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Surgical Treatment of Post-surgical Mastectomy Pain Utilizing the Regenerative Peripheral Nerve Interface

NCT04530526

Surgical treatment of post-surgical mastectomy pain utilizing the regenerative peripheral nerve interface (RPNI)

PROTOCOL SUMMARY

Title:	**Surgical treatment of post-surgical mastectomy pain utilizing the regenerative peripheral nerve interface (RPNI)**
Summary:	Up to 40% of patients who undergo mastectomy suffer from chronic pain, defined as pain lasting greater than three months. Chronic post-mastectomy pain due to nerve injury leads to long-term opioid use and diminished quality-of-life. A novel surgical approach to neuroma treatment, the regenerative peripheral nerve interface (RPNI) developed to treat painful neuromas associated with limb amputation has shown significant reductions in patient-reported pain. RPNI surgery is now available through Michigan Medicine's Multi-Disciplinary Peripheral Nerve (MDPN) Clinic to improve post-mastectomy pain and definitively treat intercostal neuromas following mastectomy. Using patient-reported outcomes and clinical data we will evaluate the use of RPNI surgery to reduce persistent post-mastectomy pain in women seeking surgical consultation through the Plastic Surgery or MDPN clinics.
Objectives:	**Our central hypothesis is that intercostal nerve RPNI surgery significantly reduces chronic post-mastectomy pain without neuroma recurrence.** We will employ an observational study design with patients serving as their own controls prior to surgery to assess pain levels before and after RPNI surgery for intercostal neuroma.
Population:	Adult female patients (≥18 years old) presenting to Michigan Medicine's MDPN Clinic with post-mastectomy pain persisting at least six months removed from mastectomy will be eligible for participation.
Number of Sites:	Single Center - University of Michigan
Study Duration:	Two years (NIH funded). Three years total.
Subject Participation Duration:	Approx. 12 months.
Description of Intervention:	Survey based patient reported outcomes from patients undergoing RPNI surgery, clinical data collection
Enrollment Period:	12 months
Estimated Sample Size:	25 patients

1. KEY ROLES

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2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Up to 40% of patients who undergo mastectomy suffer from chronic pain, defined as pain lasting greater than three months. Even three years after surgery, nearly 25% of patients continue to report moderate pain (3, 4). However, mastectomy remains a mainstay of treatment for over 25% of breast cancer patients (5), necessitating novel, adequate solutions for the significant and debilitating issue of chronic pain.

Previous studies have documented that breast cancer patients with post-surgical pain experience worse quality-of-life with respect to patient-reported physical well-being, physical autonomy, relationships, and psychological well-being (6, 7). Nearly 11% of opioid naïve patients who undergo breast cancer surgery continue to require opioids for pain relief at least three months after surgery, and the opioid dosing regimen for these patients approaches that used for chronic opioid users (8). Even 7-9 years after surgery, many breast cancer patients report requiring opioid medication for post-mastectomy pain (9). In addition to opioids, management of chronic post-mastectomy neuropathic pain consists of non-steroidal anti-inflammatory drugs (NSAIDs) and neuropathic medications including gabapentin or amitriptyline (11). However, these strategies are often insufficient due to adverse medication effects, incomplete pain relief, and poor patient compliance.

Several reports have demonstrated that cutaneous nerve injury substantially contributes to post-mastectomy pain (12, 13). Altered sensation, including 'pins and needles' sensation and/or shock-like, burning, or stabbing pain in the known distribution of chest wall sensory nerves suggest a neuropathic etiology (14). A handful of small studies have documented the relationship between chronic post-mastectomy pain and injury to subcutaneous, sensory branches of the intercostal nerves in the chest (8, 9). Identification of patients with a neuropathic component to their pain, and development of a strategy which addresses the underlying nerve injury would offer an opportunity to definitively treat chronic post-mastectomy pain.

The regenerative peripheral nerve interface (RPNI) has emerged as a novel strategy to treat neuromas in peripheral nerves. The RPNI consists of the residual peripheral nerve end implanted in a skeletal muscle or skin graft, following surgical resection of the injured terminal nerve portion (neuroma) **(Fig. 1).** The free muscle or skin graft is separated from its native nerve innervation, leaving open neuromuscular junctions for ingrowth and attachment of nerve fibers from the implanted nerve; animals studies show that this provides a physiologic end-organ for the implanted nerve without neuroma recurrence (1, 2, 15, 16). We have performed RPNIs to treat painful neuromas associated with limb amputation, with significant reductions in patient- reported pain (10). Recently, we have performed RPNIs to treat histologically-confirmed intercostal neuromas in patients with chronic post-mastectomy pain.

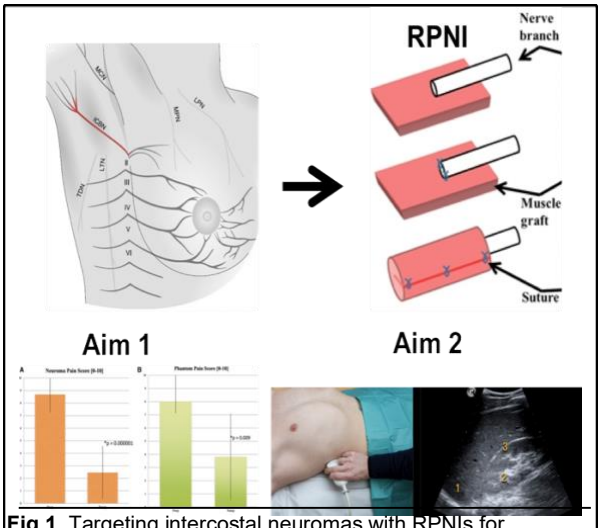

Fig 1. Targeting intercostal neuromas with RPNIs for treatment of post-mastectomy pain followed by pain evaluation (Aim 1) and neuroma evaluation (Aim 2).

Limited follow-up suggests that these patients experience substantial improvement in their pain, although formal evaluation is required.

2.2. Significance

2.2.1. **Mastectomy causes long-term pain.** Over 25% of breast cancer patients undergo surgical management with mastectomy(5) and even more with partial mastectomy (lumpectomy). In these procedures, the breast tissue is removed from the chest wall, necessitating the transection of small sensory nerves present and traveling through these tissues (**Fig 2**). Reports indicate that up to 40% of patients who undergo mastectomy report pain lasting greater than three months; even three years after surgery, nearly 25% of patients continue to report moderate pain(4). Therefore, post-mastectomy pain affects a substantial number of patients even after completion of breast cancer management.

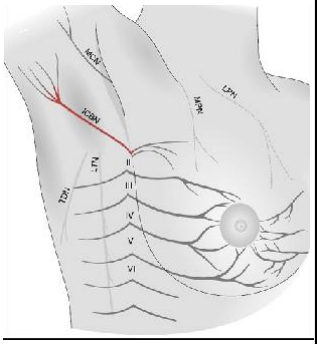

Fig 2. Nerve distribution of the chest wall and breast including contribution from intercostal nerves. (Adapted from Wijayasinghe et al 2014)

2.2.2. **Post-mastectomy pain causes substantial patient morbidity.** Studies have demonstrated that patients with post-mastectomy pain experience significantly worse quality-of-life with respect to physical well-being, physical autonomy, relationships, and psychological well-being (7). Long-term pain contributes to decreased work-function, increased healthcare utilization, and increased depression risk (6). Therefore, post-mastectomy pain has far-reaching physical and psychological consequences for patients.

