

Title: A Pilot Randomized Sham-Controlled Trial of MC5-A Calmare Therapy
(Scrambler Therapy) in the Treatment of Chronic Chemotherapy-Induced
Peripheral Neuropathy (CIPN)

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1. Summary

Scrambler Therapy is a personalized neuro-cutaneous method of pain relief that has been effective in reducing chronic neuropathic pain in multiple uncontrolled trials. Treatment is given with common EKG skin electrodes placed above and below the pain, and the Scrambler Therapy machine directs electrical signals across the field to simulate non-pain information. The treatment is non-invasive and takes 30 minutes a day for 10 days. To date, the pain relief has been straightforward and dramatic.

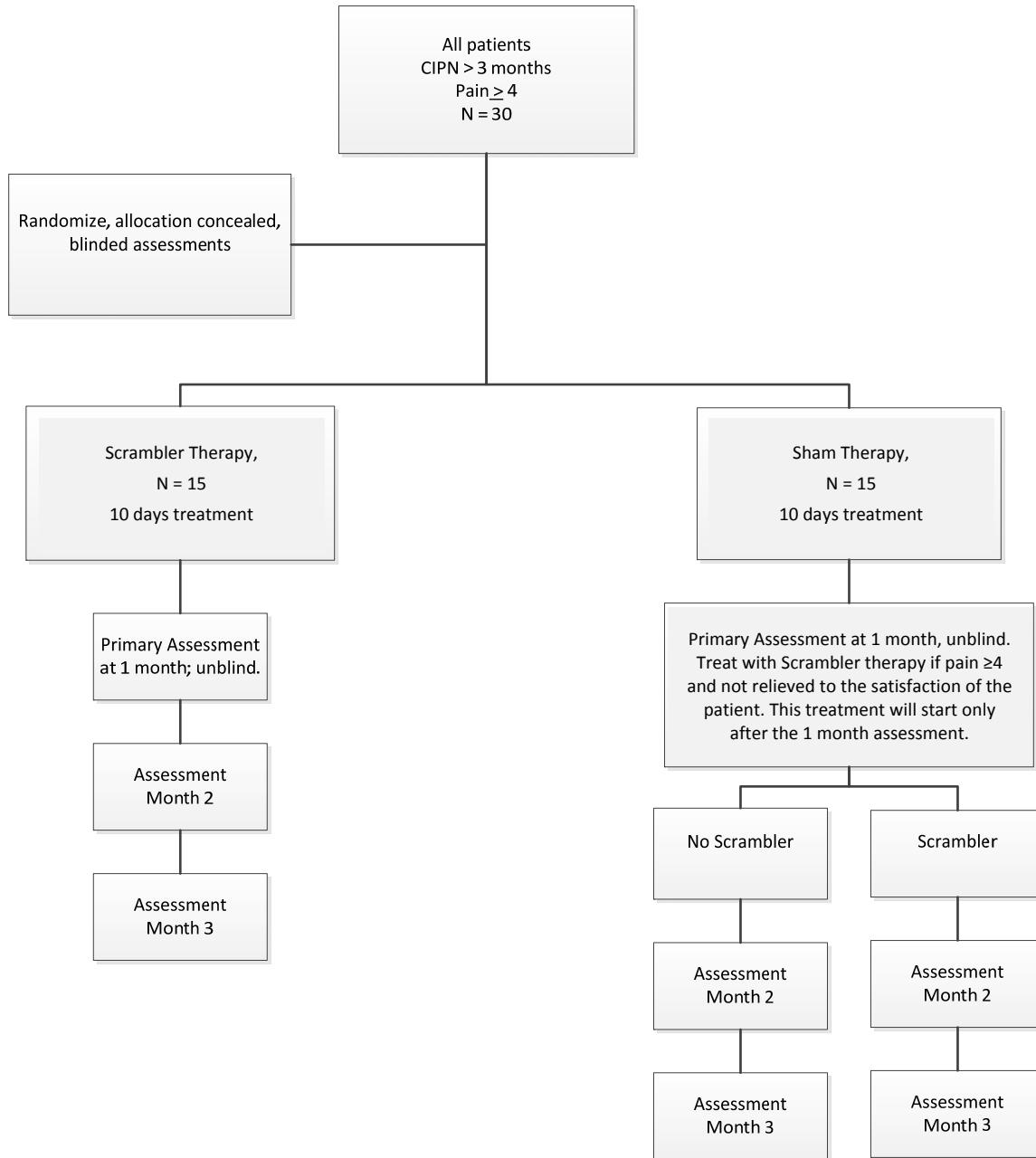
Chemotherapy induced peripheral neuropathy (CIPN) is a major and often dose-limiting side effect of antineoplastic agents. The incidence of chemotherapy-induced neurotoxicity ranges from 0 to 70% (commonly 30-40%) of patients receiving chemotherapy, related to the timing and cumulative dose. Pain is the most common symptom, usually described as a burning, stinging dysesthesia. There is no standard effective therapy for CIPN pain.

We propose a straightforward randomized controlled trial of actual Scrambler Therapy versus sham therapy (electrodes placed on the back, which does not cause pain relief but was perceived as active treatment in our pilot trials).

The primary endpoint is patient reported change in pain from day 0 to day 28, on a numeric scale of 0-10 (question #3 of the Modified Brief Pain Inventory, Appendix B). Secondary endpoints will include changes in the complete Brief Pain Inventory, the CIPN EORTC Q-20 scale, and changes in pain drug use. With 30 patients and a one-sided type I error rate of 10%, we have 87% power to detect a 50% reduction in pain observed in single arm trials and a 10% reduction in pain with sham treatment, in patients with a starting pain score of ≥ 4 .

Subjects enter the study and get scrambler therapy or placebo for 10 sessions, usually as weekdays, for 2 weeks. Then, they are followed without any protocol treatment until Day 28 when the primary endpoint is assessed. After the primary assessment is done the groups are “un-blinded” and informed of their study treatment, real or sham. Those in the sham group with scores ≥ 4 will be offered the standard 10 scrambler sessions. All patients are followed for a total of 3 months.

2. Schema



3. Objectives

3.1 Primary

3.1.1 To determine the change in pain from day 0 to day 28 with scrambler therapy in patients with chemotherapy induced peripheral neuropathy and pain (CIPN). This endpoint also serves to get preliminary information for planning future, larger, phase III studies.

The primary measurement tool for pain will be the Brief Pain Inventory (BPI) (modified specifically for CIPN by the originator, Dr. Charles Cleeland, and used with permission) which gives information on Pain Now, Worst, Least and Average Pain, and Interference with Normal Activity.

3.2 Secondary

3.2.1 The secondary endpoints will include changes in the complete Brief Pain Inventory, the CIPN EORTC Q-20 scale, and changes in pain drug use.

3.2.2 The primary measurement tools used to determine if MC-5A Calmare therapy will improve endpoints include the following: neuropathy (European Organization for Research and Treatment of Cancer Quality of Life Cancer Chemotherapy Induced Peripheral Neuropathy-20 Instrument (CIPN-20)); opiate use (morphine oral equivalent daily dose, MOED) and other drug (anti-depressant, anti-convulsant) use. We will also study the duration of the effect.

4. Hypotheses

4.1 Primary

- Scrambler Therapy will improve pain related to chemotherapy-induced neuropathy significantly more than sham therapy at day 28.

4.2 Secondary

- Scrambler Therapy will result in significant improvements in the total CIPN modified Brief Pain Inventory score and the motor and sensory subscales of the CIPN 20 compared to sham therapy.
- Pain medication and morphine oral equivalent dose (MOED) daily amounts will decrease by at least 20% more from the start of treatment Day 1 (pre) to Day 30 days (post), in the group receiving scrambler therapy versus those who received sham therapy.

5. Background and Rationale

5.1 Neuropathy due to chemotherapy agents (CIPN)

CIPN is a major and often dose-limiting side effect of antineoplastic agents¹ including the taxanes (paclitaxel and docetaxel), platinums (carboplatin, cis-platinum, and oxaliplatin), vinca alkaloids (vincristine, vinblastine, and vinorelbine), proteosome inhibitors (bortezomib²), immunomodulating drugs such as lenalidomid³, and epithelones such as ixabepilone⁴. 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.⁵ Unlike chronic diabetic nerve damage, it is not caused by nutritional starvation but rapid damage to microtubules of the nerves.⁶ Pain is the most common symptom, usually described as a burning, stinging dysesthesia. However, many patients also complain of numbness and being unable to do activities of daily living because they cannot feel their fingertips or toes. This numbness is often progressive over the day such that sensation is lost by the end of the day.

