

Protocol No. AX-CL-PANC-PI003347**A Pilot Randomized Feasibility Trial Comparing an Investigational Hand Therapy Intervention to a Traditional Occupational Therapy Intervention to Prevent Chemotherapy-Induced Peripheral Neuropathy of the Hands in Patients Receiving Albumin Bound Paclitaxel plus Gemcitabine-Containing Combination Chemotherapy**

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Principal Investigator

Date

Printed Name

TABLE OF CONTENTS

INVESTIGATOR AGREEMENT.....	2
PROTOCOL SUMMARY.....	5
1. BACKGROUND AND SIGNIFICANCE.....	7
1.1. Anatomy and Physiology Related to CIPN.....	8
1.2. Prevention and Treatment.....	9
1.2.1. Prevention of CIPN.....	9
1.2.2. Treatment of CIPN.....	10
1.3. Hand Therapy.....	11
2. STUDY DESIGN.....	11
2.1. Objectives.....	11
2.1.1. Primary Objective.....	11
2.1.2. Secondary Objectives.....	12
3. PATIENT SELECTION.....	12
3.1. Inclusion Criteria.....	12
3.2. Exclusion Criteria.....	12
3.3. Informed Consent.....	12
3.4. Assignment of Patient Numbers.....	13
4. TREATMENT PLAN.....	13
4.1. Group 1 (Traditional Occupation Therapy).....	13
4.2. Group 2 (Investigational Hand Therapy).....	13
5. SCHEDULE OF PROCEDURES.....	13
5.1. Consent Visit/Screening Period.....	13
5.2. Demography and Medical History.....	13
5.3. Concomitant Medications.....	13
5.4. Physical Examination.....	14
5.5. CTCAE-4.0.....	14
5.6. Karnofsky Performance Status (KPS).....	14
5.7. Hand Therapy Assessments & Treatment.....	14
5.8. Table I Schedule of Events.....	15
6. DURATION.....	16
7. FOLLOW-UP.....	16
8. DATA ANALYSIS.....	16
8.1. General Considerations.....	16
8.2. Randomization.....	16
8.3. Blinding.....	17
8.4. Sample Size Determination.....	17
8.5. Analysis Sets.....	18
8.6. Statistical Analyses.....	18
8.6.1. Completion of the Study and Withdrawals.....	18
8.6.2. Demographics and Baseline Characteristics.....	18
8.6.3. Efficacy Analysis.....	18
8.6.4. Primary Endpoints.....	18
8.6.5. Secondary Endpoints.....	19
8.6.6. Safety Analysis.....	19

8.6.7. Adverse Events.....	19
8.6.8. Karnofsky Performance Status.....	19
8.6.9. Physical Exam and Medical History.....	19
9. ADMINISTRATION.....	19
9.1. Retention of Study Documentation.....	19
9.2. Ethics Considerations.....	20
9.3. Publication Policy.....	20
10. REFERENCES.....	21
11. APPENDICES.....	25
11.1. APPENDIX 1 INVESTIGATIONAL HAND THERAPY INTERVENTION.....	25
11.2. APPENDIX 2 TRADITIONAL OCCUPATIONAL THERAPY.....	25
11.3. APPENDIX 3 CTCAE-4.0.....	26
11.4. APPENDIX 4 THE KARNOFSKY PERFORMANCE SCALE.....	27
11.5. APPENDIX 5 QuickDASH.....	28
11.6. APPENDIX 6 Elevated Arm Stress.....	28
11.7. APPENDIX 7 Phalen's Test.....	28
11.8. APPENDIX 8 Elbow Flexion Test.....	28
11.9. APPENDIX 9 Tinel's Test at the Cubital Tunnel.....	28
11.10. APPENDIX 10 Tinel's Test at the Volar Wrist.....	29
11.11. APPENDIX 11 Semmes Weinstein Monofilaments for Pressure Threshold Screening...	29
11.12. APPENDIX 12 TEN Test.....	29
11.13. APPENDIX 13 Static Two-Point Discrimination Screening.....	29
11.14. APPENDIX 14 Visual Analog Pain Scale.....	29
11.15. APPENDIX 15 Subject Daily Diary.....	31

PROTOCOL SUMMARY**Protocol No. AX-CL-PANC-PI003347****A Pilot Randomized Feasibility Trial Comparing an Investigational Hand Therapy Intervention to a Traditional Occupational Therapy Intervention to Prevent Chemotherapy-Induced Peripheral Neuropathy of the Hands in Patients Receiving Albumin Bound Paclitaxel plus Gemcitabine-Containing Combination Chemotherapy**

Study Title:	A Pilot Randomized Feasibility Trial Comparing an Investigational Hand Therapy Intervention to a Traditional Occupational Therapy Intervention to Prevent Chemotherapy-Induced Peripheral Neuropathy of the Hands in Patients Receiving Albumin Bound plus Gemcitabine Containing Combination Chemotherapy
Sponsor:	Scottsdale Healthcare Hospitals DBA HonorHealth (HonorHealth)
Study Rationale:	Chemotherapy-induced peripheral neuropathy (CIPN) has a dose limiting effect which can greatly affect quality of life and often limits the amount of treatment patients can receive in treating their cancer. In the discipline of hand therapy, there is a science-based body of knowledge with effective protocols to treat neuropathies associated with injury and disease. These interventions have not been explored on patients with CIPN.
Primary Objective	To determine if hand therapy intervention targeting the nervous system can prevent or delay the time to onset of CIPN of the hands as measured by Criteria for Adverse Events, version 4 (CTCAE-4.0) and Patient Reported Outcomes as compared to traditional occupational therapy intervention.
Secondary Objectives:	- To determine whether provocative testing of the upper extremity identifies/predicts patients at risk for CIPN. - To identify whether scores on the TEN TEST and the QuickDASH correlate with the (CTCAE-4.0) grades of peripheral neuropathy of the hands in patients who develop CIPN.
Study Design:	- Pilot, feasibility, randomized exploratory study - Patients will be randomized to two groups: 1) Investigational hand therapy (IHT) intervention targeting the nervous system, or 2) Traditional occupational therapy intervention targeting compensatory strategies (TOT).
Setting:	Patients will be recruited from a single institution and will receive treatment onsite or at a single center outpatient hand therapy clinic.

