Local Effects of Acupuncture on the Median and Ulnar Nerves in Patients with Carpal Tunnel Syndrome: A Pilot Mechanistic Study

NCCIH Protocol

Alexandra Dimitrova, MD, MA, Charles Murchison, MS, Yunpeng Luo, DAOM,
Jau-Shin Lou, MD PhD, Barry Oken, MD, MS

Study Principal Investigator:

Alexandra Dimitrova, MD, MA
Assistant Professor of Neurology
Oregon Center for Complementary and Neurologic Disorders (ORCCAMIND)
Oregon Health & Science University

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STUDY TEAM ROSTER

Alexandra Dimitrova, MD, MA – Principal Investigator
Oregon Health & Science University
Oregon Center for Complementary and Alternative Treatments in Neurologic Disorders (ORCCAMIND)
3181 SW Sam Jackson Park Road, Mail Code CR 120
Portland, OR 97239
tel. (503) 494-0744
fax. (503) 494-0966
email: dimitroa@ohsu.edu

Charles Murchison, MS
Oregon Health & Science University
Parkinson Center of Oregon
Department of Neurology, OP-32
3181 SW Sam Jackson Park Road
Portland, Oregon 97239-3098
Phone: (503) 494-7231
Fax: (503) 494-9059
Email: murchiso@ohsu.edu

Tabatha Memmott, BA/BS
Oregon Health & Science University
ORCCAMIND
Same contact info as Dr. Dimitrova
Email: memmott@ohsu.edu

Diana Dimitrova, PhD
Oregon Health & Science University
ORCCAMIND
Same contact info as Dr. Dimitrova
Email: dimitrov@ohsu.edu

Yunpeng Luo, DAOM, LicAc
Oregon Health & Science University
Center for Women's Health
808 SW Campus Dr, Portland, OR 97239
Phone: (503) 418-4500
Fax: (503) 494-1678
Email: luoy@ohsu.edu

Annette (Zoe) Fallian, MS, LicAc
Oregon Health & Science University
ORCCAMIND
Same contact info as Dr. Dimitrova
Email: fallian@ohsu.edu

Jau-Shin Lou, MD, PhD, MBA
University of North Dakota School of Medicine and Health Sciences
700 1st Avenue S
Fargo, ND 58103
Phone: (701) 234-4036
Fax: (701) 234-4151
Email: jaushin.lou@med.und.edu

Barry Oken, MD, MS
Oregon Health & Science University
ORCCAMIND
Same contact info as Dr. Dimitrova
Email: oken@ohsu.edu

PARTICIPATING STUDY SITE - Oregon Health & Science University (OHSU)

PRÉCIS

Study Title: Local Effects of Acupuncture on the Median and Ulnar Nerves in Patients with Carpal Tunnel Syndrome (CTS): A Pilot Mechanistic Study

Objectives: The purpose of this study is to measure the local effects of acupuncture on the median and ulnar nerves in patients with median neuropathy at the wrist (carpal tunnel syndrome), using nerve conduction studies (NCS) and quantitative sensory testing (QST) as outcomes. Our secondary aim is to compare acupuncture's effect on the functioning of a diseased nerve (median nerve in CTS) to its effect on a healthy nerve (ulnar). Additionally, we aim to compare the local, nerve-specific effect of manual acupuncture to that of low-frequency electroacupuncture and of high-frequency electroacupuncture.

Design and Outcomes: In a mechanistic study of acupuncture, 60 subjects with carpal tunnel syndrome (CTS) will be randomized to manual acupuncture (MA), low-frequency electroacupuncture (LF-EA) and high-frequency electroacupuncture (HF-EA) groups. Baseline measurements will consist of QST (vibration and cold detection thresholds), as well as NCS of both median and ulnar nerves. Then, each group will undergo acupuncture to the median nerve (Pericardium channel points) and to the ulnar nerve (Heart channel points), one week apart, order counterbalanced, followed by post-acupuncture NCS and QST measurements in both nerves (**See Figure 1 below**).

During the study initial visit (Week 1) baseline QST and NCS measurements will be obtained, followed by acupuncture (manual, low- or high-frequency) intervention to the ulnar or to the median nerve (based on treatment randomization) and repeat post-intervention QST and NCS measurements to both median and ulnar nerves.