2.2.3. **Post-mastectomy pain leads to opioid dependence.** Using a national data set of insurance claims, Lee et al showed that 11% (2,451 out of 22,379) of opioid naïve patients who underwent mastectomy continued to require opioids for pain relief at least three months after surgery (8). These patients often require opioid doses that approximate doses used by chronic opioid users, equivalent to six tablets of 5-mg hydrocodone per day (8). These effects are long-lasting, as even 7-9 years after surgery, mastectomy patients report requiring pain medication (9).

2.2.4. **Nerve injury contributes substantially to post-mastectomy pain**. Several studies have demonstrated that sensory nerve injury provides a substantial contribution to post-mastectomy pain (12, 13). This is not surprising given that multiple sensory nerves are at risk during mastectomy including the intercostobrachial nerve, pectoral nerves, and segmental intercostal nerves (**Fig 2**)(14); pain in these nerve distributions is characteristic of patients with post-mastectomy pain. Physical exam findings such as altered sensation including pins and needles sensation and/or shock-like, burning, or stabbing pain all provide diagnostic evidence of a painful neuroma caused by nerve injury. Histologically, we have found that neuromas at limb amputation sites demonstrate disorganized axonal growth, with excessive connective tissue and fibroblasts. We have observed gross anatomic findings consistent with intercostal neuroma including the presence of a mass of scar in continuity with nerve fiber (**Fig 3**); histologically these sites demonstrate findings consistent with neuroma as described above. These findings provide strong evidence that neuromas contribute to post-mastectomy pain.

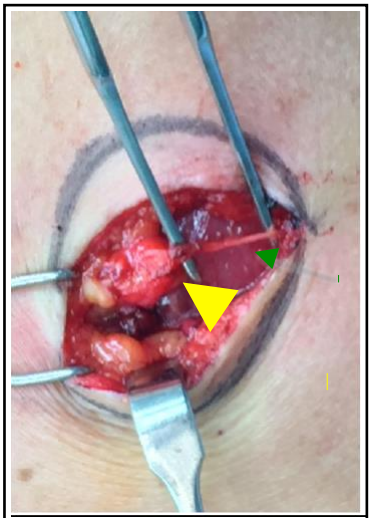

Fig 3. Typical finding of intercostal neuroma showing mass of scar (yellow arrow) in continuity with intercostal nerve (green arrow)

2.2.5. **Current pharmacologic treatment strategies for symptomatic neuromas are insufficient.** Current pharmacologic pain management strategies for symptomatic neuromas include opioids, non-steroidal anti-inflammatory drugs (NSAIDs), and neuropathic drugs including gabapentin or amitriptyline (11). However, these strategies are often insufficient due to incomplete pain relief, poor compliance, and adverse effects including chronic dependence (opioids), gastrointestinal distress (NSAIDs), and dizziness and fatigue (neuropathic drugs). Therefore, a definitive strategy to reduce pain associated with symptomatic neuromas is needed.

2.2.6. Emerging surgical treatment modalities for post-surgical neuropathic pain require improvement

Multiple surgical techniques have been described for addressing neuroma pain (21-27); however, none are widely used because of poor reliability and frequent recurrence of neuroma symptoms. Currently, the most frequently performed surgical intervention for a symptomatic neuroma is to bury the end of the nerve into normal (innervated) local muscle tissue after excision of the end neuroma (23, 24). A critical limitation is that none of these techniques permit regenerating axons to form new neuromuscular junctions with muscle fibers, a physiologic phenomenon that precludes neuroma recurrence. Furthermore, these operations have only been sparingly reported for chest wall pain (28, 29). Therefore, a surgical strategy treating post-mastectomy pain deserves further investigation.

2.3. Innovation

2.3.1. Formation of a multidisciplinary peripheral nerve clinic which treats patients with post-mastectomy pain.

We now recognize the underappreciated association between intercostal sensory nerve injury and pain in mastectomy patients. To this end, we have formed an interdisciplinary treatment team, consisting of peripheral nerve surgeons, neurosurgeons, pain anesthesiologists, and physiatrists, who work together to consult on, diagnose, and treat patients with post-surgical neuropathic pain at our institution. This provides the environment to appropriately diagnose, monitor, and treat patients. This approach also allows for a standardized approach to patients, which facilitates our ability to study the response to specific interventions.

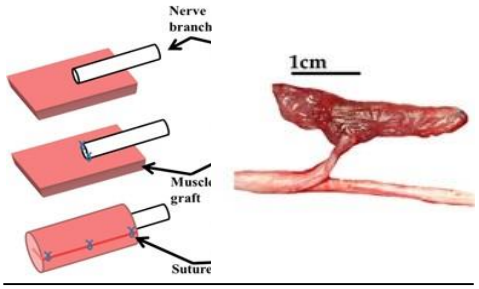

Fig 4. Schematic representation of RPNI procedure (left) and final RPNI appearance (right).(1)

2.3.2. Regenerative peripheral nerve interface (RPNI) for neuroma pain.

The Regenerative Peripheral Nerve Interface (RPNI) is a novel strategy to treat pain caused by neuroma formation at the ends of transected peripheral nerves. Following resection of the neuroma, the residual proximal end of the nerve is implanted into a free skeletal muscle or skin graft (**Fig 4**). Extensive preclinical testing in animal models demonstrated the feasibility, longevity, and durability of the RPNI at amputation sites (1, 15, 16). Histologic analysis of RPNIs has revealed: 1) muscle fibers comprising the free muscle grafts robustly regenerate within several weeks after implantation (**Fig 5**), 2) the implanted peripheral nerve ends form new neuromuscular junctions within the free muscle grafts (**Fig 6**), and 3) no evidence of neuroma was detected within the RPNIs (2). That action potentials can be transduced through the RPNI from the nerve into the muscle graft provides additional evidence that regenerating axons reinnervate muscle fibers rather than forming neuroma (2, 30). These successes in a small animal model have led to RPNI in a non-human primate model. Multiple RPNIs were implanted into two rhesus macaque monkeys and extensive histologic and electrophysiological tests were successfully conducted for up to 20 months showing RPNI nerves re-innervated the muscle graft and did not form neuromas (1). Similar studies utilizing dermal skin grafts, placed around the ends of sensory nerves, have shown similar endpoints.

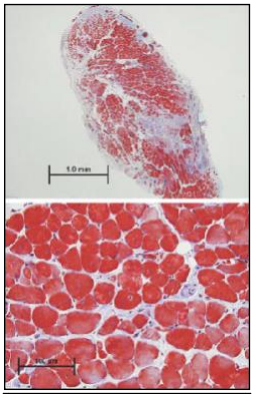

Fig 5. Healthy, innervated myofibers present in an RPNI upon histologic examination after several

Briefly, a neuroma source of pain is confirmed upon detection of characteristic pain, combined with reproducible tenderness upon mechanical stimulation over the

location of the neuroma (Tinel sign). Confirmation of the neuroma as the source of pain can be accomplished with the use of ultrasound-guided nerve blocks. In the operating room, the symptomatic neuroma(s) are then easily identified at the amputation site; the neuroma is excised from the end of the peripheral nerve and RPNI is created by implanting the nerve end into a small free muscle or skin graft. A retrospective analysis of 16 amputation patients who underwent RPNI surgery to treat symptomatic neuromas demonstrated the immense potential of this technique (10). A majority of patients in this study reported high satisfaction rates with RPNI surgery and neuroma pain scores were significantly lower post-operatively (**Fig 7**). To date, we have performed RPNI surgery in over 100 amputation patients and have data demonstrating safety and potential efficacy of RPNIs for these patients.