There is no standard effective therapy for CIPN pain. Tricyclic antidepressants (TCAs) do not work for CIPN and have significant adverse effects. Amitriptyline⁷ and Nortriptyline⁸ were no better than placebo in randomized trials. Lamotrigine had no effect on CIPN in a randomized placebo controlled trial.⁹ Gabapentin does not work for CIPN when compared to placebo.¹⁰ Magnesium and calcium infusion does not prevent oxaliplatin-induced neuropathy¹¹. Vitamin E may be helpful but may also protect the cancer; use is not suggested until larger randomized trials are completed. Acetyl-L-carnitine has been reported to reduce established CIPN in one small series¹² but the investigators caution against its use until safety and efficacy can be confirmed in larger randomized trials.¹³ Venlafaxine¹⁴ reduced the incidence or prevented oxaliplatin-CIPN from 76% to 35% but has only been tested in oxaliplatin, a drug not used in breast cancer treatment, and has not been tested as a treatment drug. Topical baclofen-amitriptyline-ketamine (BAK) gel reduced CIPN-sensory symptoms compared to placebo¹⁵, but incompletely and not in the feet – where the symptom is most common. Duloxetine (Cymbalta) is the only drug shown in a randomized trial to reduce CIPN pain scores¹⁶, but only from 6 to 5 over 6 weeks, caused side effects, and only worked for oxaliplatin neuropathy -- not for taxane-induced CIPN which is far more common in women with breast cancer.

Acupuncture reduced CIPN pain scores in small, non-randomized series of 5¹⁷ and 18¹⁸ cancer patients. In one larger trial, acupuncture relieved CIPN from paclitaxel and oxaliplatin more effectively than drug treatment with Vitamin B12 injections, 67% vs. 40%¹⁹. In one small trial, nerve conduction studies showed improvement after acupuncture: 5 of 6 patients improved clinically, correlated with improvements in mean nerve conduction velocity (NCV) (m/s) and mean amplitude (μ V) ($p=0.03$)²⁰ suggesting that CIPN-damaged nerves can indeed repair. However, none of these trials had any standard control or sham/placebo group.

5.2 Direct Nerve Stimulation in Chronic Pain Relief

There is much clinical experience that CIPN and other chronic pain syndromes can be helped by direct nerve stimulation²¹. The hypothesized mechanisms by which direct nerve stimulation reduces pain include reducing impulses from the damaged nerve, raising the “gate” threshold for pain at the spinal cord, reducing “wind up” (central sensitization of the spinal cord and brain that amplifies the abnormal feelings), and reducing psychological maladaptation to pain²². Spinal

cord stimulation has been successful in small, non-randomized series^{23 24} for chronic pain from reflex sympathetic dystrophy²⁵ and post-herpetic neuropathy²⁶ but has not been assessed in CIPN. Peripheral nerve stimulation^{27 28} is growing in use but there are no controlled trials to date. Not all therapies work, however, as the published data show that trans-cutaneous electrical nerve stimulation (TENS) is not useful in cancer pain²⁹, and TENS has not been evaluated in CIPN.³⁰

5.3 Scrambler Therapy

5.3.1 Rationale for nerve-based treatments like Scrambler Therapy

Scrambler Therapy is a novel treatment whose efficacy for CIPN is supported by clinical experience and pilot trials, but for which rigorously designed, sham-controlled trials do not exist. The goal of the device is to provide “non-pain” information to the cutaneous nerves to block the effect of pain information

The device is a cutaneous electrical stimulator that uses C fiber stimulation to transmit patterns of waveforms simulating 16 different action potentials to reset the brain to perceive non-pain from areas previously interpreted as painful. Proprietary software designs the patient-specific cutaneous electro-stimulation to reduce the abnormal pain intensity. The device consists of a multiprocessor apparatus able to simulate 5 artificial neurons by the application of surface electrodes on skin pain areas. The device synthesizes 16 different types of nerve action potentials similar to the endogenous kinds, strings them into sequences, and directly stimulates the peripheral nerves.

The scientific rationale for the observed pain relief is shown in Figure 1. The relationship between clinical pain relief and the hypothesized active principle requires further validation and independent studies, but we have some hypotheses. First, it is not just C fibre excitation; electrical C fibre excitation without information should also produce pain, whereas Calmare therapy produces pain

relief. Second, Calmare therapy is not just producing widespread paraesthesia. The patient feels the effect of stimulation only in the painful area under the electrode contact-area. Immediately after the treatment, no paresthesia or anesthesia is noted. Furthermore, the intensity of stimulation current is very low, and peaks never exceed 5.5 mA, which is likely too low to produce analgesia. Fourth, the sensation perceived by the patient (electrical current, pressure, flow, or other “bee sting” sensations under the electrodes) suggests that non-pain stimuli are being felt, not just analgesia numbing sensation. Another aspect of the hypothesized pain relief is

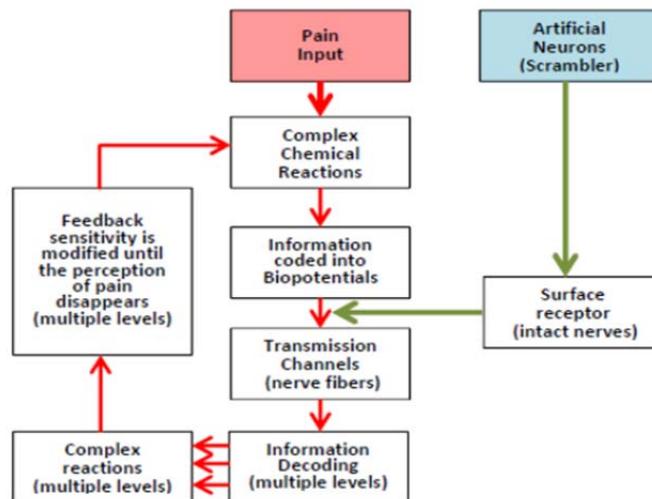


Figure 1: Mechanisms of pain and Calmare Treatment

that analgesia occurs within minutes or hours and slowly accumulates over several days, suggesting nerve remodulation or remodelling.

The exact mechanism by which similar types of nerve stimulation reduce pain is complex and not completely understood. Regardless of the mechanism, the therapy appears to work or at least warrant further testing.

5.3.2 Preliminary data on Scrambler therapy

The Scrambler Therapy device appears to work on pain based on results from multiple trials. In the first trial, 11 cancer patients (3 pancreas, 4 colon, 4 gastric) suffering from drug resistant visceral pain were studied during their first ten treatment sessions.³¹ Pain was quickly and markedly reduced and maintained until death. Nine of 11 stopped pain drugs within the first 5 applications. In the second trial, 226 patients with neuropathic pain including failed back surgery, brachial plexus neuropathy, and others were treated.³² 80% of patients responded with > 50% pain relief, 10% responded with pain relief from 25% to 49%, and only 10% had no response (P<0.0001).

Based on these results the FDA approved Scrambler therapy for cancer pain treatment February 25, 2009. In clinical practice, over 4000 patients have been treated worldwide with no reported side effects except occasional transient worsening of pain. In addition, at least one patient had some temporary bruising under the sites of the electrodes.

In the first US trial, Smith et al³³ studied 16 typical patients (median age 56, usual chemotherapy drugs) with refractory CIPN and pain scores over 6. Each patient was treated for 10 sessions of 60 minutes each, Monday through Friday. The electrodes were applied in the areas of the pain, as shown in Figure 2. The results are shown in Figure 3. *The average pain reduction was 59%, similar to direct spinal cord stimulation.* The effect on some patients was dramatic, with 4 people having no pain and several resumed normal activity. The effect was persistent, lasting weeks to months in most patients, with successful retreatment if needed.

Mayo Clinic investigators have now replicated these results in a pilot trial, with a 47% reduction in CIPN pain.³⁴ The 10 day time period is too short for any



Figure 2:MC5-A Scrambler Therapy for CIPN, application of electrodes for

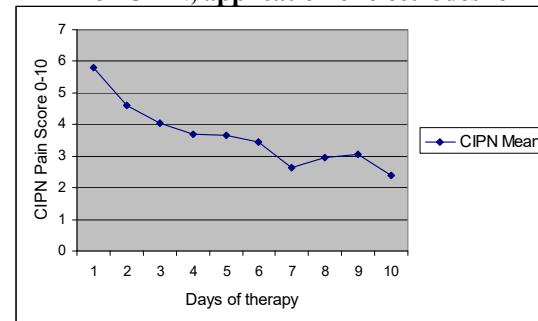


Figure 3: Scrambler Therapy and CIPN Results, Smith et al.