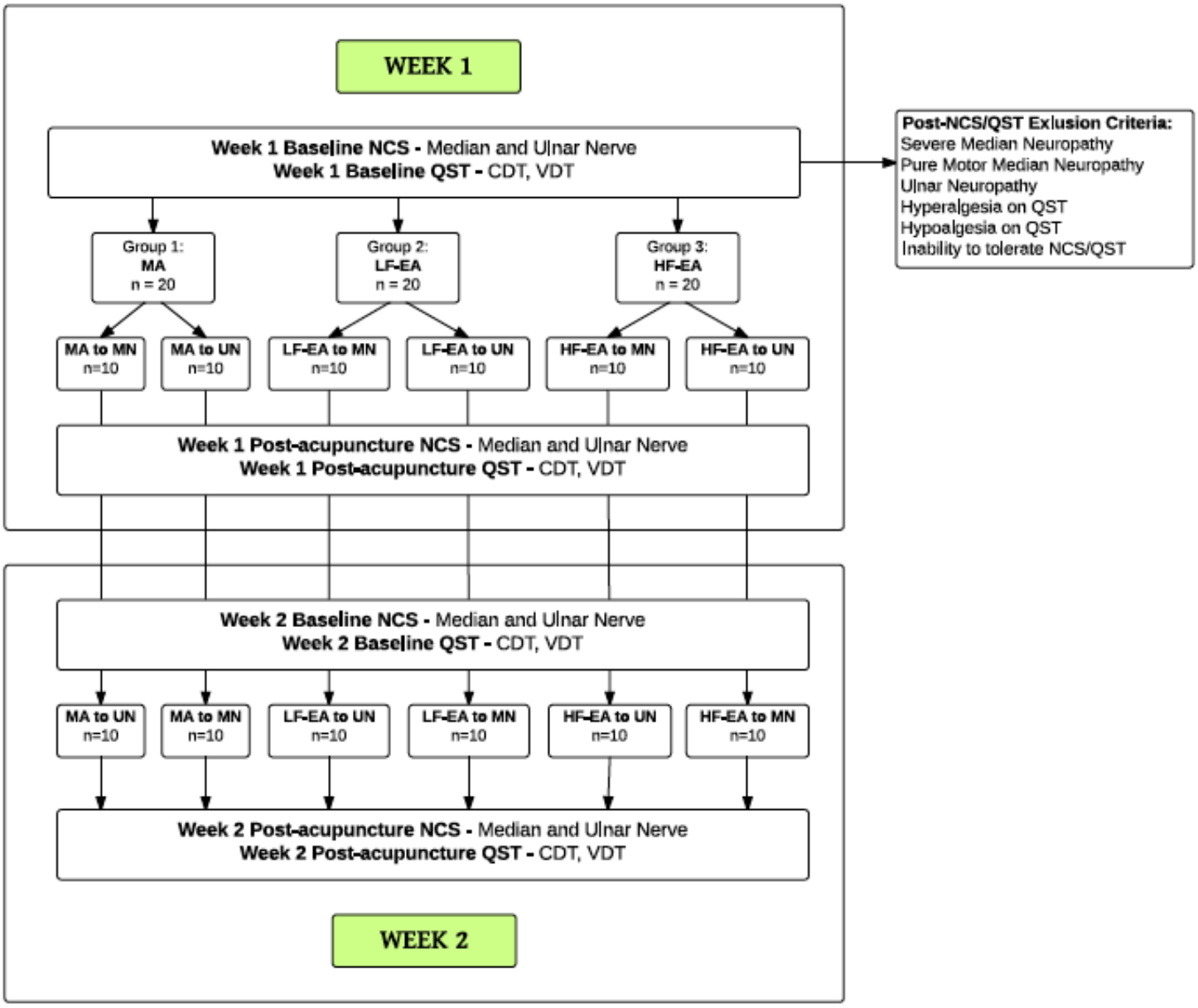
During the study second and final week (Week 2), baseline QST and NCS measurements will be obtained again, followed by acupuncture (MA, LF-EA, HF-EA) intervention to the nerve, which was not treated the first week. Finally, repeat post-acupuncture QST and NCS measurements will be obtained in both median and ulnar nerves (**see Figure 1 below**).

Interventions and Duration : Subjects will be randomized to 3 intervention groups as specified above: Manual, Low-frequency and High-frequency electroacupuncture. Each subject will receive the following interventions:

1. Acupuncture to PC3, 5 overlying the median nerve
2. Acupuncture to HT3,4 overlying the ulnar nerve

These will be performed one week apart, in random order. Each acupuncture session will involve 2 needles, with active treatment time 20 min and needle retention during the subsequent QST measurement. Needles will be taken out prior to the post-acupuncture NCS measurements.

Fig.1. Study Procedures Flowchart



Abbreviations: NCS=nerve conduction studies, QST=quantitative sensory testing, CDT=cold detection threshold, VDT=vibration detection testing, MA= manual acupuncture, LF-EA=low-frequency electroacupuncture, HF-EA=high-frequency electroacupuncture, MN = median nerve, UN = ulnar nerve

Sample Size and Population: We plan to enroll 60 subjects with mild-moderate carpal tunnel syndrome, ages 18-75, male and female. In addition to basic eligibility criteria described in detail below and based on a subject's medical history, we anticipate the need to screen 75-80 subjects in the lab with baseline QST and NCS in order to make the determination for study eligibility (see Figure 1 above). Subjects will be recruited from OHSU's EMG lab and neuromuscular clinic.

Once determined eligible and meeting the baseline QST and NCS enrollment criteria, subjects will be randomized using stratified randomization (with stratification factors of age and gender), to 3 groups of 20 subjects each - Manual Acupuncture (MA) group, Low-frequency Electroacupuncture (LF-EA) group and High-frequency Electroacupuncture (HF-EA) group.

1. STUDY OBJECTIVES

1.1. Primary Objective

Specific Aim 1: Characterize the effects of acupuncture on QST (cold and vibration sensation thresholds) and nerve conduction study parameters in the Median and Ulnar nerves.
Hypothesis: Acupuncture will cause decrease in cold and vibration detection thresholds (improve sensation) in the underlying nerve sensory distribution only. Acupuncture will cause NCS changes, characteristic of improved nerve function.

1.2. Secondary Objectives

Specific Aim 2: Compare the effects of acupuncture on a diseased nerve (Median) to those of a healthy nerve (Ulnar), using QST (cold and vibration sensation thresholds) and NCS parameters.
Hypothesis: There will be greater change in cold and vibration detection thresholds and NCS parameters in the median nerve compared to the ulnar, due to the lower functional baseline of the median nerve.

Specific Aim 3: Compare the effects of manual acupuncture to those of low-frequency and high-frequency electroacupuncture.
Hypothesis: High-frequency electroacupuncture will have greater effect on NCS, QST followed by low-frequency electroacupuncture and manual acupuncture, in accordance to traditional practices.