Duration:	Patients will participate until the time of onset of CIPN of the hands or through 84 days of treatment if no symptoms of CIPN. At time of initial onset of any grade of CIPN of the hands, the patient will end participation in the study. The patient may continue on study if CIPN occurs only in the feet. Duration of overall study will be 12 months.
Planned Sample Size:	Up to 60 patients Total of 40 evaluable patients, 20 patients in each arm
Inclusion Criteria:	• Patients with adenocarcinoma of the pancreas who will receive chemotherapy with albumin bound paclitaxel plus gemcitabine containing combination • Patients who have no prior evidence of peripheral neuropathy of the hands • Age 18 years or older • Able to sit for minimum of 30 minutes for hand therapy sessions
Exclusion Criteria:	• Patients who have received at least one dose of chemotherapy with albumin bound paclitaxel plus gemcitabine during the past 6 months • Patients taking duloxetine or gabapentin • History of peripheral neuropathy of the hands due to chemotherapy, diabetes, or other causes • Inability to sit for minimum of 30 minutes • Documented cognitive problems limiting ability to participate in hand therapy
Study Assessments	• QuickDASH • Upper extremity provocative testing (See Appendices 6-10) • TEN Test • Screening for pressure threshold sensation and static two-point discrimination sensation • CTCAE-4, peripheral sensory neuropathy and peripheral motor neuropathy of the hands • KPS • VAS Pain Estimated time of above testing is 15-20 minutes.
Data Evaluation	Standardized report forms will be constructed for the study.
Statistical Analysis	The number and proportion of efficacy evaluable patients without CIPN (any grade) of the hands at the completion of Cycle 3 will be summarized for both hand therapy groups. The Fisher's Exact Test will be utilized to test for difference in proportions between the two treatment groups. A 90%

	confidence interval around the difference in proportions between the two treatment arms will also be calculated. Time to onset of CIPN of the hands will be summarized using Kaplan-Meier methods (median, number censored, 90% CI) for both treatment groups. The patient test scores for each upper extremity provocative testing procedure will utilize descriptive summary statistics to summarize (by hand therapy arm) each time these tests are administered. Descriptive statistics include N, mean, standard deviation, median, range (minimum and maximum) for continuous variables, and frequency counts and percent for categorical variables. Correlation coefficients will be used to quantify the level of correlation of QuickDASH and TEN TEST scores to grades of peripheral neuropathy (grading by CTCAE-4).
Study period	Planned start date: April 2016 First Patient Consented: August 1, 2016 Planned accrual closure: April 30, 2020

1 BACKGROUND AND SIGNIFICANCE

Many people who have been treated with chemotherapy complain of upper extremity neuropathy that interferes with their activities of daily living including work and negatively impacts their overall quality of life. Certain chemotherapy agents are known to cause this problem but are necessary for best medical management. It has been reported that 30 to 40% of patients receiving chemotherapy experience CIPN (Gutierrez-Gutierrez, Sereno, Miralles, Casado-Saenz, & Gutierrez-Rivas, 2010), and as more aggressive pharmacological agents are developed and survival rates increase in the future, this number is projected to grow.

CIPN is defined as somatic or autonomic signs or symptoms resulting from damage to the peripheral nervous system (PNS) or autonomic nervous system (ANS) caused by chemotherapeutic agents. CIPN can affect feet and/or hands and can be sensory or motor or both. CIPN tends to be worse in patients with pre-existing nerve entrapments or neuropathies. The most common assessment tool for CIPN used in clinical trials and by oncology providers is the Common Terminology Criteria for Adverse Events (CTCAE) (U.S. Department of Health and Human Services, 2010). However, this instrument does not separate occurrences in the hands versus the feet in the grading of CIPN, thus it is impossible to determine the actual time to onset of CIPN specifically occurring in the hands versus the feet.

In the oncology literature, there are no studies of hand therapy in prevention or treatment for patients with chemotherapy-induced upper extremity peripheral neuropathy. Many articles in oncology journals (Gutierrez-Gutierrez et al., 2010) (Wolf, Barton, Kottschade, Grothey, & Loprinzi, 2008) (Windebank & Grisold, 2008) (Kaley & DeAngelis, 2009) define treatment for CIPN as medication only. Some articles do mention physical therapy and occupational therapy in general but do not mention the potential value

of hand therapy in particular. To date there are no studies testing the potential benefit of hand therapy in treating CIPN.

1.1 Anatomy and Physiology Related to CIPN

Peripheral nerves are comprised of nerve fibers with varied myelination, morphology, functions, and chemical features. These differing fibers vary in their resistance to and response to the toxicity of chemotherapy drugs. Most nutritional, metabolic, and toxic neuropathies are axonopathies, meaning the pathology is axonal. The axon or the Schwann cell is typically the site of the lesion. The vulnerability of a nerve to chemotherapy is influenced by its length. Longer nerves are more vulnerable than shorter nerves. In general, sensory fibers tend to be at higher risk to anticancer drug toxic effects than motor fibers (Gutierrez-Gutierrez et al., 2010).

Any portion of the PNS or the central nervous system (CNS) or even muscle can be injured by anticancer drugs. Symmetrical distal polyneuropathy is the most common pattern of symptoms. Other patterns of peripheral nerve disease in CIPN are radiculopathy, plexopathy, polyradiculoneuropathy, mononeuropathy, and multiple mononeuropathy (aka mononeuritis multiplex). While the deficits of CIPN can be sensory or motor or autonomic, most polyneuropathies are purely sensory. Paresthesias initially occur distally in a glove and stocking distribution and are the worst on volar surfaces of the hands and plantar surfaces of the feet. Allodynia (experiencing pain with stimuli that is not typically painful), occurs especially in response to hot or cold. Motor impairment occurs less frequently and usually has a later onset. Purely autonomic symptoms are uncommon but some autonomic involvement combined with PNS involvement is common (Gutierrez-Gutierrez et al., 2010).

Fine motor skills are affected, impairing activities such as buttoning, donning earrings, doing clasps, handling or manipulating small objects. Sensory ataxia is more severe when the eyes are closed or the lighting is low. Proprioceptive sensory disturbances also occur, as demonstrated by a positive Romberg sign, which is a loss of balance that occurs when the patient stands with the eyes closed. Motor neuropathy presents with signs of weakness, cramps, atrophy, and fasciculation. Like sensory symptoms, the onset is typically distal.