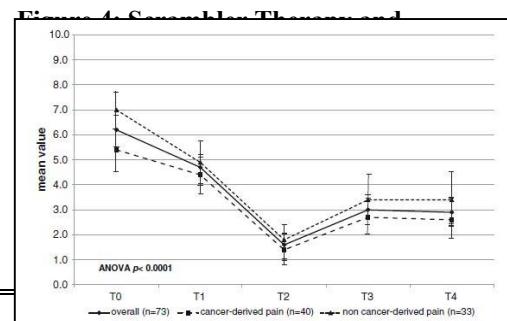
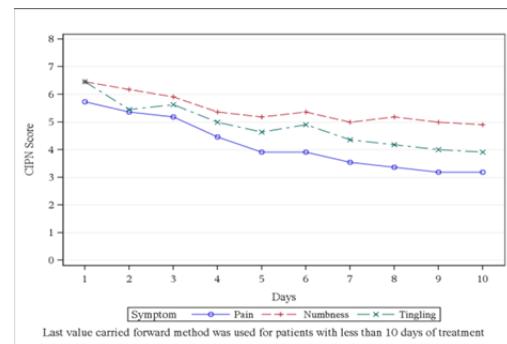


Figure 5: Scrambler Therapy and Neuropathic Pain, Ricci et al.

natural reduction in CIPN, making this unlikely to be natural resolution. (Figure 4)

Ricci et al treated 47 cancer pain patients (many types of pain, not just CIPN) with Scrambler therapy. Pain intensity decreased by 74% from 4.7 (SD 2.9) at baseline to 2.5 (SD 2.3) at the end of the second week of treatment and 2.6 (SD 2.6) at one month. (Figure 5) Nearly all patients found it satisfactory or very satisfactory and would continue using it.³⁵

In a pilot randomized trial³⁶, 52 patients with chronic neuropathic pain (spinal cord stenosis, failed back syndrome, post-herpetic neuropathy) were randomized to Scrambler therapy or treatment by the same expert group following standard pharmacology guidelines³⁷. The patients had post-surgical failed back, post herpetic, or spinal stenosis neuropathy. These results are shown in Figure 6. The mean pain intensity score at outset was 8.1. At one month, the Scrambler therapy group had a 91% decrease in pain to 0.7 points, and the standard therapy group had a 28% reduced pain score, which was maintained for 3 months. Pain drug consumption decreased by 72% in the Scrambler therapy group, including opiates, anti-depressants, and anti-convulsants. Allodynia, or pain on normal touching of the skin, was reduced in the Scrambler therapy patients from 77% to 15% at 3 months. All differences were both clinically and statistically significant.

Other small series show a >50 % reduction in refractory post –herpetic pain³⁸ and cancer pain³⁹.

In a large series of complicated pain patients, including spinal pain, neuralgia, chronic regional pain syndrome, and multisite pain, D'Amato and colleagues reported a significant reduction in pain scores across all diagnostic groups⁴⁰. (Figure 7)

In a recent trial, Pachman et al treated 13 patients with refractory low back pain at the Mayo Clinic. Mean average daily pain scores decreased by 54% from baseline to day 10 of treatment. Median weekly pain scores decreased by 70% after 10 weeks of follow up, as shown in Figure 8. Patients also reported improvements in quality of life that persisted through 10 weeks of follow up. The data suggest that scrambler therapy effectively treats chronic low back pain, supporting the conduct of a placebo-controlled, randomized trial. (Pachman D, et al. submitted for publication)

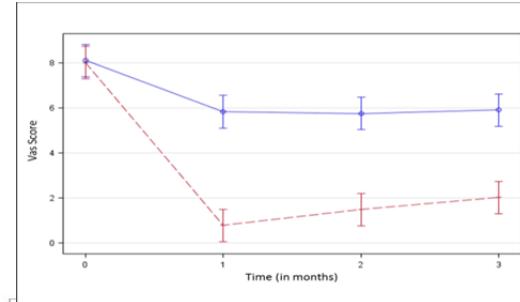


Figure 6: Scrambler Therapy (top) compared to best medical management

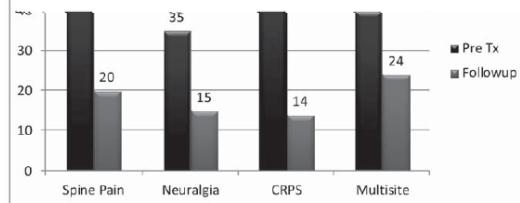


Figure 7: Reduction in Chronic Pain with Scrambler Therapy

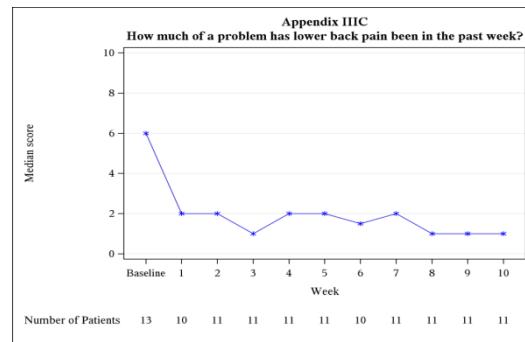


Figure 8: Pilot trial of Scrambler therapy for low back pain

In the most recent trial, Smith and colleagues treated 33 patients with CIPN and found a significant reduction in pain persisting to 90 days (Figure 9) and dramatic improvement in how the pain interfered with normal life (Figure 10).⁴¹

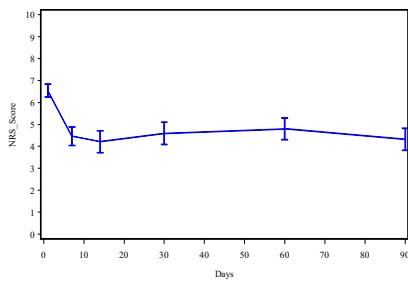


Figure 9: Impact of Scrambler Therapy on neuropathic pain

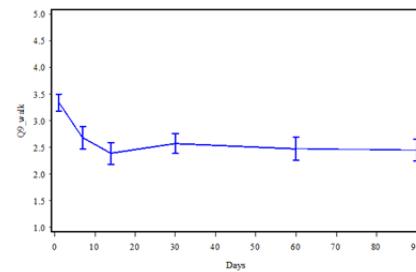


Figure 10: "How much does pain interfere with walking?"

In this trial of 39 patients, Smith et al also saw significant improvements in both the motor and sensory subscales of the CIPN-20. (All p values < 0.001) Again, this was a single arm trial with no sham or placebo group.

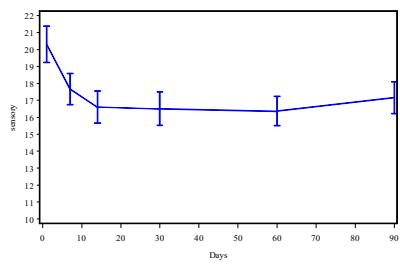


Figure 11: Reduction in sensory symptoms

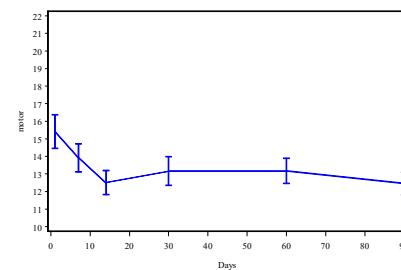


Figure 12: Reduction in motor symptoms

While these results in CIPN are promising, there are NO sham or placebo controlled trials. The results to date could potentially be due to placebo effect, as seen in one small trial of high frequency spinal cord stimulation⁴², but typical placebo CIPN effects are only about 10% pain relief over 3 months⁸⁻¹⁵. In the recent successful trial of duloxetine for CIPN¹⁶, the CIPN placebo group had reduced pain scores of only 0.1-0.2 points (on a 10-point scale) over 6 weeks, whereas the Scrambler Therapy 2-4 point drop happened within 10 days. Another alternative explanation is that the CIPN resolves over time, but the 10 day time period of treatment is likely to be too short for CIPN to resolve. We need sham or placebo-controlled trials to ensure that the treatment actually works, and if it works, the duration of effect.

While several hundred thousand CIPN patients stand to benefit, the bigger group of beneficiaries is the 116 million Americans with chronic pain⁴³. Evaluating if Scrambler Therapy works in one well-defined pain group will stimulate the needed research with other pain patients.

6. Patient Population

6.1 Inclusion Criteria

- 6.1.1 Men and women, 18 years of age or older with cancer.
- 6.1.2 English speakers.
- 6.1.3 CIPN neuropathy: Received neurotoxic chemotherapy in any setting as cancer treatment; including taxanes-such as paclitaxel or docetaxel; platinum-based compounds such as carboplatin or cis-platinum or oxaliplatin; or, vinca alkaloids such as vincristine, vinblastine, or vinorelbine, or proteosome inhibitors such as bortezimib.

NOTE: Patients should no longer be receiving the therapy that caused the CIPN, or have recently started a new treatment that may worsen CIPN. Patients on a treatment that may cause CIPN for a period of time where CIPN does not appear to be worsening may be allowed at discretion at the Principal Investigator.

- 6.1.4 Pain or symptoms of peripheral neuropathy of >3 month's duration attributed to chemotherapy-induced peripheral neuropathy.
- 6.1.5 An average daily pain rating of ≥ 4 out of 10, using the following question from the BPI:

Please rate your pain by circling the one number that best describes your leg and/or feet pain/discomfort (it is understood that the neuropathy discomfort from chemotherapy is not always called a 'pain' by all patients, but, for this study, that 'discomfort' should be considered to be a 'pain') from the chemotherapy related neuropathy on average over the past week. (Scale 0-10; 0= No pain, 10= Pain as bad as you can imagine)

- 6.1.6 Life expectancy >3 months
- 6.1.7 ECOG Performance Status 0, 1, 2, or 3 (see Appendix A).
- 6.1.8 Patient understands the study regimen, its requirements, risks, and discomforts, and is able and willing to sign an informed consent form.