2. BACKGROUND AND RATIONALE

2.1. Acupuncture Background

Acupuncture is an ancient therapeutic modality, traditionally involving needling techniques, based on ancient Chinese theories of acupoints located along energy channels called meridians. More recently acupuncture has emerged as an important integrative medical treatment, both in the hospital and outpatient setting (1, 2). In 1998 an NIH Consensus Development Panel concluded that acupuncture is efficacious in adult post-operative and chemotherapy-induced nausea and vomiting, and that acupuncture is helpful in other conditions, including stroke rehabilitation (3). More recent evidence-based reviews have shown the therapeutic benefits of acupuncture for chronic low-back pain (44, 45), migraine and tension headache (46, 47), chemotherapy-induced nausea and vomiting (48), among other conditions.

In spite of acupuncture's increased acceptance, its mechanism of action remains unknown. There is debate as to whether there is point-specific response in acupuncture or whether it induces a more generalized response, perhaps related to endogenous opioid or placebo response. Early research suggested that the effects of acupuncture are mediated on a systemic level by the endogenous opioid system (4, 5, 6). Acupuncture seems to increase cerebrospinal fluid levels of endorphins, enkephalins, and adrenocorticotropic hormone and its effect can be blocked by the endorphin antagonist naloxone (4, 6). The immune effects of acupuncture seem to be mediated

via increased activity of splenic NK cells and levels of interferon-gamma (7). Acupuncture may also affect the gene expression of neuropeptides and their receptors (8, 9). A centrally acting agent/mechanism, however, cannot explain why acupuncture is conventionally applied in close proximity to the locus of pain and why the analgesic effects of acupuncture are often limited to the ipsilateral side (10, 11).

For many decades acupuncture practitioners and anatomists have attempted to correlate the location of acupuncture points to peripheral nerves, spinal segments and spinal plexuses (12-17, 18). This neuroanatomical theory of acupuncture suggests that acupuncture's effect is mediated via afferent input through the peripheral nervous system, eliciting a reflex at the level of the spinal cord via the sympathetic plexuses and via efferent to the visceral organs and skeletal muscle (19, 20). The neurophysiologic testing to support these theories is lacking so far and further study on the local effects of acupuncture on the peripheral nervous system is needed. There is a consensus, however, that the nervous system is vital in processing the effects of acupuncture.

2.2. Significance

The lack of understanding of acupuncture's mechanism of action is a major obstacle to its wider acceptance. The lack of objective physiologic measurements of acupuncture's effect has posed many difficulties in designing acupuncture research studies involving dose response and efficacy.

Our research will address this knowledge gap by measuring the local effects of acupuncture on an underlying nerve by focusing on Nerve Conduction Study (NCS) parameters and Quantitative Sensory Testing (QST) in the territory of that nerve. Additionally, we will isolate these effects by comparing them to those of a neighboring nerve. Quantifying acupuncture's effects using physiologic parameters and discreet values could standardize treatment regimens and measure therapeutic effect in tangible ways. As acupuncture practices vary widely, with various treatment modalities and point selection, the ability to measure direct effects on the peripheral nerves may help compare treatment regimens and standardize practices by developing efficient protocols.

This line of research is expected to substantiate the proposed association between acupuncture meridians and peripheral nerves in the arm and leg and translate the explanatory constructs of channels and Qi, drawn from TCM into an acceptable western physiologic paradigm of nerve physiologic changes based on redistribution of charge.

2.3. Innovation

While fascia changes have been implicated in chronic pain conditions (50), likely mediated by a local inflammatory response, the analgesic effects of acupuncture cannot be explained by fascia changes alone, without involvement of the nervous system. Langevin and Sherman (51) recently hypothesized that acupuncture causes changes in mechano- and nociceptive receptors in connective tissue. Recent histological studies of fascia have shown it to be very rich in Ruffini and Pacinian corpuscles and free nerve endings and it is therefore believed to be involved in proprioception (32). The proposed research is innovative, in our opinion, because it does not seek to disprove or adopt the fascia mechanistic theory of acupuncture, but rather focuses on the

peripheral nervous system's processing of acupuncture as a final common pathway before further mediation and potentiation occur at the level of the spinal cord and cerebrum.

QST and NCS have both been used in acupuncture research before, however their use has been to assess therapeutic clinical improvements in the patient (21, 42). These measurements have never been targeted to a particular nerve distribution and used to study anatomical correlations between acupoints/channels and an underlying peripheral nerve, with the goal of assessing for acupuncture-induced functional changes in the nerve. We hope that this line of research will lead to a cohesive understanding of acupuncture's mechanism of action, which incorporates the fascia and the peripheral nervous system effects.

2.4. The "DeQi" Sensation and the Peripheral Nerves

According to traditional acupuncture teachings, it is essential to elicit a sensation called "DeQi", in order to achieve therapeutic results. This sensation is accomplished by manipulation of the acupuncture needle after its insertion in the acupuncture point. It has been described as aching, soreness, heaviness/pressure, fullness, warmth, coolness, tingling, numbness and dull pain at the site of the needle (29) or radiating paresthesias (30). It appears that this sensation is mediated by the peripheral nerves. In clinical practice patients often report that manipulation of the acupuncture needles causes a sensation "like hitting one's funny bone" and neuropathy patients, when undergoing acupuncture of local points in the feet, liken the sensation to an exacerbation of their neuropathy symptoms. Langevin et al (31) have suggested that the sensation of DeQi is elicited by fascia manipulation, however muscle fiber contraction surrounding the needle remains a possibility. From a neurologic perspective, both muscle or fascia manipulation would result in mechanical compression and possibly release of inflammatory factors, leading to small and larger peripheral nerve fiber activation.