Patients with metastatic adenocarcinoma of the pancreas receiving treatment with nab-paclitaxel, currently known as “albumin bound paclitaxel”, plus gemcitabine experience CIPN that can cause disruption or discontinuation of potentially life-saving treatment. Taxanes produce a symmetric, axonal, mixed, predominantly sensory, distal neuropathy (Sioka & Kyritsis, 2009). Taxane-induced neurotoxicity has been associated with micro-tubule damage and subsequent dysfunction of axonal transport (Toyooka & Fujimura, 2009). Symptoms of CIPN caused by taxanes include numbness or tingling of hands and/or feet, burning of hands or feet, loss of touch sensation, loss of positional sense, weakness and cramping in hands and/or feet, and difficulty with fine motor tasks such as buttoning clothes. Fingers and toes are most commonly involved, and the symptoms may move gradually upward into a stocking-glove distribution. Symptoms caused by taxanes usually increase gradually and can become worse with each additional dose of chemotherapy (Cella, Peterman, Hudgens, Webster, & Socinski, 2003). They are usually the worst immediately after a chemotherapy treatment and tend to lessen just before the next treatment. If the neuropathy diminishes, it usually does so gradually over several months, but in some cases it may be irreversible.

Time to onset of symptoms of CIPN is variable. In a phase 3 study of patients treated with nab-paclitaxel plus gemcitabine, n= 431, median time to onset of grade 1 CIPN was 70 days (Celgene, 2013), and of grade 3 was 140 days (Von Hoff, 2013). In general with taxanes, symptoms of CIPN may disappear when the chemotherapeutic agents are discontinued, but some symptoms may persist even after the medications have been stopped.

1.2 Prevention and Treatment

1.2.1 Prevention of CIPN

Campone, Berton-Rigaud et al performed a double-blind, randomized phase II study evaluating safety and efficacy of Acetyl-L-Carnitine (ALC) versus placebo in prevention of the epothilone B derivative, sagopilone-induced peripheral neuropathy in patients with ovarian cancer or castration-resistant prostate cancer. 150 patients enrolled, with 75 patients per treatment arm. They found no significant difference in overall peripheral neuropathy incidence between treatment arms, but there was a significantly lower incidence of peripheral neuropathy $\geq$ grade 3 in the ALC arm in ovarian cancer patients (Campone et al., 2013).

Hershman, Unger et al (2013) studied ALC for the prevention of taxane-induced neuropathy in women undergoing adjuvant breast cancer therapy. They performed a 24-week randomized double-blind placebo-controlled trial. 409 patients were evaluated. They concluded that there was no evidence that ALC affected CIPN at 12 weeks but ALC significantly increased CIPN by 24 weeks. They reported that their study was the first to show that a nutritional supplement increased the CIPN. They stated that “Patients should be discouraged from using supplements without proven efficacy” (Hershman et al., 2013).

Melatonin has been found to have neuroprotective effects in animal studies. Zahleh et al performed a pilot trial to assess whether melatonin given during taxane chemotherapy for breast cancer would decrease the incidence and/or severity of neuropathy. Twenty-two consecutive patients were treated. Neuropathy occurred in 45% of patients, with 23% experiencing grade 1 and 22% experiencing grade 2 neuropathy. No grade 3 neuropathy was reported in this non-randomized study. The authors concluded that ‘melatonin may be useful in the prevention or reduction of taxane-induced neuropathy and in maintaining quality of life’ but cautioned that “larger trials are warranted to further explore the role of melatonin in neuropathy treatment and prevention” (Nahleh, Pruemer, Lafollette, & Sweany, 2010).

Ghoreshi et al performed a randomized double blind placebo controlled trial investigating the efficacy of omega-3 fatty acids in reducing the incidence and severity of paclitaxel-induced peripheral neuropathy among patients with breast cancer. Twenty-one patients (70%) of the group taking omega-3 fatty acid supplements (n=30) did not develop peripheral neuropathy, as compared to 11 patients (40.7%) in the placebo group (n=27). The difference in incidence was significant (p=0.029). There was a non-significant trend for differences of peripheral neuropathy severity between the two study groups, but the frequencies of peripheral neuropathy in all scoring categories were higher in the placebo group (p=0.054) (Ghoreshi et al., 2012).

In a prospective phase II pilot randomized double blinded clinical trial of vitamin E for prevention of oxaliplatin-induced peripheral neuropathy, 18 patients were randomized to the vitamin E group and 16 patients were randomized to the placebo group. Results revealed cumulative incidence of 83% with grades 1 or 2 peripheral neuropathy in the vitamin E group versus 68% in the placebo group. Patients who received vitamin E demonstrated a trend towards more diarrhea ($P=0.06$). These authors concluded no significant decrease in the incidence of acute oxaliplatin-induced peripheral neuropathy was demonstrated through vitamin E use (Afonseca et al., 2013). Wolf et al. agreed that “no drugs to date have been proven to prevent CIPN” (Wolf et al., 2008). Pachman et al concurred, stating that “although many therapies have been investigated for the prevention and/or treatment of CIPN, there is no well-accepted proven therapy” (Pachman, Barton, Watson, & Loprinzi, 2011).

A review of 42 randomized control trials utilizing pharmacologic agents to prevent CIPN showed no evidence of benefit (Hershman, 2014). Thus, to date there are no known pharmacologic interventions proven to prevent CIPN and additional research is recommended.

1.2.2 Treatment of CIPN

Literature regarding treatment for patients with CIPN cites investigations of numerous interventions including acupuncture, herbs, and various medications. Gabapentin has been tried as a treatment for CIPN. Rao et al (2014) performed a phase 3 randomized, double-blind, placebo-controlled, crossover trial in which patients with painful CIPN were randomized to receive either 2700 mg gabapentin daily or placebo for 6 weeks with crossover after a washout period of 2 weeks. 115 patients were randomly assigned and the groups were well-matched. The trial failed to demonstrate any benefit to using gabapentin to treat symptoms of CIPN (Rao et al., 2014).

Current Oncology Nursing Society (ONS) guidelines include a review of the evidence for treatment of CIPN and conclude that “there are no interventions that can be recommended for nursing practice as of December 2006”. The guidelines state that effectiveness had not been established for carbamazepine, acetyl-L-Carnitine, alpha-Lipoic acid, amifostine, calcium and magnesium, glutamine, glutathione, nortriptyline, recombinant human leukemia inhibitory factor (rhuLIF), vitamin E, acupuncture, capsaicin, pulsed infrared light therapy, spinal cord stimulation or TENS (Visovsky, Collins, Abbott, Aschenbrenn, & Hart, et al. 2007).