6.2 Exclusion Criteria

- 6.2.1 Any of the following: pregnant women, nursing women, women of childbearing potential or their sexual partners who are unwilling to employ adequate contraception (condoms, diaphragm, birth control pills, injections, intrauterine device [IUD], surgical sterilization, subcutaneous implants, abstinence, etc.).
- 6.2.2 Use of an investigational agent for pain control concurrently or within the past 30 days.
- 6.2.3 History of or previous intolerance to transcutaneous electronic nerve stimulation.
- 6.2.4 Patients with implantable drug delivery systems, e.g. Medtronic Synchromed.
- 6.2.5 Patients with heart stents or metal implants such as pacemakers, automatic defibrillators, cochlear implants, aneurysm clips, vena cava clips and skull plates. (Metal implants for orthopedic repair, e.g. pins, clips, plates, cages, joint replacements are allowed).
- 6.2.6 Patients with a history of myocardial infarction or ischemic heart disease within the past six months.
- 6.2.7 Patients with history of epilepsy, brain damage, or symptomatic brain metastases.
- 6.2.8 Prior celiac plexus block, or other neurolytic pain control treatment.
- 6.2.9 Other identified causes of painful parasthesias existing prior to chemotherapy (e.g., radiation or malignant plexopathy, lumbar or cervical radiculopathy, pre-existing peripheral neuropathy of another etiology: e.g., carpal tunnel syndrome, B12 deficiency, AIDS, monoclonal gammopathy, diabetes, heavy metal poisoning amyloidosis, syphilis, hyperthyroidism or hypothyroidism, inherited neuropathy, etc.) that might be responsible for the patient's current neuropathic symptoms.
- 6.2.10 Skin conditions such as open sores that would prevent proper application of the electrodes.
- 6.2.11 Currently receiving anti-convulsants (such as gabapentinoids, e.g. gabapentin (Neurontin) or pregabalin (Lyrica). Because of data that support that patients do not do as well when on gabapentin or pregabalin, all patients on these medications will be weaned off them prior to study initiation. The study team will provide instructions on how to do this.
- 6.2.12 Other medical or other condition(s) that in the opinion of the investigators might compromise the objectives of the study

6.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

7. Study Design and Treatment Plan

7.1 Summary

We propose a straightforward randomized controlled trial of actual Scrambler Therapy versus sham therapy (electrodes placed on the back, which does not cause pain relief but is perceived as active treatment in a pilot trial). This study also serves to get preliminary information for planning future, larger, phase III studies.

7.2 Recruitment

Patients will be recruited through the Kimmel Cancer Center's outpatient oncology clinics. Participants may also be referred from other centers to consider participation; however, direct recruitment strategies are not planned.

7.3 Determination of Eligibility

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

For patients who reach the study team without the referral of their treating oncologist, a member of the patient's care team will be consulted to confirm that s/he believes that the participant is appropriate for protocol participation.

Study intervention cannot begin until the patient is successfully registered and after randomization has taken place (per below).

7.4 Randomization and Blinding

Upon eligibility confirmation, participants will be randomized to the Scrambler Therapy or sham treatment group. A list will be tabulated by a study statistician and provided to a member of the study team not directly involved in recruitment or provided in a way that the next assignment is not known (i.e., prepared, sealed envelopes to be opened at the time of randomization). The randomization assignments will be made as close as possible the planned day 1 of intervention and made available to the study team member who will administer the Scrambler intervention.

Whenever possible, for any outcome other than a patient-reported outcome, such as diary entries, the data will be recorded or reviewed by the study coordinator, not the treatment person. If possible, the study coordinator will meet with participants prior to or after the treatment session such that the coordinator interacting with the participant is not aware of the treatment assignment.

All participants will be asked whether they thought that they received Scrambler Therapy or sham therapy. This will be evaluated at the end of the first treatment and after the last treatment.

All patients will be un-blinded after the Day 28 data collection is complete. Participants randomized to the sham group who still have an average daily pain rating of ≥ 4 after the day 28 data collection is complete (for the primary endpoint) will be offered 10 Scrambler Therapy sessions. This group will not be separately analyzed or considered part of the primary endpoint;

however, their pain scores recorded after the primary endpoint is assessed will be summarized with the rest of the sham group using an intent-to-treat approach. We will keep to the original 2 and 3 month time periods for assessment, and not add a two week delay, in order to finish at 3 months total. These originally sham-randomized participants with an average daily pain rating of <4 after the day 28 data collection is complete may be offered 10 Scrambler Therapy sessions at the discretion of the Principal Investigator.

7.5 Methods and Intervention

7.5.1 Scrambler Therapy

The locations of symptoms will be assessed on both the upper and lower extremities. Treatment will be given to both arms and legs based on the number of electrodes available and the desire to have a short, defined period of treatment.

7.5.1.1 Treatment Days

Day 1/Treatment Initiation:

1. Treatment should be initiated by turning on the stimulus for the first electrode pair. The intensity of the stimulus is increased until the patient can first feel some sensation associated with one or both of the electrodes.
2. Then, over a few seconds, the intensity is increased to what is maximally tolerated.
3. Once the intensity is at its maximum setting, the research therapist will evaluate the level of pain. If the pain level is not decreased, the machine will be reset to zero, the electrodes will be repositioned and the machine will be restarted in the manner described above. If the pain is not completely resolved with one set of electrodes, a second set will be applied in a similar fashion. Once satisfactory electrode placement and stimulus intensity is determined, therapy is maintained for a total of 30 minutes. The exact assessment and electrode location process is outlined in The Calmare Manual.
4. The same process will be followed for the opposite foot.
5. 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 evaluated. Considerations include subjective patient intolerance, stimulation of a cutaneous nerve branch, or exacerbation of hyperesthesia or allodynia associated with the neuropathic process. These problems can be addressed by moving one or both of the electrodes farther away from the area of pain. For the electrodes that were moved, the intensity should again be increased and maintained at maximum for 30 minutes as described above.
6. Once placement of the electrodes have been finalized, photographs may be taken of the sites of the electrodes including lower arms, hands, lower legs, feet, and lower back to document the placement of the electrodes on each day. These photographs will be documented in the patients' electronic medical record and will not include any identifying features.

Days 2-10:

1. Treatment will be administered using the same principles (each day evaluated independently and not necessarily reproducing the electrode arrangements and

stimulation parameters of the previous day) for 30 minutes on consecutive days (Monday-Friday for 2 weeks).

2. Up to two or three days may be skipped to allow for weekends and/or holidays, if needed. If the participant presents without any pain, then the treatment will be “held” for that day and this information will be recorded.
3. Treatment does not proceed if the patient does not have pain.

7.5.1.2 Dose and Application

1. Electrodes are applied on the skin in the pain-affected area.
2. The electrodes are never applied directly on the pain area, unless there is no pain free area. In that case, the electrode will be applied to the most pain free area, as per the manufacturer’s and inventors instructions.

7.5.2 Sham Treatments

The sham treatment has been extensively tested at the Mayo Clinic with half of the 10 patients able to discern that their treatment was a sham. (Loprinzi, Barton, Pachman, Smith, unpublished data)

7.5.2.1 Treatment Days

1. The Sham procedure will be implemented in exactly the same way as the Scrambler Therapy procedure, except that the placement of the electrodes will occur on the back, **not near the spinal column** (away from the main region of pain, which in CIPN is nearly always maximal in the feet).
2. The distal electrode (black) will be placed on the back midway from the posterior axillary line and the midline on the left side in the T8 dermatome.
3. The proximal electrode (non-black) will be placed on the back midway from the posterior axillary line and the midline on the left side in the T4 dermatome.

7.5.2.2 Dose and Application

The electrodes will be applied and sessions will continue similarly as in the Scrambler Therapy group, with the exception of the different placement areas noted.

We will attempt to control for bias by having the lead-placer use the same script and follow exactly the same procedures, asking the exact same questions (“Do you feel any sensation?” “Let me know when you feel the sensation.” “Let me know when you feel the sensation is at your limit of tolerance.”) when placing “real” or sham leads.

7.5.3 Calmare Device

The device has FDA 510(k) approval, "Scrambler ST 5 TENS Device," (K081255) granted in February 2009.

A device has been provided to SKCCC by the manufacturer, Competitive Technologies, Inc. The device has passed approval by Johns Hopkins Clinical Engineering.

7.5.4 Additional Information

We will include information in the informed consent form to suggest that participants wear loose fitting clothing where electrode placement may be easily placed underneath clothing to avoid the need to change into an exam gown at each visit.