2.5. Introduction to Acupuncture Modalities – Manual and Electroacupuncture

Manual acupuncture consists of placing needles in acupuncture points, at a point-specific pre-determined depth, based on established guidelines from the Traditional Chinese Medicine literature. Following insertion the needles are manually manipulated with rapid clockwise or counter-clockwise rotation or small vertical adjustments in the scale of millimeters. This manipulation (aka needle stimulation) is carried out for 45 sec – 1-2 minutes, typically until the subject feels the "De Qi' sensation. The needles are then left in for 15-20 minutes. Often times a second stimulation session is performed midway in the course of the treatment, depending on the acupuncturist's style of practice.

Electroacupuncture is an acupuncture modality, which gained wide acceptance in the 1950s simultaneously in China, Germany and Japan (43). It consists of placing acupuncture needles in traditional acupuncture points, then connecting them to an electrostimulating device. Electrical current is applied to connect 2 needles to an anode and cathode. Typically alternating current in the range of 10-80 milliamps is applied, with a voltage range of range of 40-80 volts. Frequency varies from 2-100 Hz. In general lower frequencies (2-10Hz) are considered to be toning/stimulating of the nerves and higher frequencies (80-100 Hz) are considered inhibitory and are used for analgesia (43). Typical electroacupuncture treatment usually lasts 10-20 minutes.

2.6. Quantitative Sensation Testing (QST)

Computer-assisted Sensory Evaluation (CASE) aka Quantitative Sensation Testing (QST) has been in clinical use since the late 1970s, when Dyck, O'Brien et al introduced the concept of an automated system to evaluate touch-pressure vibration and thermal cutaneous sensation (38). QST is administered in a lab and consists of standardized, precisely delivered computer-generated stimuli, based on careful study of physiologic perception thresholds and "just noticeable difference (JND)" of heat, cold, vibration and touch-pressure (39). Typically the lateral side of the nail bed is used to assess vibration detection threshold (VDT) in the hand and the dorsal surface of the hand is used to assess cooling (CDT) or heating detection threshold.

