	8	9	10
No numbness in toes and/or feet										**Numbness in toes and/or feet as bad as you can imagine**

Appendix VA **Patient Questionnaire: Before Each Treatment for Upper Extremity Neuropathy**

Everyone has aches and pains at some time. We are interested in your experience of numbness, tingling and pain that you have developed related to chemotherapy.

Please address these questions related to this. Please comment only on symptoms in the primarily treated area.

Initials_____
Study #_____
Date_____
Day_____

Directions: Please answer the following questions:

1. How much **numbness** do you have in your fingers or hands **right now** (circle one number)?

0 1 2 3 4 5 6 7 8 9 10
None **As bad as can be**

2. How much **numbness** have you had in your fingers or hands **at its worst over the past 24 hours** (circle one number)?

0 1 2 3 4 5 6 7 8 9 10
None **As bad as can be**

3. How much **numbness** have you had in your fingers or hands **on average over the past 24 hours** (circle one number)?

0 1 2 3 4 5 6 7 8 9 10
None **As bad as can be**

4. How much **tingling** do you have in your fingers or hands **right now** (circle one number)**?**

0 1 2 3 4 5 6 7 8 9 10
None **As bad as can be**

5. How much **tingling** have you had in your fingers or hands **at its worst over the past 24 hours** (circle one number)**?**

0 1 2 3 4 5 6 7 8 9 10
None **As bad as can be**

6. How much **tingling** have you had in your fingers or hands **on average over the past 24 hours** (circle one number)**?**

0 1 2 3 4 5 6 7 8 9 10
None **As bad as can be**

7. How much **pain** do you have in your fingers or hands **right now** (circle one number)?

0 1 2 3 4 5 6 7 8 9 10
None **As bad as can be**

8. How much **pain**, that you consider to be from your chemotherapy, have you had in your fingers or hands **at its worse over the past 24 hours** (circle one number)?

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as can be**

9. How much **pain** have you had in your fingers or hands **on average over the past 24 hours** (circle one number)?

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as can be**

10. Which is the most problematic symptom, related to the fingers or hands neuropathy, that you have had over the past day?

___Numbness

___Tingling

___Burning/shooting pain

___Other, please indicate_____
_____
_____

Appendix VB **Patient Questionnaire: Before Each Treatment for Lower Extremity Neuropathy**

Everyone has aches and pains at some time. We are interested in your experience of numbness, tingling and pain that you have developed related to chemotherapy.

Please address these questions related to this. Please comment only on symptoms in the primarily treated area.

Initials_____
Study #_____
Date_____
Day_____

Directions: Please answer the following questions:

1. How much **numbness** do you have in your toes or feet **right now** (circle one number)?

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as can be**

2. How much **numbness** have you had in your toes or feet **at its worst over the past 24 hours** (circle one number)?

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as can be**

3. How much **numbness** have you had in your toes or feet **on average over the past 24 hours** (circle one number)?

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as can be**

4. How much **tingling** do you have in your toes or feet **right now** (circle one number)**?**

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as can be**

5. How much **tingling** have you had in your toes or feet **at its worst over the past 24 hours** (circle one number)**?**

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as can be**

6. How much **tingling** have you had in your toes or feet **on average over the past 24 hours** (circle one number)**?**

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as can be**

7. How much **pain** do you have in your toes or feet **right now** (circle one number)?

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as can be**

8. How much **pain**, that you consider to be from your chemotherapy, have you had in your toes or feet **at its worst over the past 24 hours** (circle one number)?

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as can be**

9. How much **pain**, have you had in your toes or feet **on average over the past 24 hours** (circle one number)?

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as can be**

10. **Which is the most problematic symptom that you have now (over the past day)?**

___Numbness

___Tingling

___Burning/shooting pain

___Other, please indicate_____
_____
_____

Appendix VIA **Patient Questionnaire: Immediately Post Therapy for Upper Extremity Neuropathy**

Everyone has aches and pain at some time. We are interested in your experience of numbness, tingling and pain that you have developed related to chemotherapy.

Initials_____
Study #_____
Date_____
Day_____

Please complete questionnaire immediately after each daily treatment session. Please comment only on symptoms in the primarily treated area.