7.6 Patient-Reported Outcomes

7.6.1 General

In addition to the patient-reported outcomes described below and as outlined on the Study Calendar, the following information will be collected for all participants:

1. Before and after each Scrambler Therapy/Sham treatment session daily, the “pain now” question from the BPI will be asked and documented, as in prior studies: “Please rate your pain/discomfort on a scale of 1 to 10 with the one number that best tells how much pain/discomfort from the chemotherapy related neuropathy you have RIGHT NOW.”
2. Patients will be asked to state whether they believe they are receiving the active or sham therapy at the end of the 1st and last treatment.
3. Patients will be asked after the end of the last treatment: “Did the treatment help you with the pain and or numbness?” Yes/ No. “Would you want to continue the treatment if it was available?” Yes/No

7.6.2 BPI Short Form – Modified for CIPN

The Brief Pain Inventory (BPI) short form⁴⁴ is a pain assessment tool used with cancer patients to measure both severity of pain (first 5 items) and interference caused by pain (item 6 with 7 components) on 0-10 scales (0=does not interfere; 10=completely interferes.) It is widely used in cancer pain evaluation⁴⁵ and has been modified specifically for neuropathy⁴⁶.

The BPI short form will be completed at baseline, end of treatment and at 1 month (28 days), 2 months (8 weeks), and 3 months (12 weeks) after the Scrambler/Sham therapy. Those participating in sham therapy group and choosing Scrambler therapy after 28 days, will complete the BPI at the end of Scrambler therapy, and at 1 and 2 months after the Scrambler therapy. Before and after Scrambler/Sham therapy daily, the “pain now” question from the BPI (question #4) will be asked and documented, as in prior studies.

7.6.3 European Organization for Research and Treatment of Cancer Quality of Life Cancer Chemotherapy Induced Peripheral Neuropathy-20 Instrument (CIPN-20)

The EORTC QLQ-CIPN20⁴⁷ is a 20-item CIPN-specific questionnaire which includes three scales assessing sensory (9 items: #31-36, 39, 40, 48), motor (8 items: #37, 38, 41-45, 49), and autonomic (3 items: #46, 47, 50) symptoms and functioning with each item measured on a 1-4 scale (1 – not at all; 4 – very much). The EORTC QLQ-CIPN20 has been tested in cancer patients receiving a variety of chemotherapies and has been shown to have internal consistency reliability based on Cronbach’s alpha coefficients of 0.82, 0.73, and 0.76 for the three scales, respectively, with excellent validity and reliability⁴⁸. The CIPN-20 will be completed at baseline, end of treatment and at 1 month (28 days), 2 months (8 weeks), and 3 months (12 weeks) after the Scrambler/Sham therapy. Those participating in sham therapy group and choosing Scrambler

therapy after 28 days, will complete the CIPN-20 at the end of Scrambler therapy, and at 1 and 2 months after the Scrambler therapy.

NOTE: Please see questionnaires in Appendices A and B.

7.6.4 Concomitant Medications

Participants will also keep a diary where they will record each dose of pain medication (prescription and over the counter) they take in real time throughout each 24 hour period during Scrambler/sham intervention. This diary will be brought to the sessions and the study coordinator (**NOT the study team member administering the intervention**) will review the diary for completeness and clarity. Participants will also be asked to complete a diary of pain medications for a 7-day period around the time of the monthly follow-up timepoints as outlined above for the patient-reported outcomes.

The following table will be used to convert all opiates to morphine oral dose equivalents (MOEDs), when applicable:

Morphine oral dose equivalents ⁴⁹					
Drug intake for prior 24 hours	Oral Equivalent	Parental equivalent	Doses and Total mgs taken	Conversion Factor	Total MOED (mg)
Morphine immediate release	30 mg	10 mg			
Morphine sustained release	30	10			
Codeine	200 mg	100 mg			
Oxycodone immediate release	20 mg	Not available			
Oxycodone extended release	20 mg	Not available			
Hydrocodone immediate release	30 mg	Not available			
Hydromorphone	7.5 mg	1.5 mg			
Methadone	10 mg	5 mg			
Fentanyl transdermal	1 mcg/hour equivalent to 2 mg oral morphine/hour				
TOTAL					

7.7 Concomitant and Supportive Therapy

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

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

7.8 Discontinuation and Withdrawal of Subjects

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

Unless the subject refuses, follow-up will continue for the planned 12 weeks duration after the study intervention.

7.8.1 Discontinuation of Intervention

The reasons for discontinuation or protocol treatment include:

- Non-compliance with the study protocol; including, but not limited to not attending the majority of scheduled visits.
- Unacceptable major toxicity.
- Intercurrent illness or condition that would, in the judgment of the treating investigator, affect assessment of clinical status to a significant degree or require discontinuation of study intervention.
- At subject's own request. Note: The reason for discontinuation from the study must be documented. The patients will be included in the overall evaluation of response (intent-to-treat analysis) if any protocol intervention was administered prior to withdrawal.
- Study is closed or cancelled for any reason.

7.8.2 Withdrawal from Study

The reasons for withdrawal from the study include:

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

7.9 Additional Information

There will be co-investigators who require training on the MC5-A Calmare equipment in order to administer the scrambler and sham therapy. In order to best complete this training, it is not realistic to expect that these patients will stay blinded to the treatment assignment of the "scrambler" vs. "sham" treatment due to the communication between the staff performing the training.

The patients to be approached to take part in training will have a diagnosis also of peripheral neuropathy, as this will be the population in the randomized study. We will use the same, IRB-approved informed consent and the study team will explain to these patients that their participation will not be randomized, that they will receive scrambler therapy; however, that all other aspects of the study (including questionnaires, pain and medication diary collection) will continue as per the primary trial. This discussion will be documented in the medical and research records.

We expect to need 2-3 participants for training activities; however, in case of study staff changes during the study or any need for additional training, we will increase our recruitment goal by a total of 5 participants.

In case of any non-evaluable patients, we will increase our recruitment goal by a total of 5 participants. The total recruitment goal with all potential additional participants will be 40.

8. Study Calendar

Tests and procedures	Baseline		Daily during intervention	Follow-up ^{8,9}
	Prior to registration	Day 1 prior to first session		
Palliative care consult ¹	X			
Physical assessment ²		X	X	
Brief Pain Inventory “pain now”, before and after treatment			X	
Brief Pain Inventory Short Form-CIPN (Appendix B)		X		X
EORTC QLQ CIPN-20 scale (Appendix C)		X		X
Concomitant Medication Review (Appendix D) ³		X	X	X
Randomization ⁴		X		
Intervention: Scrambler Therapy/ Sham Treatment ^{5,6}			X	X
Patient preference ⁷		X		X

1. A palliative care consult will be required of all potential patients. This is needed to confirm medical history, current symptoms, and eligibility/appropriateness for the clinical trial. A member of the Palliative Care team at Johns Hopkins, who is also a study team member, will conduct this visit.
2. Prior to each Scrambler Therapy/Sham Treatment session a physical assessment will be done by a member of the study team to document any new/changes in physical symptoms related to CIPN; a full physical exam is not planned. This is to ensure good performance status, absence of sores, etc.
3. All pain medications will be recorded daily during intervention and for a 7 day period around follow-up questionnaires; opioids will be converted as described for data analyses.
4. Eligible subjects are randomized to receive Scrambler Therapy or Sham Treatment. Up to 5 additional participants will be included in a non-randomized fashion for training sessions with study staff; these participants will not count towards the overall accrual goal. NOTE: To distinguish training participants from those involved in the randomized clinical trial, these subjects will be assigned unique/different study numbers.
5. A phone call will be made 3-7 days after the last treatment session (Scrambler Therapy or Sham Treatment) to ask about any untoward symptoms that may have happened upon withdrawal of MCA-5.
6. Participants randomized to the sham group will be offered the option to receive the Scrambler Therapy, if, at Day 28 their pain is still ≥ 4 , and not relieved to their satisfaction. These patients will be “un-blinded” and offered 10 sessions of Scrambler therapy.
7. After the first and last session of Scrambler Therapy/Sham Treatment, participants will be asked whether they think they received the Scrambler Therapy or the Sham Treatment. After the final session, participants will also be asked the following questions: “Did the treatment help you with the pain and or numbness?” (Yes/No), and “Would you want to continue the treatment if available?” (Yes/No)
8. Follow-up may occur by phone/mail, if required.
9. Patients who receive Scrambler Therapy after Sham Treatment will have follow-up assessments at the same timepoints as if originally assigned to receive Scrambler Therapy; these participants will be on study for about 4 months to complete all assessments.

Note: The schedule should be followed as closely as is realistically possible; however, the schedule may be modified due to problems such as scheduling delays or conflicts (e.g., clinic closure, poor weather conditions, vacations, etc.) with the guidance of the Principal Investigator/designee, as appropriate, and will not be reportable as a deviation unless the endpoints of the study are affected.

9. Adverse Events

In the published or in-press trials to date no side effects have been reported. Since the electrodes are applied to areas that do not hurt, and if pain is observed then the electrodes are removed, there has not been pain from the device. Hypersensitivity to the gel on the skin electrode is possible. Patients may feel an electrical stimulation similar to TENS therapy.