Fallon reported that there is a lack of good-quality clinical trials regarding the use of gabapentin, pregabalin, duloxetine and tricyclics, capsaicin, and lidocaine in the treatment of cancer-related neuropathic pain (Fallon, 2013). However, Smith reported a favorable outcome in reduction of CIPN related pain in patients who were treated with duloxetine compared to placebo (Smith et al., 2013). Systematic review of trials using acupuncture concluded that further studies are needed (Franconi, Manni, Schroder, Marchetti, & Robinson, et al. 2013), (Rostock et al., 2013).

A systematic review of articles in English and Chinese on the roles of medical herbs in CIPN concluded that while “promising substances have been identified”, there was not enough evidence to establish a standard of practice regarding the use of medical herbs (Schroder, 2013).

Numerous studies have examined a variety of interventions to treat CIPN. However, with the exception of duloxetine, (Smith, 2013), no effective intervention strategies have been identified (Hershman, 2014).

1.3 Hand Therapy

Certified hand therapists are occupational therapists or physical therapists who meet criteria for designation as clinical specialists in treatment of the upper extremity. Although certified hand therapists are considered to be experts in neuromuscular rehabilitation, they have not historically been involved in treating patients with CIPN. Hand therapy treatment programs for patients with nerve injuries are based on concepts of neuroplasticity, which refers to the fact that our brains can be reorganized neuronally in response to stimuli. Neuroplasticity involves learning, habituation, memory, and cellular recovery (Calford, 2002), (Malaviya, 2003). Key concepts of neuroplasticity are:

- sensory perception is experienced by the CNS and is a dynamic process
- hand use affects sensory receptor morphology. In other words, use it or lose it. Disuse of a hand leads to deteriorative and regressive changes in sensory receptors while increased hand use is thought to stimulate new receptors (Rosen, Balkenius, & Lundborg, 2003)
- one single stimulus can excite multiple receptors because of the overlap of receptive fields of certain nerve fibers

No articles were found that referred to hand therapy as an intervention for prevention or treatment of CIPN. This protocol will be the first to study a hand therapy intervention in the prevention of CIPN among patients with pancreatic cancer being treated with a taxane, specifically albumin bound paclitaxel.

The hand therapy investigational intervention consists of manual therapy to open/decompress areas of possible compression of the peripheral nerves of the upper extremity; therapeutic exercises for range of motion and strengthening, nerve glides; and sensory re-education. Manual therapy includes joint mobilizations to stimulate pain-inhibiting mechanoreceptors and soft tissue mobilization including myofascial release of the upper extremity to restore elasticity and flexibility of soft tissues including skin, fascia, and musculotendinous structures. Therapeutic exercises promote muscle pumping, lymphatic stimulation, and improved nourishment and lubrication of collagen fibers for mechanical efficiency and strength. Nerve glides promote length and motion needed for improving axoplasmic flow of peripheral nerves which is associated with improved sensorimotor responses. Sensory re-education is performed to target and stimulate sensory receptors in order to restore/correct topographical mapping of the sensory cortex. These interventions are evidence-based treatments accepted as standard hand therapy care for patients with peripheral nerve problems not caused by chemotherapy (e.g., peripheral nerve laceration/repair or compression or overuse injuries). The investigational hand therapy intervention is described in Appendix 1. The traditional hand therapy intervention is described in Appendix 2.

2 STUDY DESIGN

A pilot randomized feasibility trial with a blinded evaluator

2.1 Objectives

2.1.1 Primary Objective

To determine if hand therapy intervention targeting the nervous system can prevent or delay the time to onset of any grade of CIPN of the hands as measured by CTCAE 4.0 and Patient Reported Outcomes as compared to traditional occupational therapy intervention.

2.1.2 Secondary Objectives

1. To determine whether provocative testing of the upper extremity identifies/predicts patients at risk for CIPN.
2. To identify whether scores on the TEN TEST and the QuickDASH correlate to the Common Terminology Criteria for Adverse Events, version 4 (CTCAE-4.0) grades of peripheral neuropathy of the hands in patients who develop CIPN.

3 PATIENT SELECTION

3.1 Inclusion Criteria

1. Patients with adenocarcinoma of the pancreas who will receive chemotherapy with albumin bound paclitaxel plus gemcitabine containing combination
2. Patients who have no evidence of past or current peripheral neuropathy of the hands.
3. Age 18 years or older
4. Able to sit for minimum of 30 minutes for hand therapy sessions

3.2 Exclusion Criteria

1. Patients who have received at least one dose of chemotherapy with albumin bound paclitaxel plus gemcitabine containing combination during the past 6 months
2. Patients taking duloxetine or gabapentin
3. History of peripheral neuropathy of the hands due to chemotherapy or other causes
4. Inability to sit for minimum of 30 minutes
5. Documented cognitive problems limiting ability to participate in hand therapy

3.3 Informed Consent

The principles of informed consent and Good Clinical Practices in FDA-Regulated Clinical Trials are described in the Code of Federal Regulations (21 CFR 50) *Protection of Human Subjects* <http://www.fda.gov/oc/gcp/regulations.html> and the Office of Human Research Protection: Protection of Human Subjects (45 CFR 46) <http://ohrp.osophs.dhhs.gov/>.

These regulations will be followed in conducting and monitoring clinical investigations.

3.4 Assignment of Patient Numbers

Randomization: All patients will be assigned to one of the 2 treatment arms by the study data specialist using a random scramble formula in EXCEL after the patient signs consent.

4 TREATMENT PLAN

Patients will be randomized to Group 1 for traditional occupational therapy (TOT) or Group 2 for investigational hand therapy (IHT). Time requirements for the home program in each group are equal.

4.1 Group 1 (Traditional Occupational Therapy)

Group 1 subjects will be instructed in joint protection, energy conservation, work simplification, and ergonomics, and they will be provided with a catalogue of occupational therapy assistive devices. This traditional occupational therapy program is based on core domain features identifying scope of practice of the profession (Commission on Practice, 2014). (See Appendix 1).

4.2 Group 2 (Investigational Hand Therapy)

Group 2 subjects will be instructed in bilateral upper extremity active range of motion (AROM), brachial plexus nerve gliding exercises, manual therapy of the forearm and hand, and sensory-re-education techniques. This evidence-based intervention is intended to maximize peripheral nerve axoplasmic flow resulting in enhanced nerve transmission (Rosen & Lundborg, 2011). (See Appendix 2)

5 SCHEDULE OF PROCEDURES

5.1 Consent Visit/Screening Period (within 14 days of the start of the study)

Procedures include a focused medical history, relevant physical examination, concomitant medication assessment, height and weight, Karnofsky Performance Status.