Directions: Please answer the following questions:

1. How much **numbness** do you have in your fingers or hands **right now** (circle one number)?

0 1 2 3 4 5 6 7 8 9 10
None **As bad as can be**

2. How much **tingling** do you have in your fingers or hands **right now** (circle one number)**?**

0 1 2 3 4 5 6 7 8 9 10
None **As bad as can be**

3. How much **pain** do you have in your fingers or hands **right now** (circle one number)?

0 1 2 3 4 5 6 7 8 9 10
None **As bad as can be**

Appendix VIB **Patient Questionnaire: Immediately Post Treatment for Lower Extremity Neuropathy**

Initials_____
Study #_____
Date_____
Day

Everyone has aches and pain at some time. We are interested in your experience of numbness, tingling and pain that you have developed related to chemotherapy.

Please complete questionnaire immediately after each daily treatment session. Please comment only on symptoms in the primarily treated area.

Directions: Please answer the following questions:

1. How much **numbness** do you have in your toes or feet **right now** (circle one number)?

0 1 2 3 4 5 6 7 8 9 10

None **As bad as can be**

2. How much **tingling** do you have in your toes or feet **right now** (circle one number)**?**

0 1 2 3 4 5 6 7 8 9 10

None **As bad as can be**

3. How much **pain** do you have in your toes or feet **right now** (circle one number)?

0 1 2 3 4 5 6 7 8 9 10

None **As bad as can be**

Appendix VII EORTC QLQ CIPN-20 Instrument

EORTC QLQ – CIPN20

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
31 Did you have tingling fingers or hands?	1	2	3	4
32 Did you have tingling toes or feet?	1	2	3	4
33 Did you have numbness in your fingers or hands?	1	2	3	4
34 Did you have numbness in your toes or feet?	1	2	3	4
35 Did you have shooting or burning pain in your fingers or hands?	1	2	3	4
36 Did you have shooting or burning pain in your toes or feet?	1	2	3	4
37 Did you have cramps in your hands?	1	2	3	4
38 Did you have cramps in your feet?	1	2	3	4
39 Did you have problems standing or walking because of difficulty feeling the ground under your feet?	1	2	3	4
40 Did you have difficulty distinguishing between hot and cold water?	1	2	3	4
41 Did you have a problem holding a pen, which made writing more difficult?	1	2	3	4
42 Did you have difficulty manipulating small objects with your fingers (for example, fastening small buttons)?	1	2	3	4
43 Did you have difficulty opening a jar or bottle because of weakness in your hands?	1	2	3	4
44 Did you have difficulty walking because your feet dropped downwards?	1	2	3	4

Please go on to the next page

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
45 Did you have difficulty climbing stairs or getting up out of a chair because of weakness in your legs?	1	2	3	4
46 Were you dizzy when standing up from a sitting or lying position?	1	2	3	4
47 Did you have blurred vision?	1	2	3	4
48 Did you have difficulty hearing?	1	2	3	4
Please answer the following question only if you drive a car				
49 Did you have difficulty using the pedals?	1	2	3	4
Please answer the following question only if you are a man	1	2	3	4
50 Did you have difficulty getting or maintaining an erection?	1	2	3	4

Appendix VIII Patient Analgesic Use Questionnaire

Initials_____
Study #_____
Date_____
Day_____

Please list all pain medications (drug, dose, and quantity) used <u>in the past 24 hours</u>.

Drug	Unit Dose	Quantity over past 24 hours
Example Acetaminophen or Tylenol	*500 mg*	*4 pills*

Appendix IXA Global Impression of Change and Patient Preference Questionnaire – Upper Extremity

SUBJECT GLOBAL IMPRESSION OF CHANGE – NEUROPATHY (Upper Extremity)

Initials_____
Study #_____
Date_____
Day_____

1. Since beginning the study treatment, my fingers or hands neuropathy symptoms are:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

2. Since beginning the study treatment, my finger or hand pain is:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

3. Since beginning the study treatment, my overall quality of life is:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

Would you recommend this therapy to other patients with problems similar to yours?