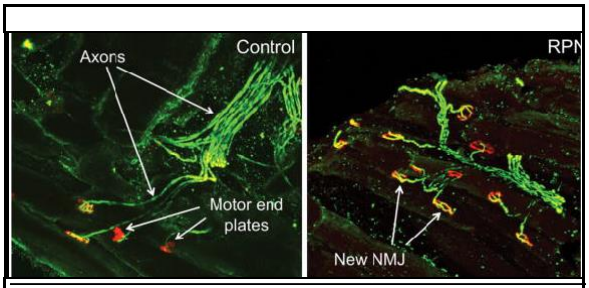

Fig 6. New neuromuscular junctions (NMJ) between muscle and free nerve end form in the RPNI (right); control image shows the appearance of NMJ in uninjured muscle (left)(2)

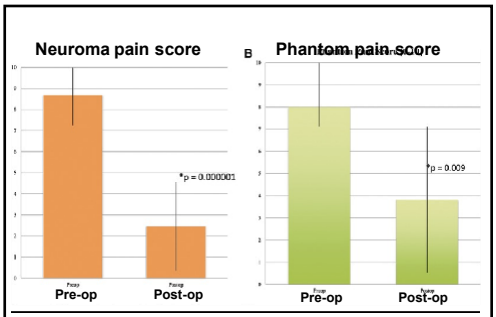

Fig 7. RPNI surgery improves neuroma pain score ($p<0.0001$) and phantom pain score ($p<0.01$) in amputation patients (10)

Recently, we applied the RPNIs surgical model to patients with post-surgical chronic chest wall pain (**Fig 8**). Although evaluation of such patients is proposed in this study is ongoing, our limited follow-up at this time suggests that these patients have experienced a substantial improvement in their pain. The promising data generated from both animal studies and human patients support execution of a prospective pilot clinical trial to evaluate the effects of RPNI surgery on post-mastectomy patient-reported outcomes and durability of neuroma treatment. Upon completion of this proposal, we expect to have sufficient preliminary data to begin a multi-institutional clinical trial, leveraging our current collaboration with other institutions for the management of chronic pain in post breast-surgery patients (31).

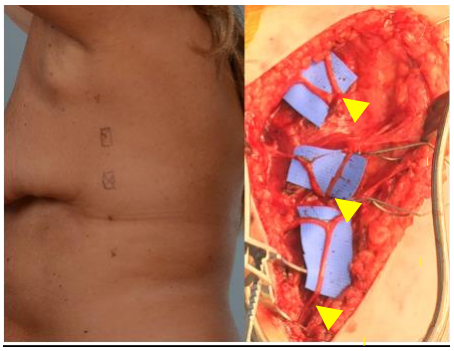

Fig 8. Intraoperative image of intercostal RPNI surgery showing multiple intercostal nerves requiring RPNIs (yellow arrows)

The central hypothesis for this study is that intercostal RPNI surgery significantly reduces chronic post-mastectomy pain with absence of painful neuroma recurrence.

Aim 1: To examine the use of RPNI surgery to reduce post-mastectomy pain and opioid consumption. We will obtain patient-reported outcomes (PRO's), using previously validated tools, to examine the effect of RPNI surgery on post-mastectomy pain and opioid use. Patients who are at least six months removed from mastectomy and exhibit clinical signs and symptoms of neuropathic pain will be asked to enroll in this IRB-approved study. Patients will be excluded if mastectomy occurred less than six months prior or if they have had previous surgical interventions to treat pain. Upon completion of Aim 1, we will assess the association between intercostal RPNI surgery and neuropathic pain in post-mastectomy patients.

Aim 2: To demonstrate absence of neuroma recurrence in post-mastectomy patients after intercostal RPNI surgery. Neuroma recurrence in patients treated with intercostal RPNI will be evaluated using physical exam findings and ultrasound (14, 17-20). Patients will be assessed immediately following enrollment, preoperatively, and at subsequent intervals (3 and 9 months) following RPNI. Upon completion of Aim 2, we will demonstrate that intercostal RPNI surgery provides durable relief from neuroma recurrence.

2.4. Potential Risks and Benefits

2.4.1. Potential Risks

Risks related to study participation are minimal. This study only evaluates chronic post-mastectomy pain in patients seeking a potential surgical intervention (RPNI). Risks of surgery are not considered part of the study and patients who are considering undergoing RPNI implantation, but later decide against it may still be included. Patients may feel inconvenienced when spending time on study requirements such as questionnaires. To minimize this risk, investigators have reviewed all survey instruments and reduced the questionnaire panel to minimally necessary items. To further reduce study time requirements, investigators have incorporated existing clinical measurements that are part of standard care and evaluation, such as physical exam and ultrasound measurements to collect outcomes data and avoid additional, study-only testing procedures. All study requirements and time commitments will be stated prior to enrollment.

Additionally, as with many studies, there is a risk of confidentiality in participation. Although rare, the study team will take precautions to secure both hard copy and electronic data and train all study staff on the importance of data security and privacy.

2.4.2. Known Potential Benefits

The prescribing of opioid medications to treat pain, including chronic pain following surgery, has become a critical issue across the U.S. Reports indicate that 10% of opioid naïve patients who undergo mastectomy require opioids for pain relief at least three months after surgery and up to 40% of patients who undergo mastectomy report post-surgical pain lasting greater than three months. Three years after surgery, nearly 25% of patients continue to report moderate persistent pain after the mastectomy procedure which involves the transection of small sensory nerves present and traveling through excised breast tissues. This study is a novel approach to improving post-mastectomy quality of life and reducing dependence on pain medications and the ensuing risk of dependence and addiction.

3. Hypotheses and Objectives

Aim 1: To examine the use of RPNI surgery to reduce post-mastectomy pain and opioid consumption.

3.1. Hypothesis: Neuroma resection and RPNI surgery to treat intercostal neuromas will reduce patient-reported post-mastectomy pain, depression/anxiety scores, and opioid use to a greater degree than will conservative neuropathic pain management.

3.1.2. Objective: Identify patients with post-mastectomy pain who have been referred to the Multi-Disciplinary Peripheral Nerve (MDPN) or Plastic Surgery Clinics and evaluate their neuropathic pain, depression and anxiety levels, and opioid use pre- and post-treatment.

We will enroll patients seeking surgical treatment for chronic post-mastectomy pain upon referral to our institutional Multi-Disciplinary Peripheral Nerve Pain (MDPN) Clinic or Plastic Surgery. The presence of neuropathic pain will be evaluated by the combined efforts of plastic surgeons, peripheral nerve surgeons, anesthesia pain providers, and physiatrists. Each patient's medication usage will be logged at pre- and post-surgical timepoints.

Aim 2: **To demonstrate absence of neuroma recurrence in post-mastectomy patients after intercostal RPNI surgery.**

3.2. Hypothesis: Intercostal nerves treated with RPNI will remain free of neuroma recurrence through nine months after RPNI surgery.

3.2.2. Objectives: Evaluate patient reported outcomes of intercostal RPNI surgery and clinical indicators such as routine ultrasound review and physical exam.

3.3. Study Outcome Measures

Upon successful execution of **Aim 1**, we will demonstrate that:

1) RPNI surgery improves patient-reported physical and psychosocial well-being (patient reported depression and anxiety) within three months after surgery.

2) Patients who undergo RPNI surgery will report reduced daily opioid consumption within 3 months after surgery.

Upon successful execution of **Aim 2**, we will demonstrate that:

1) RPNI surgery provides long-term protection from neuroma recurrence based on physical exam and ultrasound.

4. Study Design

4.1. Methodology: Patients seeking surgical consultation for RPNI surgery in the Multidisciplinary Peripheral Nerve Clinic for chronic post-mastectomy pain will be recruited for this study and followed longitudinally at four time points to evaluate pain, medication usage, anxiety and depression reporting compared to preoperative levels.