5.2 Demography and Medical History

Demographic data will include sex, age, race, and ethnicity. A focused medical history will include date of diagnosis of pancreatic cancer, histology, and current stage of disease. Current ongoing medical conditions will be collected at screening including any history of past or present peripheral neuropathy.

The history must include assessment for the presence of peripheral neuropathy including pain, altered sensation or numbness of the hands and feet. Symptoms of the hands and feet must be described separately.

5.3 Concomitant Medications

Documentation of medications will be taken from time of consent through end of study. Concomitant medications include any prescriptions, over the counter vitamins or natural/herbal preparations taken or administered during the study.

The only prohibited medication is duloxetine.

5.4 Physical Examination

A relevant physical examination must be performed by a medically qualified individual such as a licensed physician, a nurse practitioner, or physician assistant. The examination must include weight, brief neurological examination of the upper extremities including reflexes, strength, and neurological sensory testing (See Appendix 14).

5.5 CTCAE-4.0

CTCAE-4.0 assessment of peripheral sensory and motor must also be performed (See Appendix 3).

5.6 Karnofsky Performance Status (KPS)

(See Appendix 4)

5.7 Hand Therapy Assessments & Treatment

The consent visit will be followed by an occupational therapist visit #1. (See Table 1- schedule of events.)

- Visit #2: Between days 8 and 15,
- Visit #3: Between days 22 and 29,
- Visit #4: Between days 50 and 57,
- Visit #5: at end of study.

The following assessments will be performed: QuickDASH, brief battery of upper extremity provocative testing, pressure threshold screening, Ten test, static two-point discrimination screening, VAS Pain Scale. Therapy treatment will be implemented according to the randomized assignment.

5.8 Table 1. Schedule of Events (for both intervention groups)

Procedure	Consent Visit	Hand Therapy Visit 1 ^a	Chemo D1	Chemo D8	Hand Therapy Visit 2 ^b	Chemo D15	Hand Therapy Visit 3 ^c	Chemo D22,43,64	Hand Therapy Visit 4 ^d	End of Study Visit ^e
Informed Consent / HIPAA	X									
Inclusion/Exclusion criteria	X									
Demography	X									
Focused Medical History	X		X	X		X		X		X
Medication Review	X		X	X		X		X		X
Relevant Physical Examination	X ^g		X	X		X		X		X
Review of Pt Diary		X ^f	X ^f	X ^f		X ^f		X ^f		X ^f
KPS (performance Status)	X		X	X		X		X		X
QuickDASH		X			X		X		X	X
Elevated Arm Stress Test		X			X		X		X	X
Phalen's Test		X			X		X		X	X
Elbow Flexion Test		X			X		X		X	X
Tinel's Test at Cubital Tunnel		X			X		X		X	X
Tinel's Test at Volar Wrist		X			X		X		X	X
Semmes-Weinstein Monofilaments Screening		X			X		X		X	X
TEN Test of Finger Pads		X			X		X		X	X
Static Two-Point Discrimination Screening		X			X		X		X	X
VAS Pain		X			X		X		X	X

^a Within 14 days prior to start of chemotherapy

^b Between days 8-15

^c Between days 22-29

^d Between days 50-57

^e At time of onset of CIPN or if no CIPN Day 84 (up to + 7 days)

^f Patient diary will be collected and reviewed for completion by study staff weekly

^g To be completed at investigator's discretion; this is optional for this visit as it is not required to determine eligibility

6 DURATION

Patients will participate until the time of onset of CIPN of the hands or through completion of 84 day treatment schedule of chemotherapy if symptom-free. At the time of onset of CIPN of the hands, the patient will end study participation.

The patient may continue on study if CIPN occurs only in the feet.

For purposes of this study, CIPN will include neuropathy of the hands of greater than one hour duration.

Length of overall study will be 12 months.

7 FOLLOW-UP

Those patients who are in the traditional occupational therapy arm who develop CIPN of the hand will be offered the investigational hand therapy off study, if desired.

8 DATA ANALYSIS

8.1 General Considerations

Protocol AX-CL-PANC-PI003347 is a randomized feasibility study designed to evaluate the comparison of an investigational hand therapy intervention to a traditional occupational therapy intervention to prevent CIPN of the hands in patients receiving albumin bound paclitaxel plus gemcitabine combination chemotherapy. Other objectives include determining whether provocative testing of the upper extremity identifies/predicts patients at risk for CIPN and to identify whether scores on the TEN TEST and the QuickDASH correlate with the (CTCAE-4.0) grades of peripheral neuropathy of the hands in patients who develop CIPN.

Data will be summarized by treatment group with respect to enrollment and disposition summaries, demographics and baseline characteristics, concomitant medications, efficacy, and safety measures. Summary (i.e. descriptive) statistics will include N, mean, standard deviation, median, range (minimum, maximum) values for continuous variables and frequencies, and percentages for categorical variables. Time-to-event analyses will be summarized using Kaplan-Meier survival analysis and K-M plots for the estimated median time. 90% confidence intervals will be reported as appropriate. All study data documented on the CRFs will be included in the study data listings.

8.2 Randomization

All patients will be randomly assigned to one of the 2 treatment arms by the study data specialist using a random scramble formula in EXCEL after the patient signs consent. The data specialist will know the treatment assignment and will provide the hand therapist with the patient assignment in writing.

Patients may be replaced at the sponsor's or investigator's discretion if over the duration of the study they:

- Have missed $\geq 25\%$ of scheduled assessments
- Have completed $< 50\%$ of prescribed hand therapy intervention
- Have not completed 84 day schedule of chemotherapy treatment if no symptoms of CIPN.

8.3 Blinding

The health care providers and the patients will be blinded to the intervention assignment.

8.4 Sample Size Determination

This is the first study to evaluate the prevention of CIPN of the hands using investigational hand therapy intervention versus a traditional occupational therapy intervention in patients receiving - albumin bound paclitaxel plus Gemcitabine combination chemotherapy; therefore, there are no previous data on which to base formal sample size calculations. The data generated in this study will assist with ongoing clinical development of intervention hand therapy in chemotherapy patients.