___ No
___ Yes
___ Unsure

Comments:

_____
_____
_____
_____

Appendix IXB Global Impression of Change and Patient Preference Questionnaire – Lower Extremity

SUBJECT GLOBAL IMPRESSION OF CHANGE – NEUROPATHY (Lower Extremity)

Initials_____
Study #_____
Date_____
Day_____

---

1. Since beginning the study treatment, my toes or feet neuropathy symptoms are:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

2. Since beginning the study treatment, my toe or foot pain is:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

3. Since beginning the study treatment, my overall quality of life is:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

Would you recommend this therapy to other patients with problems similar to yours?

___ No
___ Yes
___ Unsure

Comments:

_____
_____
_____
_____

Appendix XA Daily Scrambler Treatment Log and Adverse Event Assessment

Patient Name: _____

Date: _____

Initials_____
Study #_____
Date_____
Day

Pain Area #1 _____

VAS Score: Pre: _____ During: _____ Post: _____

Cable 1 Max Setting: _____ Total Treatment Time: _____ (mins)
Cable 2 Max Setting: _____ Total Treatment Time: _____ (mins)
Cable 3 Max Setting: _____ Total Treatment Time: _____ (mins)
Cable 4 Max Setting: _____ Total Treatment Time: _____ (mins)
Cable 5 Max Setting: _____ Total Treatment Time: _____ (mins)

Pain Area #2 _____

VAS Score: Pre: _____ During: _____ Post: _____

Cable 1 Max Setting: _____ Total Treatment Time: _____ (mins)
Cable 2 Max Setting: _____ Total Treatment Time: _____ (mins)
Cable 3 Max Setting: _____ Total Treatment Time: _____ (mins)
Cable 4 Max Setting: _____ Total Treatment Time: _____ (mins)
Cable 5 Max Setting: _____ Total Treatment Time: _____ (mins)

Adverse Effects Assessment: Please note any toxicities/adverse effects of treatment

_____
_____
_____

Notes/Comments:

_____
_____
_____
_____
_____
_____

Appendix XB Daily TENS Treatment Log and Adverse Event Assessment

Initials_____
Study #_____
Date_____
Day_____

Patient Name: _____

Pain Area #1 _____

Cable 1 Max Setting: _____ Total Treatment Time: _____ (mins)

Pain Area #2 _____

Cable 2 Max Setting: _____ Total Treatment Time: _____ (mins)