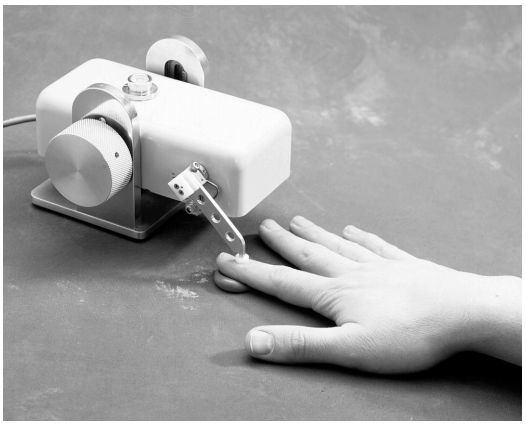


Fig.2. CASE IV Vibration Stimulator

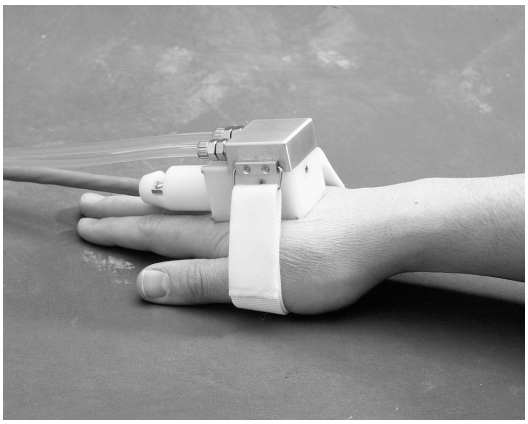


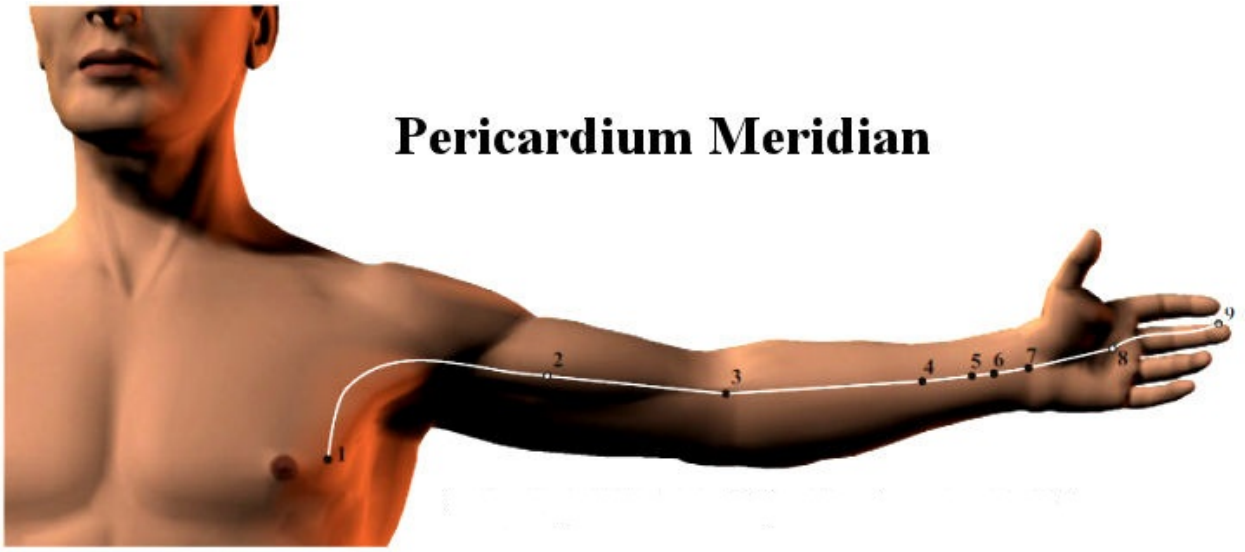
Fig.3. CASE IV Thermal Stimulator

The creators of the CASE system created various algorithms for assessing hyper- and hypoalgesia in peripheral neuropathy patients. QST performed with the fourth generation system (CASEIV) have been shown to be efficient, reproducible, and validated against other algorithms of sensory testing (40). The correlation coefficients for vibratory detection threshold (VDT) and cooling detection threshold (CDT) have been found by greater than 0.9 (40). While QST has become a widely-used research tool, the validity of its results is highly dependent on the subject's ability to cooperate and sustain focused attention on stimulus presentation. Therefore, QST cannot be administered when the patient is inattentive, uncooperative, demented, sedated, or too ill to cooperate.

2.7. Study Rationale - Acupuncture for Carpal Tunnel Syndrome, PC6 and the Median Nerve

One area of acupuncture research, which has yielded successful results, is the efficacy of acupuncture in the treatment of Carpal Tunnel Syndrome (CTS). Acupuncture has shown to be effective for mild-moderate CTS with lasting effects on Nerve Conduction Studies (NCS) a year post-treatment (21). Additionally, laser acupuncture and TENS applied to the wrist has been shown to be effective in the treatment of CTS, with symptom improvement still present on 1-3 year follow-up (22, 23). Interestingly the above treatment protocols all involved acupuncture regimens with needles placed in the Pericardium channel (PC), most commonly PC6 (21, 24) and PC7 (21, 22, 23, 25) and PC3 (25), **see Figure 4 below.**

Fig.4. Anatomical Correlation of the Pericardium Meridian/Channel and the median nerve



The anatomical connection of the acupuncture point PC6 and the Median nerve has been well established both in cadavers (26) and in live subjects using ultrasound (27, 28), most strikingly with a documented case of the acupuncture needle piercing through the Median nerve sheath, with absence of any symptoms in the subject (28).

All these studies raise the question of the effect of acupuncture in the Pericardium channel on the underlying Median Nerve.

2.8. Pilot Data

So far we have shown that the procedure is safe, tolerable and capable of producing the projected outcome variables in an accurate and consistent manner. We have achieved lab consistency in QST and NCS outcome measures. We have completed testing of 3 pilot subjects with the following findings:

Pilot 1: 65 yo woman with moderate CTS. Treated with HF-EA to Median nerve (Week 1), followed by HF-EA to Ulnar nerve (Week 2). Cold detection threshold in the Median nerve territory improved with acupuncture from 13.1 to 8.7 units. Ulnar territory cold detection was unchanged with acupuncture. Median nerve compound muscle action potentials (CMAP) amplitude at the wrist and elbow increased with acupuncture by a third, whereas Ulnar CMAP were unchanged with acupuncture. She reported symptomatic improvement at Week 2.

Pilot 2: 69 yo man with moderate CTS. Treated with HF-EA to Median nerve (Week 1), followed by HF-EA to Ulnar nerve (Week 2). No significant changes were seen in QST with acupuncture, however the subject had new Sensory Nerve Action Potentials (SNAP) in the Median nerve during Week 2, which were absent in Week 1 prior to acupuncture intervention. He also had symptomatic improvement at Week 2.

Pilot 3: 43 yo woman with moderate CTS. Treated with HF-EA to Median nerve (Week 1), followed by HF-EA to Ulnar nerve (Week 2). Both cold and vibration detection threshold in the Median nerve territory improved with acupuncture (12.5 to 8.4 and 8.7 to 3.9, respectively).

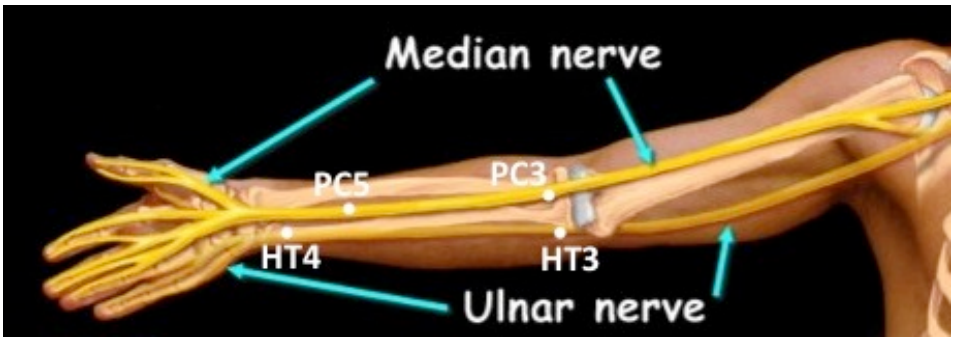
Median motor nerve conduction velocity increased from 54.5 to 59.3 m/s with acupuncture. Median sensory nerve conduction velocity (NCV) increased from 42.3 to 50.2 m/s in Week 1 during treatment. Ulnar sensory NCV did not change in Week 1, but increased from 66.7 to 78.6 m/s in Week 2 with treatment, with an associated Ulnar SNAP increase. Of note, after Week 2 this subject was completely symptom free and remained so 2 months after the conclusion of the study (she called the lab).