Assuming 30% of Traditional OT Intervention patients will develop CIPN by the end of Cycle 3 (Day 84), the following power analysis table describes the various scenarios that could result from this study given $n=20$ evaluable patients (per arm). As noted in the table, if 30% of traditional OT intervention therapy patients develop CIPN compared to 5% for investigational therapy, the lower bound of 90% CI will be $>0\%$.

Approximate* Power and 90% CI bounds for Difference Between Treatment Groups in the Prevention or Delay of CIPN

Traditional OT Hand Therapy	Investigation OT Hand Therapy	N (per group)	Power	Difference Between Therapies	Lower bound of approximate 90% CI	Upper bound of approximate 90% CI
30%	5%	20	54%	25%	6.3%	43.7%
	10%	20	34%	20%	$<0.0\%$	40.1%
	15%	20	19%	15%	$<0.0\%$	36.4%
	20%	20	11%	10%	$<0.0\%$	32.4%

NOTE: other assumptions include 1:1 randomization, $\alpha=0.10$ (two-sided), 90% CI around the difference in proportions between treatment groups.

In order to obtain 20 evaluable patients per group (40 total) an enrollment of approximately 60 patients is necessary assuming approximately 20%-25% of patients will not complete through 3 cycles of treatment.

Simple random sampling methodology is employed for this investigation. Patients are randomly assigned to one of two treatment arms. To adjust for screen failures and consideration of the final number of evaluable patients ($N = 40$), the randomization scheme will be modified to allow for equal enrollment for each of the treatment arms.

8.5 Analysis Sets

The safety analysis set is defined as those patients enrolled, randomized, and received at least one session of hand therapy.

The efficacy evaluable analysis set will be comprised of all safety patients with the additional requirement of having completed at least through 3 cycles of therapy (84 days). However, if a patient drops-out prior to the completion of Cycle 3 (Day 84) but has CIPN of the hands, this patient will be considered evaluable for efficacy analysis.

8.6 Statistical Analyses

8.6.1 Completion of the Study and Withdrawals

The number and percentage of patients who complete the study will be summarized by treatment arm. The number and percentage of patients who withdraw from the study (and their reasons) will be tabulated by treatment arm at time of withdrawal.

8.6.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics (i.e., age at screening, gender, weight, height, body mass index (BMI), race, ethnicity, etc.) will be listed for individual patients and summarized by treatment arm using summary statistics for continuous variables and frequency distributions for categorical variables.

8.6.3 Efficacy Analysis

For data analysis of efficacy endpoints those patients that ended participation prior to completing assessment of 84 days of treatment and have CIPN of the hands will be classified as an evaluable patient. Those patients who ended participation prior to completing assessment at 84 days of treatment and do NOT have CIPN of the hands will not be evaluable for efficacy analysis and patient may be replaced.

8.6.4 Primary Endpoint

The number and proportion of patients without CIPN (any grade) of the hands at the completion of 84 days of chemotherapy treatment will be summarized for both hand therapy treatment groups. The Fisher's Exact Test will be utilized to test for difference in proportions between the two treatment groups. A 90% confidence interval around the difference in proportions between the two treatment

groups will also be calculated.

Time to onset of CIPN of the hands will be summarized using Kaplan-Meier methods (median, number censored, 90% CI) for both treatment groups.

8.6.5 Secondary Endpoints

Each upper extremity provocative testing procedure (see Table 1, Schedule of Events and Appendices 5-14) will utilize descriptive summary statistics to summarize these test results (by treatment group) each time these tests are administered. Descriptive statistics include N, mean, standard deviation, median, range (minimum and maximum) for continuous variables, and frequency counts and percent for categorical variables.

Correlation coefficients will be used to quantify the level of correlation of QuickDASH and TEN TEST scores to grades of peripheral neuropathy (grading by CTCAE-4).

8.6.6 Safety Analysis

All patients enrolled, randomized, and received at least one session of hand therapy will be included in safety analysis.

8.6.7 Adverse Events

There have been no known or documented adverse events of the hand therapy interventions used in this study. All interventions performed by the occupational therapist for manual therapy will be gentle, non-forceful, with no joint mobilization beyond grade 1. All exercises will be active and self-administered with instructions to avoid any unpleasant or painful experience.

If there is an adverse event (AE) reported due to the hand therapy intervention, these AEs will be presented in by-patients listings (by treatment group) for further medical review.

8.6.8 Karnofsky Performance Status (KPS)

A descriptive summary of KPS results for each visit that KPS is assessed will be displayed.

8.6.9 Physical Exam and Medical History

A by-patient listing of each individual patient's physical exam results and medical history will be included for further medical review if necessary.

9 ADMINISTRATION

This study will be conducted in compliance with the protocol, the principles of CFR, ICH GCP and the Declaration of Helsinki as amended in Edinburgh (2000).

9.1 Retention of Study Documentation

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. Documents include the protocol and

protocol amendments (if applicable), CRFs, CRF query forms, IRB and regulatory authority approval with correspondence, informed consent, screening and enrollment logs, staff resumé and authorization forms and other appropriate documents and correspondence. Patient clinical source documents will include patient clinical records, physician's and nurse's notes, appointment schedule, pathology and special assessment reports, and other relevant documents and correspondence.

The patient's involvement in the study should be clearly documented in the clinical records. Details should include the study protocol number, the hospital/ clinic unit code, the patient's identification number, the patient's consent to take part in the study (including the date of consent), the dates of all study visits, and the dates of dispensing treatment.

Copies of the CRFs must be retained by the Investigators, for as long as is legally required after completion of the study, to comply with CFR/ICH GCP guidelines. All data relating to the study, including study master file contents, CRFs and source data will be stored by the Investigator for at least 15 years.

The Sponsor, as the owner of the data, will retain the following documentation pertaining to the trial: the protocol and protocol amendments (if applicable), standard operating procedures (SOPs), all written opinions on the protocol and procedures, the original copies of the CRFs on each trial patient, any raw/source data supplied final report and audit certificate(s) (if available).

9.2 Ethics Considerations

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, Part 56) and the Office of Human Research Protection (45 CFR 46). The Investigators will inform the IRB of subsequent protocol amendments.

The co-principal investigators must ensure that the study will be carried out in accordance with the Declaration of Helsinki as amended in Edinburgh.