Upon enrollment, patients will complete baseline questionnaires including a self-reported medication log (Time 1) and continue their standard non-surgical management plan while awaiting surgery. As an elective surgery, patients' scheduled surgery dates usually occur approximately 3 months after initial consultation. Note: although investigators expect some variability on surgery scheduling, the average time of study involvement for each patient will be 12 months. This represents approximately three months before surgery and nine months after surgery.

Approximately two weeks prior to surgery (during the patient's scheduled preoperative visit), participants will complete the panel of surveys, including medication log (Time 2) and again following RPNI implantation at three (Time 3) and nine months (Time 4) post procedure. The validated PRO instruments will be used to evaluate patients' reported pain experiences, depression, and anxiety (see below). The medication logs will document the details of each patient's medication use over time (see Appendix B Patient Medication log). Study duration will allow patients enrolled during the first 12 months to be followed for the entire study duration.

Presence of neuropathic pain will be confirmed based on detailed history, physical exam findings (e.g. Tinel sign or pins/needles, burning, or shock-like sensations) and local anesthetic nerve blocks which are all part of routine assessment and evaluation at the clinic.

4.2. Data Collection

With the exception of **4.2.1. Patient Reported Outcome (PRO) instruments**, all other collected data will be derived from standard clinical care for patients seeking surgical management of post-mastectomy chronic pain.

4.2.1. Patient Reported Outcome (PRO) instruments: As a specific type of pain, neurological pain or neuroma pain is typically reported as burning, stinging or tingling sensations. To distinguish between specific forms of pain in patients reporting chronic post-mastectomy pain, a broad scope of pain dimensions will be measured using the following validated instruments:
1.Short-form McGill Pain Questionnaire (SF-MPQ-2) to characterize patients' pain experience (33-35). SF-MPQ-2 has been validated for use in clinical trials studying neuropathic pain (31-33).
2. Patient-Reported Outcomes Measurement Information System or PROMIS instruments (36) will measure Pain Intensity(37), Pain Interference(38), and Neuropathic Pain Quality (39)
3. The Pain Catastrophizing Scale (PCS) – will measure pain catastrophizing, or an exaggerated reaction to pain or anticipated pain thought to play a role in chronic pain reporting. (https://www.practicalpainmanagement.com/pain/other/co-morbidities/pain-catastrophizing-what-clinicians-need-know).
4. The Patient Health Questionnaire (PHQ) (40) – measures the patient's reported depression level.
5. The Generalized Anxiety Disorder measure (GAD-7) evaluates anxiety (41).
6. The West Have-Yale Multidimensional Pain Inventory (WHYMPI)- provides a brief psychometrically-sound, and comprehensive assessment of the components of chronic pain. (Kerns, R.D., Turk, D.C., & Rudy, T.E. (1985). The West Haven-Yale Multidimensional Pain Inventory (WHYMPI). Pain, 23, 345-356.)
7. Self-Reported socio-demographic questions such as highest educational level attained, and marital status will be included in both the baseline and 9-month postoperative time points.

Please see Appendix A for instruments.

4.2.2. Pain Medication Use: Because prescribed dosage of medications may differ from actual usage, details of each patient's pre- and post-operative pain medication use will be documented at each study time point using a self-reported medication log. The log will be integrated with the study questionnaires. Study

staff will use the patient reported log to complete a detailed clinical version (see Appendix C) for comparison and analysis purposes. For example, after reviewing patient reporting of medication usage, study staff will quantify opioid use based on narcotic type, daily frequency, and amount.

4.2.3. Surgery Cancellation: If patients cancel surgery it will be documented as an outcome of interest.

4.2.4. Physical Exam: Physical exam will be performed at the time of patient enrollment and subsequent follow-up visits. Exam will be performed as part of routine clinical evaluation, and includes evaluation of burning, shooting, or tingling pain in intercostal nerve distribution, and/or Tinel sign (hyperesthesia with tapping on RPNI or nerve end).

4.2.5. Ultrasound: Ultrasound, also part of routine clinical evaluation, will be performed at time of patient enrollment, and follow-up. Findings suggestive of neuroma will include presence of hypoechoic mass in continuity with nerve (43).

4.2.6. RPNI Implantation: RPNI operations will occur at Michigan Medicine. RPNI operations are routinely covered by patients' insurance. Under general anesthesia, the symptomatic intercostal neuroma will be identified and excised. One free muscle or skin graft for each RPNI will be harvested from surrounding musculature. The nerve will be implanted into the central portion of the free muscle or skin graft and edges of the graft will be wrapped around the nerve and closed with 6-0 monofilament sutures. In most cases, the muscle or skin graft will measure approximately 3-4 cm in length and 0.5-0.7 cm in thickness.

4.2.7. Clinical Details: Chart review will be performed by a trained research coordinator to collect data such as date of mastectomy and breast reconstruction (if relevant), comorbidities, surgical complications, number of nerves resected and additional RPNI surgeries.

5. Study Enrollment and Withdrawal

Potential subjects will be recruited either in-person in the Multidisciplinary Peripheral Nerve Clinic or the Plastic Surgery Clinic at Domino's Farms by study staff during a consultation for chronic post-breast surgery pain, or remotely with initial telephone contact followed by a mailed consent document. Although all patients seeking a consultation with plastic surgeons at the clinics are seeking surgical treatment for persistent pain, patients who decide not to undergo RPNI surgery after enrolling may still be included.

5.1. Eligibility Criteria:

5.1.1. Subject Inclusion Criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

Provide signed and dated informed consent form

Female, at least 18 years of age

Reporting post-mastectomy pain at least six months removed from mastectomy or partial mastectomy (lumpectomy).

Willing to comply with all study procedures and be available for the duration of the study

Fluent in English

Women of reproductive potential must use highly effective contraception (specify methods of contraception acceptable for the study, e.g., licensed hormonal methods) and/or willingness to

undergo a pregnancy test.

5.1.2. Subject Exclusion Criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

Previous surgical management for chronic post-mastectomy pain

Signs/symptoms which are not suggestive of neuropathic pain based on physical exam at time of consultation. See 4.2.4 above.

Pregnancy or lactation

Men will not be enrolled in this study due to the low prevalence of male mastectomy.

Anything that, in the opinion of the investigator, would place the subject at increased risk or preclude the subject's full compliance with or completion of the study.

5.3. Strategies for Recruitment and Retention

Study investigators feel that thorough training and orientation about the study will help to ensure that patient enrollment runs efficiently. All clinic staff will be briefed and updated as necessary on the study's purpose and timeline. The site coordinator will screen clinic schedules for eligible patients weekly and be prepared to meet with eligible candidates immediately following the surgical consultation, thereby reducing the time spent on study activities for patients. The study team will also use telephone and mailing strategies to increase enrollment success.

To maximize retention in the study, the site coordinator will perform all appointment scheduling for patients and integrate data collection events with the clinic schedule to avoid additional clinic trips. Additionally, to maximize efficiency and make best use of patient time, questionnaires will be offered in both electronic form (via a computer) and in hard copy.

5.4. Reasons for Withdrawal

A study subject will be discontinued from participation in the study if:

Any clinical adverse event (AE), laboratory abnormality, intercurrent illness, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.

Subjects are free to withdraw from participation in the study at any time upon request.

6. Study Schedule

6.1. Study Timeline: The proposed pilot study will run for two years and include three phases: 1) Study initiation; 2) Enrollment and initial data collection; 3) Patient follow-up and final data collection. Investigators plan on beginning in advance of grant funding, so total study time is estimated to be three years. Details of the three phases are provided below.

Phase 1- Study Initiation Month 0-1	Phase 2 – Enrollment and Initial Data Collection Months 1-12	Phase 3 – Patient Follow-up and Final Data Collection Months 13-24

Phase 1: Month 1 involves study training and set-up. Note: Personnel and IRB approval will be in place

prior to Month 1 so Phase 2 (enrollment) will begin as soon as possible.