3. STUDY DESIGN

This is a pilot mechanistic study in which the local effects of acupuncture on the median and ulnar nerves will be investigated, by applying acupuncture to points in the Pericardium and Heart meridians, which appear to track the path of the median and the ulnar nerves, respectively (**see Figure 5 below**). All subjects will have a diagnosis of carpal tunnel syndrome, which is a median nerve entrapment at the wrist.

Subjects will be randomly allocated to one of 3 intervention groups – manual acupuncture (MA), low-frequency electroacupuncture (LF-EA) and high-frequency electroacupuncture (HF-EA). All subjects will have a diagnosis of carpal tunnel syndrome (median nerve entrapment at the wrist). The intervention will be acupuncture (MA, LF-EA or HF-EA) and the outcome variables – post-acupuncture NCS of the median and ulnar nerves and quantitative sensory testing (QST) measurements in the palmar median and ulnar nerve distributions (specifically cold and vibration detection thresholds), see **Figure 1** above. In each group there will be 2 treatments in random order, in which acupuncture will be applied to the median nerve/Pericardium meridian and the ulnar nerve/Heart Meridian.

Fig.5. Anatomic correlation of the median nerve and Pericardium Channel (PC) and of the ulnar nerve and Heart Channel (HT).



<u>The healthy ulnar nerve will serve as a control in two ways:</u>

1. Local Effects - the ulnar nerve, being in close proximity to the median nerve, will be investigated for possible effects when acupuncture is delivered to Pericardium channel points (over the median nerve). In this way we will explore whether acupuncture has effects only on the underlying nerve, or also on a neighboring nerve. This will be accomplished by measuring post-acupuncture QST and NCS in both the median and ulnar nerves, when the intervention is done over the median nerve.

Hypothesis: Acupuncture will cause decrease in cold and vibration detection thresholds (improve sensation) in the underlying nerve sensory distribution only. Acupuncture will cause NCS changes, characteristic of improved nerve function.

2. Healthy vs Diseased nerve Effect – The intervention will be delivered over the ulnar nerve (healthy) as well, using Heart channel acupuncture points. This will enable us to compare the acupuncture effect on a healthy nerve, compared to a diseased nerve (Median nerve in patients with CTS).
Hypothesis: There will be greater change in cold and vibration detection thresholds and NCS parameters in the median nerve compared to the ulnar, due to the lower functional baseline of the median nerve.

Our third goal involves comparison among the 3 intervention groups , specifically we aim to compere the effects of manual acupuncture (MA) to those of low-frequency (LF_EA) and high-frequency electroacupuncture (HF-EA).
Hypothesis: High-frequency electroacupuncture will have greater effect on NCS, QST followed by low-frequency electroacupuncture and manual acupuncture, in accordance to traditional practices.

3.1. Study subjects
60 subjects with carpal tunnel syndrome will be randomized to 3 intervention groups as described above with stratification for age and gender. Subjects will be both male and female, ages 18-75. Subjects will be recruited from OHSU's EMG lab and neuromuscular clinic.

3.2. Study site
OHSU will be the only study site for this protocol

3.3. Experimental duration and follow-up
Study procedures will be carried out over 2 consecutive weeks (**see Figure 1**). As this is a mechanistic study involving immediate effects of acupuncture on a peripheral nerve, there will be no follow up period beyond Week 2. This study employs 3 commonly practiced, well established interventions, which are considered low-risk: nerve conduction studies (NCS), quantitative sensory testing (QST) and acupuncture to the forearm. Subjects will be given all necessary follow-up contact information in case of unanticipated adverse events, as described in Section 7 (Safety Assessments).

3.4. Blinding
As this is a mechanistic study comparing acupuncture to acupuncture intervention, it is impossible to blind subjects in the conventional sense. Depending on a subject's knowledge of anatomy and acupuncture, however, a subject may or may not be aware as to which nerve is targeted for intervention on each week.

All QST assessments will be performed in blinded fashion and the investigators assessing the outcome measures will not be delivering the intervention (acupuncture). QST assessments will be performed by a blinded investigator (Tabatha Memmott), who will be seated behind a screen with the subject's arm, needles and QST probes not visible. The PI will not be involved in QST measurements. Additionally, the PI will be blinded to the acupuncture intervention, which will be delivered by a licensed acupuncturist (Annette Fallian or Yunpeng Luo).

Week 1 QST and NCS baseline will be assessed in non-blinded fashion, prior to randomization. Following these initial measurements, the PI will screen the subject for Secondary Exclusion criteria. Once the subject is determined eligible, the PI will leave the room. PI will be blinded to randomization (MA, LF-EA or HF-EA) and treatment assignment (median or ulnar nerve). Randomization will be performed by the study acupuncturist and the other investigators will be blinded to it.

The PI will return to the room once the acupuncture intervention has been completed, the post-acupuncture QST measurements obtained and acupuncture needles removed, in order to perform the post-acupuncture NCS and remain blinded to the intervention.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1. Inclusion Criteria

Participants must meet all of the following inclusion criteria to participate in the study:

- Age 18-75
- Both male and female subjects
- Presence of mild-moderate sensorimotor or sensory median neuropathy, established by pre-existing NCS/EMG study AND
- **Baseline NCS study within the past 2 years**, consistent with mild-moderate median entrapment neuropathy (CTS) defined as meeting any of the 3 conditions below (33, 34):
  1. Prolonged distal Median sensory AND/OR motor latency
  2. Reduced Median sensory nerve action potentials (SNAP) amplitude by no more than 50%
  3. Amplitude of the compound muscle action potential (CMAP) recorded from APB > 50% of normal
- Presence of neuropathy symptoms consistent with CTS for <u>at least 3 months</u> (36)

4.2. Exclusion Criteria

Patients will be excluded on initial screening in the EMG lab or the Neuromuscular clinic at OHSU based on the following Exclusion Criteria:

<u>Conditions in which acupuncture/electroacupuncture may be contraindicated:</u>

- Coagulopathy/ Current anti-coagulation treatment
- Epilepsy
- History of CAD or pacemaker insertion
- Pregnancy
- Presence of any skin condition in the arm, such as dermatitis, bruises, weeping skin, skin lesions, infected skin, or necrotic skin.