Adverse Effect Assessment: Please note any adverse effects of treatment

_____
_____
_____

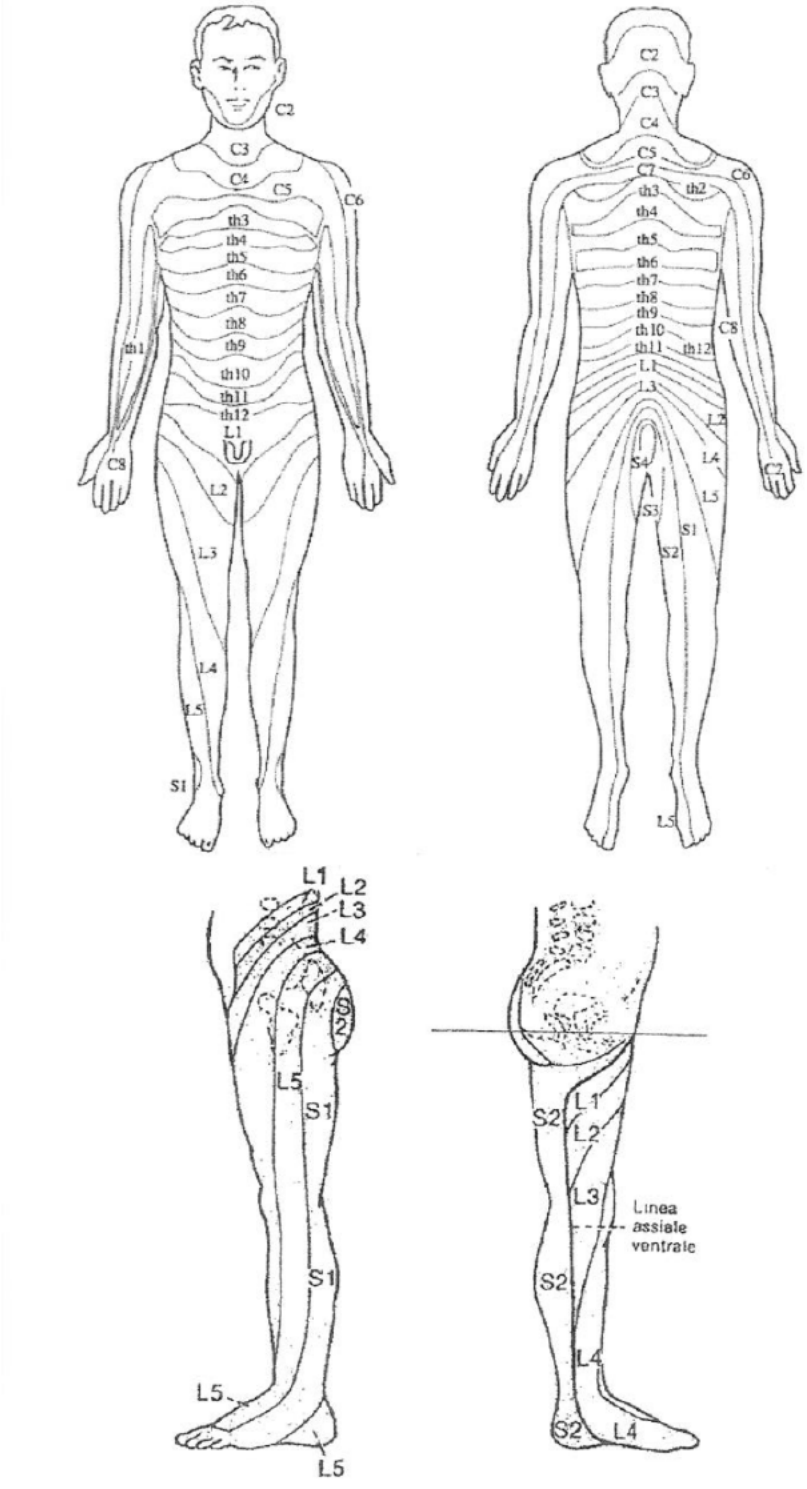
Notes/Comments:

_____
_____
_____
_____
_____
_____

Appendix XI Individual Patient Dermatome Map

(page 1)