9.3 Publication Policy

All the results are the property of the Sponsor. The investigators may not submit for publication or presentation the results of this study without allowing the Sponsor 30 working days in which to review and comment upon the pre-publication manuscript. The Sponsor may request delay of the publication for a further 90 days to allow for intellectual property protection. The Sponsor also agrees that before it publishes any results of this study, it shall provide the Investigator with at least 30 working days for full review of the pre-investigation manuscript prior to the submission of the manuscript to the publisher. In accordance with generally recognized principles of scientific collaboration, co-authorship with any company personnel will be discussed and mutually agreed upon before submission of a manuscript to a publisher.

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11 APPENDICES

APPENDIX 1: INVESTIGATIONAL HAND THERAPY INTERVENTION (IHT)

Patient will be instructed by the occupational therapists on the following.

Bilateral Upper Extremity Active Range of Motion

- Shoulder circles – 5 reps, once daily
- Upper extremity punches – 5 reps, once daily
- Overhead fist pumps – 5 reps, once daily

Nerve Glides

- Brachial plexus – 3 reps, once daily
- Median nerve at wrist – 3 reps, once daily

Manual therapy

- Carpal tunnel stretch with palmar fascial release – 2 mins, once daily
- Massage of forearm muscles – 2 mins, once daily

Sensory Re-Education

- Find objects in bowl of dried beans with eyes closed – 2 minutes, daily
- Touch/rub/tap fingerpads on clothes, towel, upholstery, etc. – 1 minute, daily

Mark on your home program diary 100% if you have completed all the above exercises as instructed for that day. Mark $\geq 50\%$ on your home program diary if you complete at least 2 exercises for that day.

APPENDIX 2: TRADITIONAL OCCUPATIONAL THERAPY

Patient will be instructed by the occupational therapist on the following:

Joint Protection – incorporate 1 intervention from the list provided

Examples include:

- Handwriting with enlarged pen
- Using kitchen devices that decrease strain on your hands
- Avoid activities that put strain on painful or stiff joints
- Hold heavier objects with both hands and hold objects close to your body

Energy Conservation – delegate 1 task to someone else or choose to not do an activity that normally causes you to be fatigued or have sore joints

Examples include:

- Ask for help when carrying in grocery bags
- Have someone else lift heavy laundry baskets or pots/pans

- Collect all necessary cooking items so that you can sit on a stool for preparations

Work Simplification – simplify 1 task during the day

Examples include:

- Avoid unnecessary bending, reaching, or carrying
- Place the items you use most within easy reach, such as rearranging your kitchen to decrease extended reaching or bending
- Take breaks before becoming fatigued
- Practice task rotation or streamline the steps of a task by gathering all the materials needed for an activity before you begin the activity

Ergonomics – you are mindful of good posture during work and homemaking tasks

Examples include:

- Rearrange desk/computer station/other home areas per ergonomic guidelines. This would incorporate good standing and sitting posture, set-up of key-board to avoid strain to arms and wrists.

Mark your home program diary 100% if you have added at least one or more modifications from the list above for that day.

APPENDIX 3: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 National Institutes of Health and National Cancer Institute)

The CTCAE-4.0 is the most common assessment tool for CIPN used in clinical trials and by oncology providers.

Nervous system disorders

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
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Definition: A disorder characterized by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and warmth that are experienced in the absence of a stimulus.

Peripheral motor neuropathy	Asymptomatic, clinical or diagnostic observations only; intervention not indicated	Moderate symptoms, limiting instrumental ADL	Severe symptoms; limiting self care ADL; assistive device indicated	Life-threatening consequences, urgent intervention indicated	Death
Peripheral sensory neuropathy	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent	Death

		instrumental ADL		intervention indicated	
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Definition: A disorder characterized by inflammation or degeneration of the peripheral sensory nerves.

Reference: CTCAE 4.03 – June 14, 2010: Nervous system disorders

APPENDIX 4: The Karnofsky Performance Scale (Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: Reliability, validity, and guidelines. J Clin Oncology. 1984; 2:187-193).

The Karnofsky Performance Scale is an assessment tool intended to assist clinicians and caretakers in gauging a patient's functional status and ability to carry out activities of daily living. Documentation of Karnofsky scores over time may be very useful in following a patient's course of illness, and can help a disabled patient in his/her application for disability benefits. It also is used for some research applications.

**KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%)
CRITERIA**

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

APPENDIX 5: QuickDASH (Kennedy, Beaton, Solway, McConnell, & Bombardier, 2011) (Beaton, Wright, Katz, & Upper Extremity Collaborative Group, 2005)

The QuickDASH is a shorter version (11 items) of the DASH Outcome Measure, which is a 30-item, self-report questionnaire that is designed to measure symptoms and physical function in people with any of a variety of musculoskeletal disorders involving the upper limb. It is often used to monitor changes in function and symptoms over time. The shorter version is valid, reliable and responsive and is popular for use in clinical programs and in research. A variety of translations are available.

A copy of the QuickDASH form will be submitted separately from the protocol.

APPENDIX 6: Elevated Arm Stress Test (EAST) (Rayan, 1998), (Pratt, 1986), (Brantigan & Roos, 2004), (Oates & Daley, 1996).

Also called Roos' test, the EAST is performed by holding the arms in a position of 90 degrees of abduction and external rotation ("stick-up position"). The patient then opens and closes the hands slowly for a period of 3 minutes. Reproduction of symptoms in the entire extremity or rapid fatigue of the extremity constitutes a positive test result. Patients with thoracic outlet syndrome (TOS) typically cannot complete this test. Many authors describe this as the most reliable test for TOS. The test is of the most diagnostic benefit when symptoms occur rapidly after elevation of the arm. One study showed reproduction of symptoms in 94% of patients with neurogenic TOS. This maneuver can reproduce symptoms of other pathologies, including carpal tunnel syndrome, cubital tunnel syndrome, and rotator cuff syndrome.

APPENDIX 7: Phalen's Test (Phalen, 1966), (MacDermid & Doherty, 2004).

Phalen's test involves passive flexion of the wrist for 15 to 60 seconds. A positive test produces numbness and tingling in the distribution of the median nerve. Researchers have reported that this test is one of two clinical tests with the highest overall accuracy in testing for median nerve compression at the wrist.

APPENDIX 8: Elbow Flexion Test (Novac, Mackinnon, 2005)

The Elbow Flexion test is one of the most sensitive and specific tests for identifying ulnar nerve compression at the cubital tunnel. With the shoulder in neutral position, manual pressure is applied to the ulnar nerve in the cubital tunnel as the elbow is placed in terminal flexion with the forearm supported in supination. Maintain the wrist in neutral. Hold the position for 60 seconds.