Phase 2: Months 1-12 of the study will be dedicated to the enrollment and initial follow-up of the RPNI study subjects. All enrollment of subjects will be completed by Month 12 to allow for a complete follow-up period for all patients including an approximate 3 month preoperative and 9 month postoperative period. Additionally, periodic process evaluation and data auditing will occur to assure adherence to study protocol, timeline and sample size goals. Initial data analysis will take place at this time, including descriptive statistics for the study population.

Phase 3: Months 13-24 of the study will involve the conclusion of follow-up data collection for study patients and RPNI surgery for patients enrolled during months 9-12. Data will be reviewed for completeness and cleaned for analysis by the study's biostatistician. Dissemination of study findings will begin during this phase.

Final analyses, report generation, and manuscript submission will take place in the 3-6 months following completion of the funded study during a no-cost extension period.

6.2. Schedule of Events for Enrolled Patients

	Time 1	Time 2	Time 3	Time 4
	Baseline Visit	Preop Visit	3 Months Post Visit	9 Months Post Visit
PRO's	X	X	X	X
Pain Measures	X	X	X	X
CDL	X	X	X	X
Med Log	X	X	X	X
Physical Exam	X	X	X	X
Ultrasound*	X			X

* results recorded from routine diagnostic care

Time 1 – Baseline

Enrollment: Immediately following the initial consultation, the site coordinator will be available to meet with patients to describe the study. If in-person enrollment is not possible, the site coordinator will contact the patient via telephone and if interested mail a study packet with consent documents to the patient-provided mailing address. The coordinator will provide a full description of the study, answer questions, and obtain written informed consent in accordance with the IRB-approved protocol. Each patient will follow their standard non-surgical treatment plan of NSAIDs, neuropathic analgesics, opioids, and physical therapy until the surgery, estimated to be about three months.

Patient Reported Outcomes (PRO's): Patients will be asked to complete the study's initial panel of questionnaires including a demographic survey, questions about pain experience, anxiety and depression.

Medication Log: Each patient will complete a medication log (integrated with the PRO surveys) to record all medications currently being used. See Appendix B for log.

Clinical Data Log: The site coordinator will also collect key clinical data such as date of mastectomy, previous pain management therapy, ultrasound results and comorbidities. These data will be captured through the University's electronic medical records system and entered into the study's database.

Time 2 - Preoperative

Patient Reported Outcomes (PRO's): Preoperatively, patients will be asked to complete the study's panel of questionnaires describing self-reported pain experience, anxiety and depression and socio-demographic characteristics.

Medication Log: Each patient will complete a medication log (integrated with the PRO surveys) to record all medications currently being used. See Appendix B for log.

Clinical Data Log: The site coordinator will also collect additional clinical data such as changes in health history, ultrasound results and details of the pre-operative pain management. These data will be captured through the University's electronic medical records system and entered into the study's database.

Time 3 – Three Months Post-Surgery

Patients will be scheduled for a 3-month post-surgical visit at the peripheral nerve clinic. During this visit, the following data will be collected.

Patient Reported Outcomes (PRO's): Patients will be asked to complete the study's panel of questionnaires describing self-reported pain experience, anxiety and depression.

Medication Log: Each patient will complete a medication log (integrated with the PRO surveys) to record all medications currently being used. See Appendix B for log.

Clinical Data Log: The site coordinator will also collect additional clinical data such as changes in health history, ultrasound results, surgical detail, and surgical complications. These data will be captured through the University's electronic medical records system and entered into the study's database.

Time 4 – Nine Months Post-Surgery

Patients will be scheduled for a 9-month post-surgical visit at the peripheral nerve clinic. During this visit, the following data will be collected.

Patient Reported Outcomes (PRO's): Patients will be asked to complete the study's panel of questionnaires describing self-reported pain experience, anxiety and depression and socio-demographic characteristics.

Medication Log: Each patient will complete a medication log to record all medications currently being used. See Appendix B for log.

Clinical Data Log: The site coordinator will also collect additional clinical data such as changes in health history, ultrasound results, complications and details of the post-operative pain management regimen. These data will be captured through the University's electronic medical records system and entered into the study's database.

7. Assessment of Safety

7.1. Adverse Events

There is minimal perceived risk associated with this study. The PI and study team will appropriately manage any adverse outcomes, psychological or otherwise, and report them to the IRB per institutional guidelines.

7.2. Unanticipated Problems

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

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

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

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

An incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in order to protect the safety, welfare, or rights of subjects or others. Examples of corrective actions or substantive changes that might need to be considered in response to an unanticipated problem include:

changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to subjects

modification of inclusion or exclusion criteria to mitigate the newly identified risks

implementation of additional procedures for monitoring subjects

suspension of enrollment of new subjects

suspension of research procedures in currently enrolled subjects

modification of informed consent documents to include a description of newly recognized risks

provision of additional information about newly recognized risks to previously enrolled subjects.

Unanticipated problems will be recorded and reported throughout the study.

7.3 Safety Oversight

The RPNI study will have a Data Safety and Monitoring Plan to oversee data security and adherence to study protocols. The study principal investigator, Dr. Brown will be ultimately responsible for ensuring proper data procedures and security. In addition, a Data Safety and Monitoring Committee, headed by Dr. Paul. Cederna, Section Chief of Plastic Surgery at the University of Michigan will also oversee the safety of the data processes and convene if necessary.

8. Statistical Considerations

Twenty-five patients will be enrolled into the study (~50% of patients seen in the Multidisciplinary Peripheral Nerve Clinic with post-mastectomy pain in a single year), and of them we expect 23 patients to choose to undergo RPNI surgery (over 90% of the expected enrollment number). Assuming about 10% non-response

or dropout rate, the expected sample size of 20 patients receiving RPNI is expected to give 80% power to detect a mean improvement in post-operative outcome between T1 and T4 (including the primary outcome of pain) of 1.11 standard deviation (SD) or larger using a 0.05 level two-sided test. From our preliminary data based on limb amputations, we expect the pain reduction to be at least 6 points for neuroma pain with an SD of the change of about 1.8 points, which corresponds to a minimum change of 3.3 SD (= 6/1.8). Hence the proposed sample size is expected to give more than adequate power to detect a clinically meaningful level of improvement. For the outcome of opioid use, the proposed sample size is expected to have 83% power using McNemar's test to detect a reduction in opioid use from 78% prior to RPNI to 22% after RPNI at 9 months.

Data will be collected longitudinally to assess trends in patient reported outcome (PRO) measures over time (Aim 1). We will assess the distribution of all PRO measures for skewness or outlying values and report summary descriptive statistics at baseline and postop time points for each measure. The extent of non-response at each timepoint will be assessed and reported as a variable of interest. Data will be visualized graphically to see if the reduction in pain occurs gradually or if all pain reduction is complete by a specific time but maintained afterwards. We will model the longitudinally collected follow-up outcomes data using mixed-effects regression models with baseline values of the selected outcome measure and follow-up time as predictors. Using the regression model, we will look for potential predictors of variation in follow-up outcomes. Covariates such as age, race and ethnicity will be examined.

To assess if RPNI surgery results in durable protection from neuroma recurrence (Aim 2), we will monitor physical exam findings at each of the RPNI sites including Tinel sign or evidence of altered sensation in the corresponding dermatome. The initial evaluation at the time of enrollment will provide a baseline of the number of altered sensation categories the patient experiences (shooting pain, burning pain, or tingling). Ultrasound will provide baseline information regarding presence/absence of neuroma, and size of the neuroma. We expect the changes to be in the direction of improvement, but two-sided tests will be used to evaluate 1) presence or absence of any altered sensation physical exam finding, 2) number of altered sensation physical exam findings, 3) presence or absence of ultrasound evidence of neuroma, 4) size of neuroma (if present). As the data will be collected longitudinally at multiple follow-up visits (3 and 9 months postop), we will assess trends in these outcome measures over time.