<u>Conditions in which QST testing may be contraindicated:</u>

- Significant cognitive impairment such as diagnosis of Alzheimer's disease or Mental Retardation or any other condition interfering with alertness, attention and ability to participate in QST
- Hospitalization for anxiety or depression in the past 3 months
- Current psychiatric diagnoses (other than anxiety or depression)
- Illicit drug use in the past month
- Current EtOH abuse (> 2 drinks/day)
- History of significant neurological disease which may affect sensation, e.g., strokes, Multiple Sclerosis, or spinal cord disorder
- Change in neuropathy medications within the past 2 months
- Change in opioid, benzodiazepines, SSRIs or other sedating medications in the past 2 months

Conditions, which predispose to generalized neuropathy

- Abnormal thyroid function tests (by history)
- Past chemotherapy treatment

Other Contraindications:

- History of wrist or elbow fracture, past arm trauma, loss of fingers, scarring
- History of carpal tunnel release surgery or any other surgery on the arm or shoulder
- History of arthritis
- Use of any investigational drugs within the previous six months

Exclusion Criteria based on NCS within the past 2 years:

- Presence of isolated motor Median neuropathy (absence of sensory neuropathy on NCS or absence of sensory symptoms)
- Severe neuropathy symptoms leading to inability to tolerate acupuncture or QST
- **Presence of Severe Carpal Tunnel Syndrome, defined as:**
    1. Absent sensory nerve action potential recorded from the second or fifth digit.
    2. The amplitude of the compound muscle action potential recorded from the APB or ADM is less than 50% of normal (< 2.5 mv)
- Presence of Ulnar neuropathy
- Presence of Martin-Gruber anastomosis

Secondary Exclusion Criteria after WEEK 1 Baseline QST and NCS measurements (See Figure 1):

- Failure to comply with QST due to inattentiveness, etc
- Hyperalgesia on QST
- Hypoalgesia on QST
- Inability to confirm diagnosis of mild-moderate CTS (normal NCS)
- Inability to tolerate NCS/QST
- Presence Severe CTS

- Pure Motor Median Neuropathy
- Ulnar Neuropathy

4.3. Study Enrollment Procedures

Potential participants will be identified through screening OHSU's EMG lab and neuromuscular clinic patient schedules. Basic eligibility screening will be conducted using OHSU's electronic medical record database (EPIC). Patients, who pass this medical record screening will be approached by the PI. If a patient is interested, the PI will explain the objectives, risks and benefits of the study. At this point if a patient agrees to screening, the PI will proceed with an evaluation based on medical history, habits and recent (within last 2 years) EMG/NCS. The screening results will be documented using the *Subject Screening Form* (Appendix A). If a potential subject is determined to be eligible, the PI will answer all his/her questions, inform the subject that he/she may withdraw consent at any point and obtain informed consent for the study. This will involve presenting the subject with a *Lay Language Protocol Summary* and an *OHSU Consent-and-Authorization form* (as required by OHSU IRB) is also included in Appendix A.

Following enrollment, subjects will come to the lab for initial screening, consisting of QST and NCS. Following this testing, if they pass the Secondary Exclusion Criteria, subjects will be randomized to MA, LF-EA and HF-EA, using a computer-generated stratified randomization based on age and gender.

4.4. Stratified Randomization

Subjects will be randomized to the 3 intervention groups, using a specially-designed computer program which will enable stratified randomization based on 2x2 categories where one category is gender (M/F) and the other is projected median age split of 56, based on age of enrolled pilots and clinic patients with carpal tunnel syndrome (18-56/57-75).

Gender and age have confounding effect on proper estimation of NCS and QST as they vary by age and sex. Specifically, men tend to have faster nerve conduction velocities (NCV) and larger nerves than women and with age NCV declines and sensory thresholds, measured by QST tend to rise (38, 49, 55, 56). Randomization will be performed by study acupuncturist, and all outcome assessors will be blinded to it.

The randomization program is also designed to offer random order of acupuncture intervention location (median vs ulnar nerves), with a built-in ability to assign 50% of subjects within a group to median nerve first and the other 50% - to ulnar nerve first.

4.5. Accrual Plan

Subjects will be recruited from OHSU's EMG lab as the lab follows rigorous electrodiagnostic criteria for CTS diagnosis. Such criteria are usually lab-specific and take years to develop. Additionally, a recent EMG is crucial as CTS tends to fluctuate and has a relapsing-remitting course for most patients. We plan to recruit subjects in the EMG lab, immediately after completion of their NCS/EMG. The EMG lab at OHSU sees anywhere from 12-20 CTS subjects per month. Our experience with recruiting pilot subjects has been that patients are interested in the study as even 2 sessions may improve CTS symptoms and often times the alternative is more invasive such as carpal tunnel release surgery.

Of the 12-20 CTS patients seen in the lab many would not meet the eligibility criteria or would not be able to participate for reasons listed above – travel, logistics, surgery, etc. We have had great success recruiting patients local to the Portland area with mild-moderate CTS so far.