APPENDIX 9: Tinel's Test at the Cubital Tunnel (Rekant, 2012)

With the patient's elbow fully flexed and the wrist held in neutral position, the examiner taps over the ulnar nerve with the cubital tunnel. Reproduction of paresthesias in the distribution of the ulnar nerve is a positive response.

APPENDIX 10: Tinel's Test at the Volar Wrist (Evans, 2012)

The examiner taps over the carpal tunnel. Reproduction of paresthesias in the distribution of the median nerve is a positive response.

APPENDIX 11: Semmes Weinstein Monofilaments for Pressure Threshold Screening (Bell & Tomancik, 1987), (Bell-Krotoski & Buford, 1988), (Bell-Krotoski, 2012)

When calibrated and applied correctly, this test is a valid test for determining sensibility detection thresholds. Studies have clearly demonstrated their ability to accurately detect intended clinical conditions. Used in standard consistent protocols, the monofilament test is able to compare patient data in individual and multicenter studies and is providing information regarding peripheral nerve changes with treatment not previously available with less sensitive and uncontrolled instruments. When calibrated correctly, it is one of the few, if not the only, sensibility measurement instrument that approaches requirements for an objective test.

The hand screen utilizes 5 monofilaments. Test sites specific to the median nerve are the tip of the thumb, index, and proximal index. Test sites specific to the ulnar nerve are the distal little finger, proximal phalanx, and ulnar base of the palm. The test site specific for the radial nerve is the dorsal aspect of the thumb web space. The examiner retests a nonresponsive test site at least three times to ensure a monofilament is not detected at that site.

APPENDIX 12: TEN Test (Strauch et al., 1997)

In the TEN test of finger pad light sensation, the patient develops a ratio between normal light moving touch and diminished moving touch. Subsequent determinations can detect serial changes. The ratios obtained can be compared with a standard scale of sensibility with a high degree of validity and reliability. The interexaminer and intraexaminer results obtained are reliable and repeatable. Simplicity and dependability recommend this test for use in a busy clinical setting.

APPENDIX 13: Static Two-Point Discrimination Screening (Dellon, 1978), (Moberg, 1962), (Mackinnon & Dellon, 1985), (Bell-Krotoski, 2005), (Bell-Krotoski, 1995)

Two-point discrimination is a classic test of sensibility used by hand surgeons over several decades. The test is believed by many to be a test of innervation density. Some think two-point discrimination a good predictor of patient function and manipulation. Two-point discrimination testing is most accurate at the fingertips. Normal two-point discrimination is considered less than 6 mm, fair is 6 to 10 mm, and poor is 11 to 15 mm.

APPENDIX 14: Visual Analog Pain Scale (Sriwatanakul et al., 1983), (Bijur, Silver, & Gallagher, 2001)

The Visual Analog Scale (VAS) for pain is used to measure quantity of pain. A 10-cm line has 0 as no pain and 10 as worst pain imaginable. High test-retest reliability has been demonstrated. There is a high correlation between VAS and the numeric pain rating scale and a verbal description of pain.

The VAS is well described in research, and has been shown to be a valid, reliable and sensitive clinical measure of pain that is amenable to statistical analysis. It is simple to use. VAS showed significant positive correlation with numeric rating scales and the faces pain scale. Previous studies

have shown reliability, validity and clinical sensitivity of the VAS as a measure of intensity of subjective pain.

Visual Analog Scale (VAS)*



***A 10 cm baseline is recommended for VAS scales.**

From: Acute Pain Management: Operative or Medical Procedures and Trauma, Clinical Practice Guideline No. 1. AHCPR Publication No. 92-0032; February 1992. Agency for Healthcare Research & Quality, Rockville, MD; pages 116-117

APPENDIX 15: Home Program Daily Diary**INSTRUCTIONS FOR COMPLETION:**

1. Please review this diary daily and mark your completion of your home program
2. Please mark if you have any of the following symptoms on that particular day:
 - Numbness (include date of onset)
 - Tingling (include date of onset)
 - Pain in your fingers or hands (include date of onset)
3. Please bring this diary with you to each hand therapy appointment
4. Mark 100% for the day if you followed the instructions provided to you. Mark $\geq 50\%$ (greater than or equal to) for the day if you followed most of the instructions provided to you. Mark $< 50\%$ (less than) for the day if you followed some of the instructions provided to you. Mark None for the day if you didn't complete any of the exercises as instructed.

Date: _____ Subject Initials: _____	Indicate the amount of your home program you completed today ☐ 100% ☐ $\geq 50\%$ ☐ $< 50\%$ ☐ None	Did you experience any of the following in your hands today? ☐ Numbness; How Long? _____ ☐ Tingling; How Long? _____ ☐ Pain; How Long? _____
Date: _____ Subject Initials: _____	Indicate the amount of your home program you completed today ☐ 100% ☐ $\geq 50\%$ ☐ $< 50\%$ ☐ None	Did you experience any of the following in your hands today? ☐ Numbness; How Long? _____ ☐ Tingling; How Long? _____ ☐ Pain; How Long? _____
Date: _____ Subject Initials: _____	Indicate the amount of your home program you completed today ☐ 100% ☐ $\geq 50\%$ ☐ $< 50\%$ ☐ None	Did you experience any of the following in your hands today? ☐ Numbness; How Long? _____ ☐ Tingling; How Long? _____ ☐ Pain; How Long? _____
Date: _____ Subject Initials: _____	Indicate the amount of your home program you completed today ☐ 100% ☐ $\geq 50\%$ ☐ $< 50\%$ ☐ None	Did you experience any of the following in your hands today? ☐ Numbness; How Long? _____ ☐ Tingling; How Long? _____ ☐ Pain; How Long? _____
Date: _____ Subject Initials: _____	Indicate the amount of your home program you completed today ☐ 100% ☐ $\geq 50\%$ ☐ $< 50\%$ ☐ None	Did you experience any of the following in your hands today? ☐ Numbness; How Long? _____ ☐ Tingling; How Long? _____ ☐ Pain; How Long? _____
Date: _____ Subject Initials: _____	Indicate the amount of your home program you completed today ☐ 100% ☐ $\geq 50\%$ ☐ $< 50\%$ ☐ None	Did you experience any of the following in your hands today? ☐ Numbness; How Long? _____ ☐ Tingling; How Long? _____ ☐ Pain; How Long? _____