9. Source Documents and Access to Source Data/Documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Describe who will have access to records.

Source data will originate from medical records of clinical findings (MiChart), observations, and patient completed surveys.

10. Quality Control and Quality Assurance

A User's Manual containing the study's standard operating procedures (SOPs) for quality management will be developed and will include:

How data will be evaluated for compliance with the protocol and for accuracy in relation to source documents.

The documents to be reviewed (e.g., CRFs, clinic notes, product accountability), who is responsible, and the frequency for reviews. Methods of training for staff, and methods of tracking such training.

11. Ethics/Protection of Human Subjects

11.1. Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997) and the Declaration of Helsinki and Good Clinical Practice (GCP).

11.2. Institutional Review Board

Study investigators will obtain approval to conduct research from the University of Michigan's Institutional Review Board (IRB). All protocol amendments will be IRB approved prior to implementing, except when the change is for patient safety.

11.3. Informed Consent Process

Discussion of risks and possible benefits of this study participation will be provided to the subjects. Consent forms will be IRB-approved and the subject will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any procedures being done specifically for the study. The subjects will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. The consent process will be documented in detail in the participants source documents by the individual(s) who conducted the consenting process.

11.4. Exclusion of Women, Minorities, and Children (Special Populations)

None.

11.5. Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. The study protocol, documentation, data, and all other information generated will be held in strict confidence.

Any data, specimens, forms, reports, and other records that leave the site will be de-identified of any protected health information (PHI) and replaced with study identifier to maintain subject confidentiality. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, OHRP and/or any other government officials, safety monitors/committees that may need the information to make sure that the study is done in a safe and proper manner, learn more about side effects, and/or analyze the results of the study; insurance companies or other organizations that may need the information in order to pay medical bills or cost of study participation.

12. Data Handling and Record Keeping

The investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

12.1. Data Management Responsibilities

The study will be managed Plastic Surgery's Research Specialist, Jennifer Hamill. She will be responsible for the data management SOP's development and adherence. She will also be responsible for database development using the REDCap data capture system described below.

12.2. Data Capture Methods

Data capture, verification, and disposition: Data Capture will be collected using REDCap (Research Electronic Data Capture). REDCap is a secure web application designed to support data capture for research studies. It provides user-friendly web-based case report forms, real-time data entry with branching logic and validation (e.g. for data types and range checks), audit trails, a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus), procedures for importing data from external sources, and advanced features such as a data quality check module. The system was developed by a multi-institutional consortium initiated at Vanderbilt University (http://project-redcap.org/). By using a web application, all members of the study team will be able to easily and effectively contribute to and manage their data. An aggregate, de-identified database will be created once data collection is complete for each study aim.

REDCap servers are physically located in the University of Michigan MSIS data center. Application and database servers are on virtual machines (VM). The VM servers are Red Hat Enterprise Linux Server 5.6 (64-bit, 2.6.18 238 e15-smp kernel) 2x AMD Opteron 6174 5.0.95 2.2 GHz with 4 GB RAM, running Apache 2.2.3 (application servers) and MySQL (database servers). Physical security for the databases is provided in a professionally managed and equipped tier-2 data center with tightly controlled access. Remote data access employs SSL encryption and 2-tier Kerberos/Level 1 and UMHS Level 2 password challenges via LDAP authentication. Access to the application, the database, and the underlying systems infrastructure are consistent with industry best practices including HIPAA security and privacy requirements and the HITECH Act. The application provides audit trails on user access to MICHR and MSIS technical and support teams. Backup of data is managed by MSIS and vulnerability testing is performed regularly by the University of Michigan Health System Medical Center Information Technology. Risk evaluation is performed using a methodology derived from NIST Special Publication 800-53 – "Recommended Security Controls for Federal Information Systems" and is used to refine and improve operating policies and procedures.

Daily backups and VM snapshots of the application and database servers are stored on a remote storage device. The restoration of the servers from a hardware or software failure is protected for 24 hours for disaster recovery. REDCap data collection projects rely on a thorough, study-specific data dictionary defined in an iterative, self-documenting process by all members of the research team. This iterative development and testing approach results in a well-planned and implemented data collection strategy for individual studies. REDCap is flexible enough to be used for a variety of research types including multi-site clinical research trials and provides an intuitive user interface for database design and data entry. External collaborators given access to REDCap by the project lead are given Level 1/Level 2 password access. Access to the REDCap study database is provided only through a virtual private network (VPN) to the University of Michigan providing an additional layer of encryption and security of data in addition to encryption via REDCap. Data downloaded from REDCap for statistical analysis will be stored on MSIS servers in password protected folders with access restricted to UM project personnel and controlled by the PI's. External drives are password protected and are backed up nightly. Individual access to file storage is controlled through Level 1 passwords and is accessible only to UM personnel. Electronic data files are deleted from servers at the end of the project; backed up copies of the data files are retained for a short period of time (several weeks) and can be recalled by project personnel if desired. After several weeks, the

data files disappear from the server.

12.3. Study Records Retention

Study data will be retained for 7 years after the end of the study per UM record keeping guidelines.

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

NIH Clinical Terms of Award

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

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APPENDIX A: PATIENT REPORTED OUTCOMES INSTRUMENTS

Surgical treatment of post-surgical mastectomy pain utilizing the regenerative peripheral nerve interface (RPNI)

Thank you for participating in this Chronic Post-Mastectomy Pain study. Please answer a few questions about yourself below.

1. What is your date of birth? _____ (mm/dd/yyyy)

2. Which of the following categories best describes your current marital status?
   - o Married
   - o Living with significant other
   - o Widowed
   - o Separated
   - o Divorced
   - o Single, never married

3. What is the last level of education you have completed?
   - o Some high school
   - o High school diploma
   - o Some college, trade or university
   - o College, trade or university degree
   - o Some Master/Doctoral work
   - o Master/Doctoral degree

4. What is your main activity or work situation?
   - o Employed full-time
   - o Employed part-time
   - o Volunteer work
   - o Homemaker
   - o Student
   - o Retired
   - o Unable to work/disabled
   - o Unemployed/seeking employment
   - o Other (Please specify) _____

5. Can you estimate your annual gross household income?
   - o Less than $25,000
   - o $25,000 - $49,999
   - o $50,000 - $74,999
   - o $75,000 - $99,000

- o $100,000 or more

7. How would you best describe your race?
   - o American Indian/Alaska Native
   - o Asian
   - o Native Hawaiian or Other Pacific Islander
   - o Black or African American
   - o White

8. How would you best describe your ethnic background (please choose one)?
   - o Hispanic or Latino
   - o Not Hispanic or Latino

PHQ-9

Over the **last 2 weeks**, how often have you been bothered by any of the following problems *(circle **one** number on each line).*

How often during the past 2 weeks were you bothered by...	**Not at all**	**Several days**	**More than half the days**	**Nearly everyday**
1. Little interest or pleasure in doing things.....	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much.....	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating.....	0	1	2	3
6. Feeling bad about yourself, or that you are a failure, or have let yourself or your family down.....	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television.....	0	1	2	3

8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual.....	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3

General Anxiety Scale-7 (same instructions and response format)

10. Feeling nervous, anxious or on edge ……..	0	1	2	3
11. Being unable to stop or control worrying …	0	1	2	3

How often during the past 2 weeks were you bothered by...	**Not at all**	**Several days**	**More than half the days**	**Nearly everyday**
12. Worrying too much about different things…	0	1	2	3
13. Having trouble relaxing……	0	1	2	3
14. Being so restless that it is hard to sit still….	0	1	2	3
15. Becoming easily annoyed or irritable……	0	1	2	3
16. Feeling afraid, as if something awful might happen……	0	1	2	3

If you feel you may be experiencing signs of anxiety or depression you are not alone. Here are some resources for help:

- Depression Toolkit: https://www.depressioncenter.org/depression-toolkit

- Michigan Medicine's PsychOncology Clinic (877) 907-0859 offering services for any patient receiving care through the Rogel Cancer Center (https://www.rogelcancercenter.org/support/managing-emotions/psychoncology).
- Suicide Hotline – 1-800-784-2433
- Psychiatric Emergency Services, University of Michigan (734) 936-5900 Serving Washtenaw County, Service available 24 hours a day, seven days a week.