Initials_____
Study #_____
Date_____
Day_____

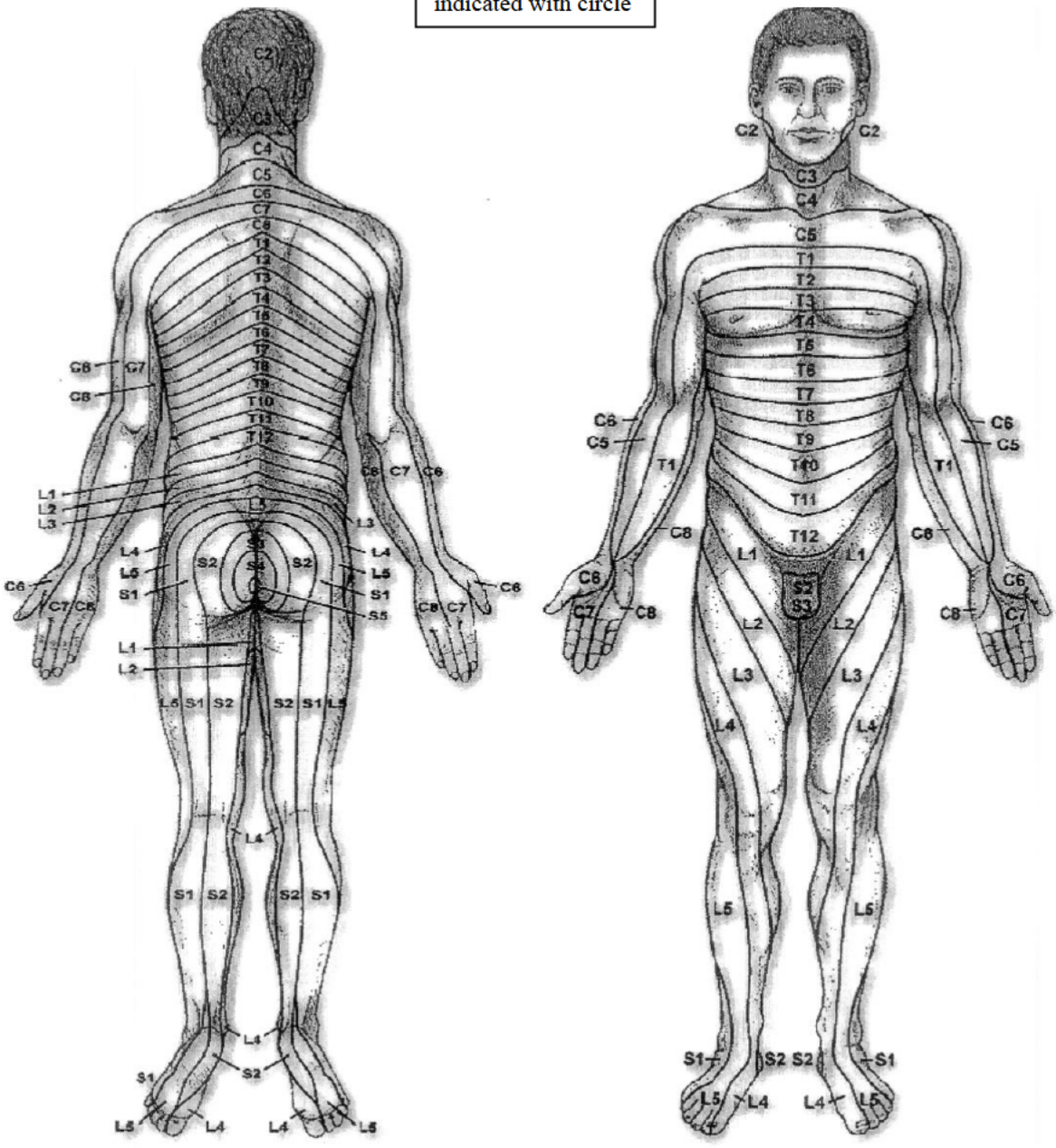


Appendix XI Individual Patient Dermatome Map (page 2)

Indicate:
Pain with "P"
Numbness with "N"
Tingling with "T"

Initials_____
Study #_____
Date_____
Day

Electrode placement indicated with circle



Appendix XIIA Patient Weekly Follow-up Questionnaire for Upper Extremity Neuropathy

Everyone has aches and pains at some time. We are interested in your experience of numbness, tingling and pain that you have developed related to chemotherapy. Please address these questions related to this.

Initials_____
Study #_____
Date_____
Day_____

Directions: Please answer the following questions about your symptoms.

1. How much of a problem has **numbness** in your fingers or hands been **in the past week**?

0	1	2	3	4	5	6	7	8	9	10
No numbness in fingers and/or hands										**Numbness in fingers and/or hands as bad as you can imagine**

2. How much **numbness** have you had in your fingers or hands **at its worst over the past 24 hours** (circle one number)?

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as can be**

3. How much **numbness** have you had in your fingers or hands **on average over the past 24 hours** (circle one number)?

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as can be**

4. How much of a problem has **tingling** in your fingers or hands been **in the past week**?

0	1	2	3	4	5	6	7	8	9	10
No tingling in fingers and/or hands										**Tingling in fingers and/or hands as bad as you can imagine**

5. How much **tingling** have you had in your fingers or hands **at its worst over the past 24 hours** (circle one number)**?**

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as can be**

6. How much **tingling** have you had in your fingers or hands **on average over the past 24 hours** (circle one number)**?**

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as can be**

7. How much of a problem has **pain** in your fingers or hands been **in the past week**?

0	1	2	3	4	5	6	7	8	9	10
No pain in fingers and/or hands										**Pain in fingers and/or hands as bad as you can imagine**

8. How much **pain**, have you had in your fingers or hands **at its worst over the past 24 hours** (circle one number)?

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as can be**

9. How much **pain**, have you had in your fingers or hands **on average over the past 24 hours** (circle one number)?

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as can be**

10. Which is the most problematic symptom that you have now (**over the past day**)?

___Numbness

___Tingling

___Burning/shooting pain

___Other, please indicate_____
_____
_____

Appendix XIIB Patient Weekly Follow-up Questionnaire for Lower Extremity Neuropathy

Initials_____
Study #_____
Date_____
Day

Everyone has aches and pains at some time. We are interested in your experience of numbness, tingling and pain that you have developed related to chemotherapy. Please address these questions related to this.