In over 4000 patients treated, and our own experience, we have not observed any significant side effects. We have had a handful of patients who reported slightly worse pain the night of the first treatment, usually with subsequent relief, but have not observed any pattern for this.

To date, 14 patients have received treatment on this study at Johns Hopkins University. There was one incident where the Scrambler Therapy machine malfunctioned resulting in the patient feeling a short, temporary jolt, which resulted in no permanent damage to the patient. There is a small risk that patients may receive a small electrical charge from the machine, which will be a surprise to the patient but is not hurtful or harmful.

9.1 General

In the case that adverse events related to the study intervention are reported, these will be recorded per the descriptions and grading scales found in the revised National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 for adverse event reporting that can be found at <http://ctep.cancer.gov/reporting/ctc.html>.

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

The adverse events related to any ongoing treatment for the patient's underlying cancer or other medical conditions will not be collected.

9.2 Reporting Procedures

All intervention-related adverse events will be captured on the appropriate study-specific report forms (CRFs) or in a designated database.

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

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

10. Measurement of Effect

The primary outcome is described Section 13.1 below.

For any outcome other than a patient-reported outcome, such as diary entries, the data will be recorded or reviewed by the study coordinator, not the treatment person.

Our statistical consultation service is headed by Dr. Gary Rosner, Professor of Oncology and Director of the Quantitative Sciences Program and Biostatistics/ Bioinformatics Division. He will appoint a masters-level statistician to continue work with us as data become available.

11. Data and Safety Monitoring

11.1 Data Management

All information will be collected on study-specific case report forms by the study staff or in a designated database.

All study data will be reviewed for completeness and accuracy by the Principal Investigator. The study data may also be periodically reviewed by the Sidney Kimmel Comprehensive Cancer Center Clinical Research Office.

11.2 Monitoring

This is a Level 1 study under the SKCCC Data Safety Monitoring Plan (06/25/2010). The Clinical Research Office QA Group will perform an audit at the end of the first year and then periodically depending on the rate of accrual and prior audit results.

The SKCCC CRO will perform data and safety monitoring, oversight of adverse events and other protocol events for this research.

All trial monitoring and reporting will be reviewed annually by the SKCCC Safety and Monitoring Committee.

12. Administrative Procedures

12.1 Protocol Amendments

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

12.2 Informed Consent

The Principal Investigator (or his designee) will explain to each subject the nature of the study, its purpose, procedures involved, expected duration, potential risks and benefits. Each subject will be informed that participation in the study is voluntary and that she may withdraw from the study at any time, and that withdrawal of consent will not affect her subsequent medical treatment. This informed consent will be given by means of a standard written statement and will be submitted for IRB approval prior to use. No patient will enter the study before her informed consent has been obtained. In accordance with the Health Insurance Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

12.3 Ethics and Good Clinical Practice

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

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

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

12.4 Regulatory Authorities

12.4.1 Institutional Review Board

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

13. Statistical Considerations

13.1 Overall

The primary endpoint is change in patient-reported pain from day 0 to day 28 as measured by the Modified Brief Pain Index, question #3 (Appendix B). This endpoint also serves to get preliminary information for planning future, larger, phase III studies.

Secondary endpoints will include the total Brief Pain Inventory score, the sensory and motor subscales of the CIPN 20, and the Morphine Oral Equivalents Dose at day 28 compared to sham therapy. We will also report the daily (days 1-10) changes in “pain now” before and after each treatment, to be comparable to all the other reported studies.

13.2 Sample Size and Accrual

We are anticipating that the starting pain score will be 4-6 based on VCU, Italian, and Mayo Clinic data. We are anticipating that the reduction in CIPN pain score will be over 50% based on the VCU, Italian, and Mayo Clinic data. We anticipate a possible 10% reduction in pain scores over 30 days based on the randomized trial data for placebo compared to gabapentin and other drugs.

The primary objective of this study is to determine if patients randomized to the Scrambler therapy have a larger reduction in pain scores than those randomized to the placebo, or sham, treatment. Power calculations were performed using a simulation approach. Pain scores were simulated using a bivariate normal distribution with a mean (SD) of 4 (2) at baseline for both groups, with means ranging from 2.8 to 3.6 (30% to 10% decrease) for the control group post-treatment and mean of 2 (50% decrease) for the Scrambler group post-treatment. Post-treatment scores for both treatment arms were assumed to have a SD = 1.5. Based on previous data, a value of 0.3 was assumed for the within-patient correlation between pre- and post-treatment scores.

Any patient with 1) a simulated pain score at baseline less than 4, or 2) a simulated pain score less than 0 post-treatment, or 3) a simulated pain score greater than 10 at either time point, was replaced until all criteria were met, to reflect the actual scores we will see. Simulated scores were then rounded to the nearest integer to also reflect the nature of the scale. The change in pain score was calculated for each patient, and differences were compared between groups with a two-sample t test. Power was defined as the proportion of simulations that yielded a one-sided p value for the t test < 0.10 . 1000 simulations for each scenario were performed. The table below shows sample sizes and resulting power for the differences between treatment arms.

Total N	Power	Percent Decrease in Treatment Arm	Percent Decrease in Control Arm
30	87.3%	50%	10%
60	86.6%	50%	20%
90	77.6%	50%	30%

To detect the proposed effect size, 30 patients total, 15 on Scrambler therapy and 15 on the sham arm, will yield 87.3% power with a 1-sided type I error rate of 10%.

We will record the same pain data on the group that receives sham treatment if they elect to receive actual Scrambler treatment at the end of their 28-day treatment period. However, this is not a “crossover” design trial wherein each patient serves as his/her own control. Data collection for the primary endpoint will occur before patients in the sham arm are given the option to receive Scrambler treatment. This data will not be formally analyzed but instead used to help plan future studies.

13.3 Analysis Plan

13.3.1 Primary Endpoint

Pain scores will be summarized for each treatment arm at each time point with summary statistics. The mean change in scores in each treatment arm will be described with one sample paired t tests. The primary endpoint will be evaluated by testing for differences in change in pain scores between the two treatment arms with a one-sided t test. We will conclude a significant difference between treatment arms if the p value < 0.10. This difference will be reported with a 90% confidence interval.

Because this is a small study that is looking for an unbiased signal of activity, and the first randomized sham-controlled study for Scrambler therapy, we did not want to set the bar too high for concluding a positive effect of the treatment. This is not the definitive phase 3 studies for this treatment but more like an early randomized phase 2 study. Instead, this study will contribute information that will be useful in planning larger studies of the potential benefit of Scrambler therapy. The estimates used in the power calculation were based on data collected from a large series of patients, and even if we see the same differences in our study, we are less likely to conclude a positive treatment effect with a significance level < 0.05 due to the smaller sample size. We chose a type I error threshold of 10% to account for this, so that a p-value of 0.07 or 0.08 for the primary endpoint, for example, would not yield a negative study but instead suggest that larger studies are worthy of pursuit.

13.3.2 Secondary Endpoints

Secondary endpoints include change in all of the pain scores (worst, least, average, right now, relief) recorded by the BPI, changes in the CIPN-20 sensory and motor subscales, and change in medication use and doses; all were measured at entry, 1, 2, and 3 months. All of these measurements will be summarized by treatment group using descriptive statistics and confidence intervals and tested for differences between treatment arms using t tests, Wilcoxon rank sum tests or Fisher’s exact tests as appropriate. Changes in scores over time will be analysed using appropriate regression models estimated with GEE or random effects to control for correlation between measurements from the same patient. All p values will be calculated for descriptive purposes only and we do not plan to control for multiple comparisons.

We will also compare baseline characteristics between treatment arms. Because treatment assignment is randomized, we do not expect to see differences. However, if we detect imbalance in variables such as concomitant medicinal use and supportive treatment, then we will control for this in the main analyses.

13.3.3 Intention to treat

Analysis will be done by intention to treat, not “as treated”, with full inclusion of subjects.

13.4 Reporting and Exclusions

Subjects who sign a consent form, but do not initiate protocol intervention for any reason (e.g., subjects who are screen failures), will be replaced and will not count towards our accrual goal. No data from subjects included as part of training will be included in the study analyses.

APPENDICES

- A ECOG Performance Status Scale
- B Modified Brief Pain Inventory (Modified for CIPN)
- C European Organization for Research and Treatment of Cancer Quality of Life Cancer Chemotherapy Induced Peripheral Neuropathy-20 Instrument (EORTC QLQ-CIPN-20)
- D Concomitant Pain Medications/Participant Diary

APPENDIX A: ECOG Performance Status Scale

Score	Definition
0	Asymptomatic (Normal activity. Fully active, able to carry on all pre-disease performance without restriction)
1	Symptomatic, fully 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	Symptomatic, in bed less than 50% of day (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	Symptomatic, in bed more than 50% of day, but not bedridden (Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.)
4	Bedridden (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.)

APPENDIX B: Modified Brief Pain Inventory

NOTE: A modified format may be presented to participants, on study-specific forms/booklets; however, all questions will be phrased/worded as below.