Short-Form McGill Pain Questionnaire-2 (SF-MPQ-2)

This questionnaire provides you with a list of words that describe some of the different qualities of pain and related symptoms. Please put an **X** through the numbers that best describe the intensity of each of the pain and related symptoms you felt during the past week. Use 0 if the word does not describe your pain or related symptoms.

1. Throbbing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
2. Shooting pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
3. Stabbing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
4. Sharp pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
5. Cramping pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
6. Gnawing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
7. Hot-burning pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
8. Aching pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
9. Heavy pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
10. Tender	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
11. Splitting pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
12. Tiring-exhausting	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
13. Sickening	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
14. Fearful	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
15. Punishing-cruel	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
16. Electric-shock pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
17. Cold-freezing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
18. Piercing	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
19. Pain caused by light touch	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
20. Itching	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
21. Tingling or 'pins and needles'	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
22. Numbness	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*

Pain Interference – Short Form 6a

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
PAININ9 1	How much did pain interfere with your day to day activities?	-- 1	-- 2	-- 3	-- 4	-- 5
PAININ22 2	How much did pain interfere with work around the	-- 1	-- 2	-- 3	-- 4	-- 5
PAININ31 3	How much did pain interfere with your ability to participate in social	-- 1	-- 2	-- 3	-- 4	-- 5
PAININ34 4	How much did pain interfere with your household	-- 1	-- 2	-- 3	-- 4	-- 5
PAININ12 5	How much did pain interfere with the things you usually do for fun?	-- 1	-- 2	-- 3	-- 4	-- 5
PAININ36 6	How much did pain interfere with your enjoyment of social	-- 1	-- 2	-- 3	-- 4	-- 5

Pain Intensity – Scale

Please respond to each item by marking one box per row.

	In the past 7 days…	Had no	Mild	Moderate	Severe	Very severe
PAINQU6	How intense was your pain at its worst?....	-- 1	-- 2	-- 3	-- 4	-- 5
PAINQU8	How intense was your average pain?.....	-- 1	-- 2	-- 3	-- 4	-- 5

		No pain	Mild	Moderate	Severe	Very severe
PAINQU21	What is your level of pain right now?.....	-- 1	-- 2	-- 3	-- 4	-- 5

Neuropathic Pain Quality 5a

Please respond to each question or statement by marking one box per row.

In the past 7 days…

		Not at all	A little bit	Some what	Quite a bit	Very much
PAQUAL27r	Did your pain feel like pins and needles?	-- 1	-- 2	-- 3	-- 4	-- 5
PAQUAL14r	Did your pain feel tingly?	-- 1	-- 2	-- 3	-- 4	-- 5
PAQUAL21r	Did your pain feel stinging?.....	-- 1	-- 2	-- 3	-- 4	-- 5
PAQUAL31r	Did your pain feel electrical?	-- 1	-- 2	-- 3	-- 4	-- 5
PAQUAL11r	Did your pain feel numb?.....	-- 1	-- 2	-- 3	-- 4	-- 5

PAIN CATASTROPHIZING SCALE (PCS)

We are interested in looking at the relationship between thoughts and pain. Please indicate the degree to which you have experienced each of the following thoughts or feelings when experiencing pain by circling a number under each statement.

When I feel pain...

1. I worry all the time about whether the pain will end.

   0 1 2 3 4

   Not at all All the time

2. I feel I can't go on.

   0 1 2 3 4

   Not at all All the time

3. It's terrible and I think it’s never going to get any better.

   0 1 2 3 4

Not at all All the time

4. It's awful and I feel that it overwhelms me.

0 1 2 3 4

Not at all All the time

5. I feel I can't stand it anymore.

0 1 2 3 4

Not at all All the time

6. I become afraid that the pain may get worse.

0 1 2 3 4

Not at all All the time

7. I think of other painful experiences.

0 1 2 3 4

Not at all All the time

8. I anxiously want the pain to go away.

0 1 2 3 4

Not at all All the time

9. I can’t seem to keep it out of my mind.

0 1 2 3 4

Not at all All the time

10. I keep thinking about how much it hurts.

0 1 2 3 4

Not at all All the time

11. I keep thinking about how badly I want the pain to stop.

0 1 2 3 4

Not at all All the time

12. There is nothing I can do to reduce the intensity of the pain.

0 1 2 3 4

Not at all All the time

13. I wonder whether something serious may happen.

0 1 2 3 4

Not at all All the time

WEST HAVEN-YALE MULTIDIMENSIONAL PAIN INVENTORY

BEFORE YOU BEGIN, PLEASE ANSWER 2 PRE-EVALUATION QUESTIONS BELOW:

1. Some of the questions in this questionnaire refer to your "significant other". A significant other is *a person with whom you feel closest.* This includes anyone that you relate to on a regular or infrequent basis. It is very important that you identify someone as your "significant other". Please indicate below who your significant other is (check one):

⍑ Spouse ⍑ Partner/Companion ⍑ Housemate/Roomate
⍑ Friend ⍑ Neighbor ⍑ Parent/Child/Other relative
⍑ Other (please describe):

---

2. Do you currently live with this person? ⍑ YES ⍑ NO

When you answer questions in the following pages about "your significant other", always respond in reference to the specific person you just indicated above.

A.

In the following 20 questions, you will be asked to describe your pain and how it affects your life. Under each question is a scale to record your answer. Read each question carefully and then circle a number on the scale under that question to indicate how that specific question applies to you.

1.Rate the level of your pain at the present moment.

0	1	2	3	4	5	6
No pain						Very intense pain

2.In general, how much does your pain problem interfere with your day to day activities?

0	1	2	3	4	5	6
No intereference						Extreme interference

3.Since the time you developed a pain problem, how much has your pain changed your ability to work?

0	1	2	3	4	5	6
No change						Extreme change

___ Check here, if you have retired for reasons other than your pain problem

4. How much has your pain changed the amount of satisfaction or enjoyment you get from participating in social and recreational activities?