Directions: Please answer the following questions about your symptoms

1. How much of a problem has **numbness** in your toes or feet been **in the past week**?

0	1	2	3	4	5	6	7	8	9	10
No numbness in toes and/or feet										**Numbness in toes and/or feet as bad as you can imagine**

2. How much **numbness** have you had in your toes or feet **at its worst over the past 24 hours** (circle one number)?

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as can be**

3. How much **numbness** have you had in your toes or feet **on average over the past 24 hours** (circle one number)?

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as can be**

4. How much of a problem has **tingling** in your toes or feet been **in the past week**?

0	1	2	3	4	5	6	7	8	9	10
No tingling in toes and/or feet										**Tingling in toes and/or feet as bad as you can imagine**

5. How much **tingling** have you had in your toes or feet **at its worst over the past 24 hours** (circle one number)**?**

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as can be**

6. How much **tingling** have you had in your toes or feet **on average over the past 24 hours** (circle one number)**?**

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as can be**

7. How much of a problem has **pain** in your toes or feet been **in the past week**?

0	1	2	3	4	5	6	7	8	9	10
No pain in toes and/or feet										**Pain in toes and/or feet as bad as you can imagine**

8. How much **pain**, have you had in your toes or feet **at its worst over the past 24 hours** (circle one number)?

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as can be**

9. How much **pain**, have you had in your toes or feet **on average over the past 24 hours** (circle one number)?

0	1	2	3	4	5	6	7	8	9	10
None										**As bad as can be**

10**.** Which is the most problematic symptom that you have now (**over the past day**)?