1. Please rate your pain by circling the one number that best describes your pain/discomfort (it is understood that the neuropathy discomfort from chemotherapy is not always called a 'pain' by all patients, but, for this study, that 'discomfort' should be considered to be a 'pain') from the chemotherapy related neuropathy at its WORST in the last 24 hours.

A horizontal scale with numerical labels from 0 to 10. The label 'No pain' is positioned above the '0' and 'Pain as bad as you can imagine' is positioned above the '10'.

2. Please rate your pain/discomfort from the chemotherapy related neuropathy by circling the one number that best describes your pain/discomfort at its LEAST in the last 24 hours.

3. Please rate your pain/discomfort by circling the one number that best describes your pain/discomfort from the chemotherapy related neuropathy on the AVERAGE.

A horizontal scale with numerical labels from 0 to 10. The label 'No pain' is positioned above the '0' and 'Pain as bad as you can imagine' is positioned above the '10'.

4. Please rate your pain/discomfort by circling the one number that best tells how much pain/discomfort from the chemotherapy related neuropathy you have **RIGHT NOW**.

5. Since starting the treatment, how much RELIEF has the treatment used in this study provided? Please circle the one percentage that most shows how much relief you have received.

Received: 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
No relief Complete relief

6. Circle the one number that describes how during the past 24 hours pain/discomfort from your chemotherapy related neuropathy has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

D. Normal work includes both work outside the home and housework

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

APPENDIX C: European Organization for Research and Treatment of Cancer Quality of Life Cancer Chemotherapy Induced Peripheral Neuropathy-20 Instrument (CIPN-20)

NOTE: A modified format may be presented to participants, on study-specific forms/booklets; however, all questions will be phrased/worded as below.

Please circle the words in the box for how much the symptoms bother you:				
Sensory subscale				
Scores	0	1	2	3
Tingling in the Fingers/Hands	None at all	A little bit	Quite a bit	Very much
Tingling in the Toes/Feet	None at all	A little bit	Quite a bit	Very much
Numbness in the Fingers/Hands	None at all	A little bit	Quite a bit	Very much
Numbness in the Toes/Feet	None at all	A little bit	Quite a bit	Very much
Shooting/burning in the Fingers/Hands	None at all	A little bit	Quite a bit	Very much
Shooting/burning in the Toes/Feet	None at all	A little bit	Quite a bit	Very much
Problems standing/walking	None at all	A little bit	Quite a bit	Very much
Difficulty distinguishing hot/cold	None at all	A little bit	Quite a bit	Very much
Difficulty in hearing	None at all	A little bit	Quite a bit	Very much
Summary Score				
<i>These are summed for each section.</i>				
Motor subscale				
Scores	0	1	2	3
Cramps in the fingers/hands	None at all	A little bit	Quite a bit	Very much
Cramps in the toes / feet	None at all	A little bit	Quite a bit	Very much
Difficulty manipulating small objects	None at all	A little bit	Quite a bit	Very much
Problems holding a pen	None at all	A little bit	Quite a bit	Very much
Difficulty opening a jar	None at all	A little bit	Quite a bit	Very much
Difficulty walking	None at all	A little bit	Quite a bit	Very much
Difficulty with stairs	None at all	A little bit	Quite a bit	Very much
Difficulty using car foot pedals	None at all	A little bit	Quite a bit	Very much
Scores				
<i>These are summed for each section.</i>				

NOTE: Used with registration and permission, EORTC.

APPENDIX D: Concomitant Pain Medications/Participant Diary

Instructions: Please note below all pain medications that you take during your participation on this study.

Completed by: _____
Participant's signature

Date:

Reviewed by: _____
Study team member's signature

Date:

REFERENCES

¹ Wolf S, Barton D, Kottschade L, Grothey A, Loprinzi C. Chemotherapy-induced peripheral neuropathy: prevention and treatment strategies. *Eur J Cancer*. 2008 Jul;44(11):1507-15.

² Broyl A, Jongen JL, Sonneveld P. General aspects and mechanisms of peripheral neuropathy associated with bortezomib in patients with newly diagnosed multiple myeloma. *Semin Hematol*. 2012 Jul;49(3):249-57. doi: 10.1053/j.seminhematol.2012.04.001. Review.

³ Delforge M, Bladé J, Dimopoulos MA, Facon T, Kropff M, Ludwig H, Palumbo A, Van Damme P, San-Miguel JF, Sonneveld P. Treatment-related peripheral neuropathy in multiple myeloma: the challenge continues. *Lancet Oncol*. 2010 Nov;11(11):1086-95. doi: 10.1016/S1470-2045(10)70068-1.

⁴ Yardley DA. Proactive management of adverse events maintains the clinical benefit of ixabepilone. *Oncologist*. 2009 May;14(5):448-55.

⁵ G. Kannarkat, E.E. Lasher and D. Schiff, Neurologic complications of chemotherapy agents, *Current Opinion in Neurology* 20 (6) (2007), pp. 719–725.

⁶ A.J. Windebank and W. Grisold, Chemotherapy-induced neuropathy, *J Peripher Nerv Syst* 13 (1) (2008), pp. 27–46.

⁷ A.-L. Kautio, M. Haanpaa and T. Saarto et al., Amitriptyline in the treatment of chemotherapy-induced neuropathic symptoms, *Journal of Pain and Symptom Management* 35 (1) (2008), pp. 31–39

⁸ Hammack JE, Michalak JC, Loprinzi CL, Sloan JA, Novotny PJ, Soori GS, Tirona MT, Rowland KM Jr, Stella PJ, Johnson JA. Phase III evaluation of nortriptyline for alleviation of symptoms of cis-platinum-induced peripheral neuropathy. *Pain*. 2002 Jul;98(1-2):195-203.

⁹ Rao RD, Flynn PJ, Sloan JA, Wong GY, Novotny P, Johnson DB, Gross HM, Renno SI, Nashawaty M, Loprinzi CL. Efficacy of lamotrigine in the management of chemotherapy-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled trial, N01C3. *Cancer* 2008 Jun 15;112(12):2802-8.

¹⁰ Rao RD, Michalak JC, Sloan JA, Loprinzi CL, Soori GS, Nikcevich DA, Warner DO, Novotny P, Kutteh LA, Wong GY; North Central Cancer Treatment Group. Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled, crossover trial (N00C3). *Cancer*. 2007 Nov 1;110(9):2110-8.

¹¹ Nikcevich DA, Grothey A, Sloan JA, et al. A phase III randomized, placebo-controlled, double-blind study of intravenous calcium/magnesium to prevent oxaliplatin-induced sensory neurotoxicity, N04C7. *Journal of Clinical Oncology*, 2008 ASCO Annual Meeting Proceedings [Abstract 4009], 2008.

¹² Maestri A, De Pasquale Ceratti A, Cundari S, Zanna C, Cortesi E, Crinò L. A pilot study on the effect of acetyl-L-carnitine in paclitaxel- and cisplatin-induced peripheral neuropathy. *Tumori*. 2005 Mar-Apr;91(2):135-8.

¹³ De Grandis D. Acetyl-L-carnitine for the treatment of chemotherapy-induced peripheral neuropathy: a short review. *CNS Drugs*. 2007;21 Suppl 1:39-43; discussion 45-6. Review.

¹⁴ Durand JP, Deplanque G, Montheil V, Gornet JM, Scotte F, Mir O, Cessot A, Coriat R, Raymond E, Mitry E, Herait P, Yataghene Y, Goldwasser F. Efficacy of venlafaxine for the prevention and relief of oxaliplatin-induced acute neurotoxicity: results of EFFOX, a randomized, double-blind, placebo-controlled phase III trial. *Ann Oncol*. 2012 Jan;23(1):200-5. doi: 10.1093/annonc/mdr045. Epub 2011 Mar 22. PMID:21427067[PubMed - indexed for MEDLINE]

¹⁵ Barton DL, Wos EJ, Qin R, Mattar BI, Green NB, Lanier KS, Bearden JD 3rd, Kugler JW, Hoff KL, Reddy PS, Rowland KM Jr, Riepl M, Christensen B, Loprinzi CL. A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCCTG trial N06CA. *Support Care Cancer*. 2011 Jun;19(6):833-41. doi: 10.1007/s00520-010-0911-0. Epub 2010 May 25.

¹⁶ Smith EM, Pang H, Cirrincione C, Fleishman S, Paskett ED, Ahles T, Bressler LR, Fadul CE, Knox C, Le-Lindquist N, Gilman PB, Shapiro CL; Alliance for Clinical Trials in Oncology. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral

neuropathy: a randomized clinical trial. *JAMA*. 2013 Apr 3;309(13):1359-67. doi: 10.1001/jama.2013.2813.

¹⁷ Wong R, Sagar S. Acupuncture treatment for chemotherapy-induced peripheral neuropathy--a case series. *Acupunct Med*. 2006 Jun;24(2):87-91.

¹⁸ Donald GK, Tobin I, Stringer J. Evaluation of acupuncture in the management of chemotherapy-induced peripheral neuropathy. *Acupunct Med*. 2011 Sep;29(3):230-3.