0	1	2	3	4	5	6
No change						Extreme change

5. How supportive or helpful is your spouse (significant other) to you in relation to your pain?

0 1 2 3 4 5 6
Not at all supportive Extremely supportive

6. Rate your overall mood during the past week.

0 1 2 3 4 5 6
Extremely low mood Extremely high mood

7. On the average, how severe has your pain been during the last week?

0 1 2 3 4 5 6
Not at all severe Extremely severe

8. How much has your pain changed your ability to participate in recreational and other social activities?

0 1 2 3 4 5 6
No change Extreme change

9. How much has your pain changed the amount of satisfaction you get from family-related activities?

0 1 2 3 4 5 6
No change Extreme change

10. How worried is your spouse (significant other) about you in relation to your pain problem?

0 1 2 3 4 5 6
Not at all worried Extremely worried

11. During the past week, how much control do you feel that you have had over your life?

0 1 2 3 4 5 6
Not at all in control Extremely in control

12. How much suffering do you experience because of your pain?

0 1 2 3 4 5 6
No suffering Extreme suffering

13. How much has your pain changed your marriage and other family relationships?

0 1 2 3 4 5 6
No change Extreme change

14. How much has your pain changed the amount of satisfaction or enjoyment you get from work?

0 1 2 3 4 5 6
No change Extreme change

__ Check here, if you are not presently working.

15. How attentive is your spouse (significant other) to your pain problem?

0 1 2 3 4 5 6
Not at all attentive Extremely attentive

16. During the past week, how much do you feel that you've been able to deal with your problems?

0 1 2 3 4 5 6
Not at all Extremely well

17. How much has your pain changed your ability to do household chores?

0 1 2 3 4 5 6
No change Extreme change

18. During the past week, how irritable have you been?

0 1 2 3 4 5 6
Not at all irritable Extremely irritable

19. How much has your pain changed your friendships with people other than your family?

0 1 2 3 4 5 6
No change Extreme change

20. During the past week, how tense or anxious have you been?

0 1 2 3 4 5 6
Not at all tense or anxious Extremely tense or anxious

B.

In this section, we are interested in knowing how your significant other (this refers to the person you indicated above) responds to you when he or she knows that you are in pain. On the scale listed below each question, **circle a number** to indicate how often your significant other generally responds to you in that particular way when you are in pain.

1. Ignores me.

0 1 2 3 4 5 6
Never Very often

2. Asks me what he/she can do to help.

0 1 2 3 4 5 6
Never Very often

3. Reads to me.

0	1	2	3	4	5	6
Never						Very often

4. Expresses irritation at me.

0	1	2	3	4	5	6
Never						Very often

5. Takes over my jobs or duties.

0	1	2	3	4	5	6
Never						Very often

6. Talks to me about something else to take my mind off the pain.

0	1	2	3	4	5	6
Never						Very often

7. Expresses frustration at me.

0	1	2	3	4	5	6
Never						Very often

8. Tries to get me to rest.

0	1	2	3	4	5	6
Never						Very often

9. Tries to involve me in some activity

0	1	2	3	4	5	6
Never						Very often

10. Expresses anger at me.

0	1	2	3	4	5	6
Never						Very often

11. Gets me some pain medications.

0	1	2	3	4	5	6
Never						Very often

12. Encourages me to work on a hobby.

0	1	2	3	4	5	6
Never						Very often

13. Gets me something to eat or drink.

0	1	2	3	4	5	6
Never						Very often

14. Turns on the T.V. to take my mind off my pain

0	1	2	3	4	5	6
Never						Very often

C.

Listed below are 18 common daily activities. Please indicate <u>how often</u> you do each of these activities by <u>circling</u> a number on the scale listed below each activity. Please complete <u>all</u> 18 questions.

1. Wash dishes.

0	1	2	3	4	5	6
Never						Very often

2. Mow the lawn.

0	1	2	3	4	5	6
Never						Very often

3. Go out to eat.

0	1	2	3	4	5	6
Never						Very often

4. Play cards or other games.

0	1	2	3	4	5	6
Never						Very often

5. Go grocery shopping.

0	1	2	3	4	5	6
Never						Very often

6. Work in the garden.

0	1	2	3	4	5	6
Never						Very often

7. Go to a movie.

0	1	2	3	4	5	6
Never						Very often

8. Visit friends.

0	1	2	3	4	5	6
Never						Very often

9. Help with the house cleaning.

0	1	2	3	4	5	6
Never						Very often

10. Work on the car.

0	1	2	3	4	5	6
Never						Very often

11. Take a ride in a car.

0	1	2	3	4	5	6
Never						Very often

12. Visit relatives.

0	1	2	3	4	5	6
Never						Very often

13. Prepare a meal.

0	1	2	3	4	5	6
Never						Very often

14. Wash the car.

0	1	2	3	4	5	6
Never						Very often

15. Take a trip.

0	1	2	3	4	5	6
Never						Very often

16. Go to a park or beach.

0	1	2	3	4	5	6
Never						Very often

17. Do a load of laundry.

0	1	2	3	4	5	6
Never						Very often

18. Work on a needed house repair.

0	1	2	3	4	5	6
Never						Very often

APPENDIX B: PATIENT-REPORTED MEDICATION LOG

Medication Log

Thank you for participating in this study. Please provide a complete list of ***all*** medications you are taking or have taken in the past month. Please include any over-the-counter medications (e.g., Tylenol, Aleve) and alternative therapies (e.g., marijuana). Try your best to list the medications as you are actually taking them (which may differ from how the prescription is actually written).

Name:

Medication Name	**Date Started**	**Dose** (for example: *5mg* OR *0.125mcg*)	**Frequency** (for example*: 2 pills twice daily* OR *half a pill once a week*)

APPENDIX C: CLINICAL MEDICATION LOG BASED ON PATIENT PROVIDED MEDICATION USAGE- DRAFT

[redacted]

RPNI CDL

Study ID:	_____
Date & Time field:	_____
[redacted]	○ [redacted] ○ [redacted]

Medication Usage

Number of medications patient is taking:	_____
Number of opioid medications patient is taking:	_____
Daily oral morphine equivalent (mg):	_____
Number of non-opioid medications patient is taking:	_____
Acetaminophen use?	○ Yes ○ No
Daily acetaminophen dosage (mg) reported:	_____
Daily acetaminophen dose category:	○ Low ○ Medium ○ High
Number of anticonvulsant medications patient is taking (e.g., Carbamazepine, Gabapentin, Oxcarbazepine, Pregabalin):	_____
Daily anticonvulsant dosage (mg) reported:	_____
Anticonvulsant dose category:	○ Low ○ Medium ○ High
Tricyclics reported (e.g., Amitriptyline, Norpramin, Dosulepin, Doxepin, Nortriptyline, Trimipramine) :	○ Yes ○ No
Number of tricyclic medications patient is taking:	_____
SSRI's reported (i.e., Citalopram, Fluoxetine, Escitalopram, Paroxetine, Sertraline):	○ Yes ○ No
Number of SSRI medications patient is taking:	_____
Number of SNRI medications patient is taking (e.g., Duloxetine, Desvenlafaxine, Milnacipran, Venlafaxine):	_____

Daily SNRI dosage (mg) reported:	_____
SNRI dosage category:	○ Low ○ Medium ○ High
Number of anxiolytics patient is taking (e.g., Alprazolam, Bromazepam, Buspirone, Chlodiazepoxide, Clorzepate, Diazepam, Lorazepam, Oxazepam):	_____
Daily anxiolytic dosage (mg) reported:	_____
Anxiolytic dosage category:	○ Low ○ Medium ○ High
Buproprion reported?	○ Yes ○ No
Cannabinoid use reported?	○ Yes ○ No
Frequency of cannabinoid usage:	○ Daily ○ Weekly ○ Intermittent
Other reported medications?	○ Yes ○ No
If other medications, please list name and dosage here:	_____
[redacted]	
[redacted]	○ [redacted] ○ [redacted]
[redacted]	○ [redacted] ○ [redacted]
[redacted]	○ [redacted] ○ [redacted]
[redacted]	○ [redacted] ○ [redacted]
[redacted]	○ [redacted] ○ [redacted]
[redacted]	○ [redacted] ○ [redacted]
[redacted]	○ [redacted] ○ [redacted]
[redacted]	○ [redacted] ○ [redacted]
[redacted]	○ [redacted] ○ [redacted]
[redacted]	○ [redacted] ○ [redacted]
[redacted]	○ [redacted] ○ [redacted]
[redacted]	○ [redacted] ○ [redacted]