___Numbness

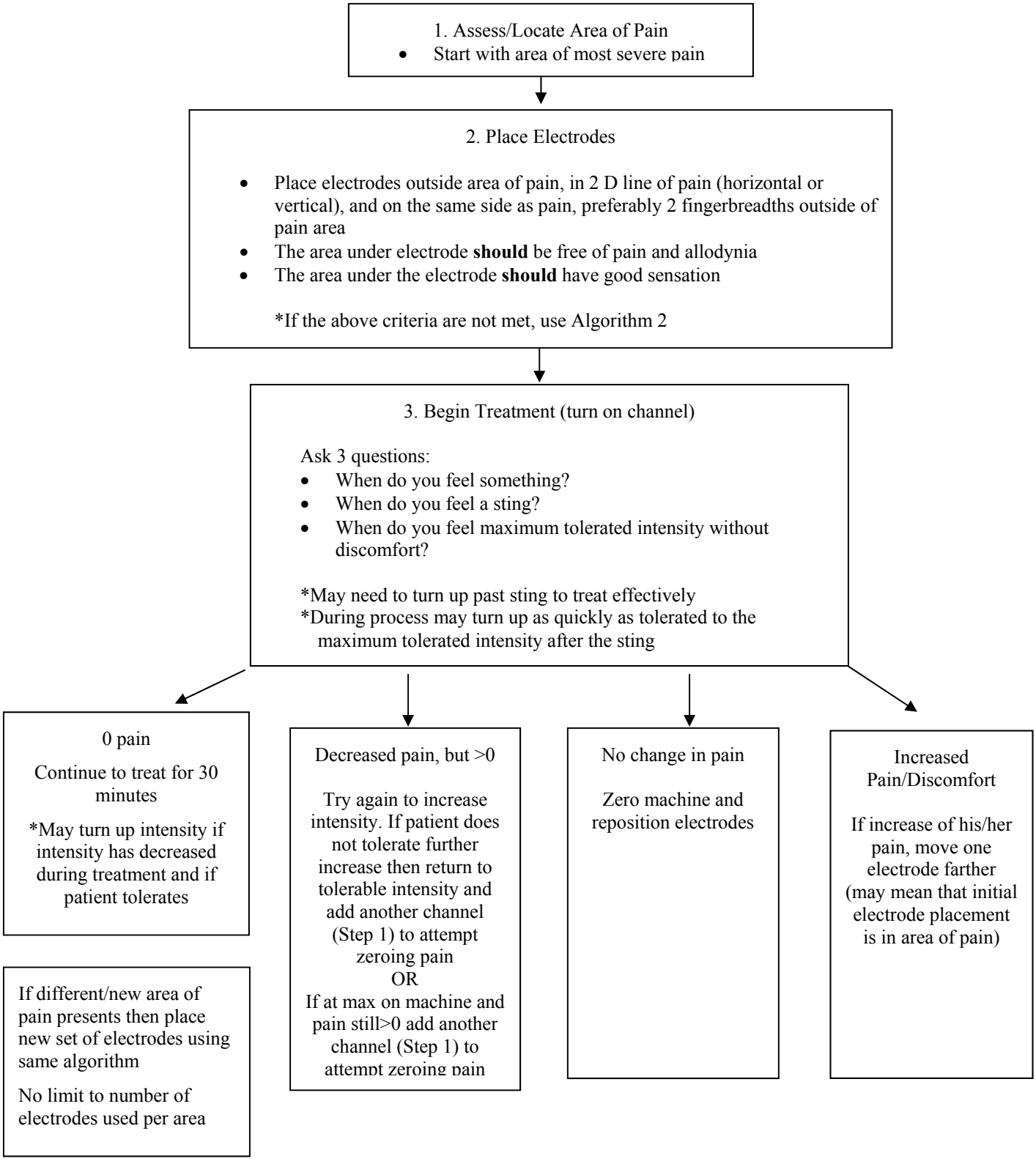
___Tingling

___Burning/shooting pain

___Other, please indicate_____
_____
_____

Appendix XIII Principals of Positioning and Titrating Scrambler Treatment

Algorithm 1: Basic Scrambler Treatment Algorithm



Algorithm 2: Advanced Scrambler Treatment Algorithm
(If patient does not meet criteria for proper electrode placement)

Option 1: Reduce Area of Pain

Place all electrodes above area of pain

- For feet, place electrodes on leg above area of pain, most likely minimum of 2 electrode sets, but may use as many as fit and are tolerated, or pain/tingling is zeroed
- For hands, place electrodes on arm above area of pain, most likely minimum of 2 electrode sets, but may use as many as fit and are tolerated, or pain/tingling is zeroed

Goal: Replace pain or tingling with new/different tingling sensation in the area of pain, in order to reduce area of pain/tingling and allow for proper placement of electrodes in next session

Treat for 30 minutes after tingling begins

* Patient assessed daily for ability to follow Algorithm 1

Option 2: Treat in area of pain

When electrode cannot be placed in area of non-pain, an electrode can be placed in the area of **least** pain and then Algorithm 1 can be followed

However, this can cause increased pain and discomfort and therefore this technique should be used based on provider experience and patient tolerability

Appendix XIVA Patient instruction form for using TENS on the upper extremities

1. You will be given a TENS machine, that you will be able to keep.
2. A nurse will provide hands-on instructions.
3. Before use, make sure that the TENS unit is charged.
4. Place a set of pads on the front and back of one wrist; then do the same thing on the other wrist with another set of pads.
5. Turn on the TENS machine.
6. Increase the intensity of the signal so that a signal is felt and it is comfortable..
7. Treat for a total of 30 minutes.

Appendix XIVB Patient instruction form for using TENS on the lower extremities

1. You will be given a TENS machine, that you will be able to keep.
2. A nurse will provide hands-on instructions.
3. Before use, make sure that the TENS unit is charged.
4. Place a set of pads below the ankle bone, inside and outside on one ankle; then do the same thing on the other ankle with another set of pads.
5. Turn on the TENS machine.
6. Increase the intensity of the signal so that a signal is felt and it is comfortable.
7. Treat for a total of 30 minutes.

Appendix XV Functional MRI (fMRI)

Data Analysis

Functional Data Analysis

Functional image data sets will be processed and analyzed using FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Processing steps will include spatial filtering, high-pass temporal filtering, motion correction, geometric unwarping of EPI images, removal of all non-brain areas in images, and mean-based intensity normalization. Patients whose scans indicate head motion that exceeds 3mm will be excluded from the study.