¹⁹ Xu WR, Hua BJ, Hou W, Bao YJ. [Clinical randomized controlled study on acupuncture for treatment of peripheral neuropathy induced by chemotherapeutic drugs] *Zhongguo Zhen Jiu*. 2010 Jun;30(6):457-60.

²⁰ Schroeder S, Meyer-Hamme G, Epplée S. Acupuncture for chemotherapy-induced peripheral neuropathy (CIPN): a pilot study using neurography. *Acupunct Med*. 2012 Mar;30(1):4-7. Epub 2011 Dec 5.

²¹ Folletti A, Durrer A, Buchser E. Neurostimulation technology for the treatment of chronic pain: a focus on spinal cord stimulation. *Expert Rev Med Devices* 2007; 4:201-14.

²² Jensen MP. A neuropsychological model of pain: research and clinical implications. *J Pain*. 2010 Jan;11(1):2-12.

²³ de Leon-Casasola OA. Spinal cord and peripheral nerve stimulation techniques for neuropathic pain. *J Pain Symptom Manage*. 2009 Aug;38(2 Suppl):S28-38.

²⁴ Mailis-Gagnon A, Furlan AD, Sandoval JA, Taylor R. Spinal cord stimulation for chronic pain.. *Cochrane Database Syst Rev*. 2004;(3):CD003783.

²⁵ Harke H, Gretenkort P, Ladleif HU, Rahman S. Spinal cord stimulation in sympathetically maintained complex regional pain syndrome type I with severe disability. A prospective clinical study. *Eur J Pain*. 2005 Aug;9(4):363-73.

²⁶ Harke H, Gretenkort P, Ladleif HU, Koester P, Rahman S. Spinal cord stimulation in postherpetic neuralgia and in acute herpes zoster pain. *Anesth Analg*. 2002 Mar;94(3):694-700.

²⁷ Al-Jehani H, Jacques L. Peripheral nerve stimulation for chronic neurogenic pain. *Prog Neurol Surg*. 2011;24:27-40. doi: 10.1159/000323017. Epub 2011 Mar 21.

²⁸ Aló KM, Abramova MV, Richter EO. Percutaneous peripheral nerve stimulation. *Prog Neurol Surg*. 2011;24:41-57. doi: 10.1159/000323023. Epub 2011 Mar 21.

²⁹ Robb K, Oxberry SG, Bennett MI, Johnson MI, Simpson KH, Searle RD. *J Pain Symptom Manage*. 2009 Apr;37(4):746-53. A cochrane systematic review of transcutaneous electrical nerve stimulation for cancer pain.

³⁰ Visovsky C, Collins M, Abbott L, Aschenbrenner J, Hart C. Putting evidence into practice: evidence-based interventions for chemotherapy-induced peripheral neuropathy. *Clin J Oncol Nurs*. 2007 Dec;11(6):901-13. Review.

³¹ Marineo G. Untreatable pain resulting from abdominal cancer: new hope from biophysics? *JOP*. 2003 Jan;4(1):1-10.

³² Sabato AF, Marineo G, Gatti A. Scrambler therapy. *Minerva Anestesiol*. 2005 Jul-Aug;71(7-8):479-82.

³³ Smith TJ, Coyne PJ, Parker GL, Dodson P, Ramakrishnan V. Pilot Trial of a Patient-Specific Cutaneous Electrostimulation Device (MC5-A Calmare®) for Chemotherapy-Induced Peripheral Neuropathy. *J Pain Symptom Manage*. 2010 Dec;40(6):883-91. doi: 10.1016/j.jpainsymman.2010.03.022.
PMID:20813492

³⁴ Deirdre R. Pachman, Breanna M. Linquist, Debra L. Barton, Kelliann C. Fee-Schroeder, Thomas J. Smith, Daniel Honore Lachance, Heshan Liu, Drew K. Seisler, Charles L. Loprinzi. Pilot study of Scrambler therapy for the treatment of chemotherapy-induced peripheral neuropathy. *J Clin Oncol* 30, 2012 (suppl; abstr 9075)

³⁵ Ricci M, Pirotti S, Scarpi E, Burgio M, Maltoni M, Sansoni E, Amadori D. Managing chronic pain: results from an open-label study using MC5-A Calmare® device. *Support Care Cancer*. 2012 Feb;20(2):405-12. Epub 2011 Mar 11.

³⁶ Guiseppe M, Vit torio I, Cristiano G, Vincenzo M, Smith TJ. MC5-A Scrambler Therapy Relieves Chronic Neuropathic Pain More Effectively Than Guideline Based Drug Management. Submitted.

³⁷ Attal N, Cruccu G, Haanpää M, Hansson P, Jensen TS, Nurmiikko T, Sampaio C, Sindrup S, Wiffen P; EFNS Task Force. EFNS guidelines on pharmacological treatment of neuropathic pain. *Eur J Neurol*. 2006 Nov;13(11):1153-69.

³⁸ Ko YK, Lee HY, Lee WY. Clinical experiences on the effect of scrambler therapy for patients with postherpetic neuralgia. *Korean J Pain*. 2013 Jan;26(1):98-101. doi: 10.3344/kjp.2013.26.1.98. Epub 2013 Jan 4.

³⁹ Park HS, Sin WK, Kim HY, Moon JY, Park SY, Kim YC, Lee SC. Scrambler therapy for patients with cancer pain - case series -. *Korean J Pain*. 2013 Jan;26(1):65-71. doi: 10.3344/kjp.2013.26.1.65. Epub 2013 Jan 4.

⁴⁰ Sparadeo F, Kaufman C, D'Amato S. Scrambler Therapy: An Innovative and Effective Treatment for Chronic Neuropathic Pain. *Journal of Life Care Planning*, Vol. 11, No. 3, (3-15), 2012.

⁴¹ Coyne PJ, Wan W, Dodson P, Swainey C, Smith TJ. A trial of scrambler therapy in the treatment of cancer pain syndromes and chronic chemotherapy-induced peripheral neuropathy. *J Pain Palliat Care Pharmacother*. 2013 Dec;27(4):359-64. doi: 10.3109/15360288.2013.847519. Epub 2013 Oct 21. PMID:24143893

⁴² Perruchoud C, Eldabe S, Batterham AM, Madzinga G, Brookes M, Durrer A, Rosato M, Bovet N, West S, Bovy M, Rutschmann B, Gulve A, Garner F, Buchser E. Analgesic Efficacy of High-Frequency Spinal Cord Stimulation: A Randomized Double-Blind Placebo-Controlled Study. *Neuromodulation*. 2013 Feb 20. doi: 10.1111/ner.12027. [Epub ahead of print]

⁴³ Institute of Medicine Report from the Committee on Advancing Pain Research, Care, and Education: *Relieving Pain in America, A Blueprint for Transforming Prevention, Care, Education and Research*. The National Academies Press, 2011.

⁴⁴ C.S. Cleeland. Measurement of pain by subjective report ,in: C.R. Chapman, J.D. Loeser (Eds.), Advances in Pain Research and Therapy, Issues in Pain Measurement, Vol. 12, Raven Press, New York (1989), pp. 391–403

⁴⁵ Cleeland CS, Body JJ, Stopeck A, von Moos R, Fallowfield L, Mathias SD, Patrick DL, Clemons M, Tonkin K, Masuda N, Lipton A, de Boer R, Salvagni S, Oliveira CT, Qian Y, Jiang Q, Dansey R, Braun A, Chung K. Pain outcomes in patients with advanced breast cancer and bone metastases: Results from a randomized, double-blind study of denosumab and zoledronic acid. *Cancer*. 2013 Feb 15;119(4):832-8. doi: 10.1002/cncr.27789. Epub 2012 Sep 5.

⁴⁶ Zelman DC, Gore M, Dukes E, et al: Validation of a modified version of the brief pain inventory for painful diabetic peripheral neuropathy. *J Pain Symptom Manage* 29:401-10, 2005

⁴⁷ Postma TJ, Aaronson NK, Heimans JJ, et al: The development of an EORTC quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy: the QLQ-CIPN20. *Eur J Cancer* 41:1135-9, 2005

⁴⁸ Cavaletti G, Cornblath DR, Merkies IS, Postma TJ, Rossi E, Frigeni B, Alberti P, Bruna J, Velasco R, Argyriou AA, Kalofonos HP, Psimaras D, Ricard D, Pace A, Galiè E, Briani C, Dalla Torre C, Faber CG, Lalising RI, Boogerd W, Brandsma D, Koeppen S, Hense J, Storey D, Kerrigan S, Schenone A, Fabbri S, Valsecchi MG; CI-PeriNomS Group. The chemotherapy-induced peripheral neuropathy outcome measures standardization study: from consensus to the first validity and reliability findings. *Ann Oncol*. 2013 Feb;24(2):454-62. doi: 10.1093/annonc/mds329. Epub 2012 Aug 21.

⁴⁹ Source : American Pain Society, Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain. 5th Ed. Glenview, IL: APS, 2003