Seed based connectivity analysis:

Functional connectivity will be measured using a seed correlation based approach (Fox, Snyder et al. 2005; Zhang, Snyder et al. 2008). For each subject, all brain time-courses will be orthogonalized to the eigen time-courses from WM and CSF extracted using a singular value decomposition (SVD)(Loan 1996) Correlation coefficients (CC) will be computed between the eigen time-course from the seed ROI and all other voxels in the brain. We will register the resulting statistical parametric maps from first-level analysis to the MNI 152 Brain (Montreal Neurological Institute) using FMRIBs Linear Image Registration Tool (FLIRT www.fmrib.ox.ac.uk/fsl). These registered CC maps will be transformed using a Fisher z-transform and entered into a mixed effects group analysis. The resulting z-statistic maps will be subjected to alternative hypothesis testing using Gaussian mixture modeling (GMM) for thresholding(Pendse, Borsook et al. 2009) with adaptive estimation of the null hypothesis.

Resting State Networks (RSN) using Independent Component Analysis (ICA):

The inherent run to run and inter data set variability of ICA will be captured by running ICA on independent data sets multiple times for each group. All ICA runs from each group will be entered into a RAICAR analysis(Yang, LaConte et al. 2008)to assess reproducibility of RSNs across runs and groups. We will compute p-values for reproducibility of each RSN using a non-parametric method. The matched ICA maps for significant RSNs from each subject group will be voxel-wise transformed to Normality followed by a mixed effects group analysis. The resulting statistical maps will be thresholded using mixture modeling that maximizes the model evidence.

Correlation Analysis:

We will carry out multivariate regression analysis across ROIs using (1) the estimated parameters for GLM and estimated sources in melodic results *versus* psychometric measures (e.g., depression scores, pain scores, anxiety levels); and (2) a fuzzy cluster analysis (FCA) that examines associations between ROIs using the psychometric measures and parameter estimates as features of interest.

Morphometric Analysis

Gray Matter Volume and Cortical Thickness: Gray Matter Volume: For cortical thickness, we will perform 2 MPRAGE scans in all subjects and average them for increased SNR. We will then construct and inflate hemisphere surfaces for the cortex based on the method defined by Dale and Fischl using Freesurfer (http://surfer.nmr.mgh.harvard.edu/) tools.(Dale, Fischl et al. 1999; Makris, Kaiser et al. 2006) This cortical mapping technique is described in an approach we have published in patients with trigeminal neuropathy(DaSilva, Becerra et al. 2008), opioid dependence(Upadhyay, Maleki et al. 2010) and migraine(Maleki, Becerra et al. 2011).

Article I. *Correlation with Functionally Defined ROI's*: We will perform the initial functional analysis of cortical areas activated during mechanical stimulation as noted above. Group statistical maps will be co-registered onto the reconstructed average surface brains of the subjects using Freesurfer. Using this surface-based approach, we can achieve precise cortical mapping and

measurements of cortical thickness leading to functionally defined ROIs identified during these chemical based experiments.

Correlation of disease frequency with Cortical Thickness: Changes in cortical thickness will be correlated with disease frequency and determine areas that seem to change with time. Other parameters, such as age, and disease duration will be regressed out.

Diffusion Tensor Imaging Analysis

Initially, we will correct all DTI datasets for eddy current distortion and head motion using FSL tools (Smith 2002). Fractional Anisotropic (FA) diffusion will be characterized on a voxel-wise basis by using a least squares fit of the tensor model to the DTI data in order to calculate the eigenvalues, λ1, λ2 and λ3, and the eigenvectors e1, e2 and e3 of each DTI dataset and determine from them the fractional anisotropy (fa)(Pierpaoli and Basser 1996; Basser and Pierpaoli 1998) Fractional anisotropy maps will be registered to a standard brain using FSL's DTI tools. Group differences will be determined from aggregate results for each group (Upadhyay, Maleki et al. 2010).

Correlation analysis:

We will correlate observed changes in fractional anisotropy (FA) values with changes in RSN and various group characteristics and measures such as disease duration and frequency.