Once the protocol is approved we anticipate enrollment of 2-4 subjects per month. This number varies due to seasonal patient volume and staffing fluctuations in the EMG lab. Other factors in recruitment are: EMG lab patients who are not local to Portland and unwilling to travel for study purposes, patients who are scheduled for carpal tunnel release surgery and who wish to proceed with surgery without delay for study participation, patients who have severe carpal tunnel syndrome, rising prevalence of marijuana use (including medical marijuana), anatomic variants or other conditions making patients ineligible for the study and lastly patients who simply are not interested in participation.

An overly conservative estimation of 2 subjects per month who meet all criteria including baseline testing in the lab would translate into 24 subjects per year and a 2.5 year period of recruitment and data collection. We have capacity to test 4-5 subjects per month and will plan to do so, if we are able to recruit this number.

5. STUDY INTERVENTIONS (See Figure 1 – Study Procedures Flowchart)

5.1. Week 1 Baseline QST and NCS testing

5.1.1. Baseline QST Measurement

Patients will be tested for vibratory detection threshold (VDT) and cold detection (CDT) using the CASEIV system, described above.

VDT

Vibration Stimuli will be delivered as 25 discrete levels ranging from 0.0 to 350 micrometers (μm) of displacement, based on previously established "Just Noticeable Difference" (JND) values (38). Each stimulus is presented with an exponential onset, and turns off with an exponential decay, in order to eliminate the touch-pressure artifact, which is caused by an instantaneous on/off. Stimulation will be delivered to the 2nd digit finger pad (median distribution) and the 5th digit finger pad (ulnar distribution), with the hand stretched out supinated (palm facing up) on an even surface.

CDT

The Thermal Stimulator use a four‑degree‑per‑second ramp up and down, and is typically operated in a range from 8 degrees to 50 degrees C., with an accuracy of 1.25 to 0.25 degrees C., depending on temperature. For high-magnitude thermal (cooling) stimuli, the absolute temperature is limited to 8 degrees C. Thermal stimuli are approximately 6 seconds in duration. CDT will be assessed over the thenar eminence (median distribution) and hypothenar eminence (ulnar distribution) with the hand on an even surface, supinated and palm facing up.

The 4, 2 and 1 stimulus presentation algorithm (to be used both for VDT and CDT)

The 4, 2, 1 stimulus presentation algorithm was developed by Dyck et al (41) as a more time-efficient alternative to forced choice, as it enables investigators to assess the sensory threshold in a given sensory modality in 2-5 minutes in most cases.

Testing will begin at an intermediate level (level 13 of 25). The stimulus will be increased (if not felt) or decreased (if felt) by four steps to the point of turnaround (felt at the higher level when not felt at lower levels, or not felt at the lower level when it had been felt at the higher level). After the first turnaround, stepping will be in steps of two. After the second turnaround, stepping will be by steps of one. A total of 20 stimulus events will be used, with five of them being randomly distributed null stimuli. If three consecutive failures are observed at level 25, testing will be terminated, and the subject will be classified as insensitive (QST hypoalgesia). If three consecutive successes were observed at level 1, testing will be terminated and the subject was classified as supersensitive (QST Hyperalgesia). Five null stimuli will be randomly interspersed among 15 non-null stimuli. A positive response (indicating perception) to more than one null stimulus will abort the program. The subject will be re-instructed, and the test will be re-run. Three failures (due to spurious answers to null stimuli) when the test is re-run twice after the test is initially aborted will indicate that the algorithm could not be used for this subject and the subject will be excluded from further participation in the study.

Following baseline QST subjects who can comply with and tolerate QST, have no hypo-or hyperalgesia will undergo baseline NCS studies.

5.1.2. Baseline Nerve Conduction Studies (NCS)

Following informed consent (obtained during subject screening), baseline nerve conduction studies will be performed according to OHSU's EMG laboratory procedures and in accordance with well established guidelines, as described by Kimura (49). These nerve conduction studies are standard clinical procedures in evaluating patients with neuromuscular diseases and will be performed using the Dantec Keypoint® G4 Workstation (Natus Medical Incorporated). Subject skin temperature will be maintained above 32 C, using a heating pad to warm up a cold hand if needed.

Specifically, the following nerve conduction studies will be performed:

a. **Median Nerve Conduction Study:**
   We will measure the sensory nerve action potential (SNAP) amplitude from the second digit, the compound muscle action potential (CMAP) amplitudes from the Abductor Pollicis Brevis, the motor and sensory distal latency, and the nerve conduction velocity in the forearm (from the elbow to the wrist).
b. **Ulnar Nerve Conduction Study:**
   We will measure the sensory nerve action potential (SNAP) amplitude from the fifth digit, the compound muscle action potential (CMAP) amplitudes from the Abductor Digiti Minimi, the motor and sensory distal latency, and the nerve conduction velocity in the forearm (from below elbow to the wrist)

Following baseline NCS, subjects who pass the Secondary Exclusion criteria (have mild-moderate CTS by electrodiagnostic criteria, are able to tolerate NCS, lack pure motor neuropathy or ulnar neuropathy), will be randomized as described above.

Subjects who meet the Secondary Exclusion criteria after Week 1 baseline QST and NCS testing will exit the study without being randomized and will be compensated for their time, as stated in the *OHSU Consent-and-Authorization form* (Appendix A).

5.1.3. Acupuncture Delivery (See Figure 1)
Studies will be randomized to 3 acupuncture modalities (MA, LF-EA and HF-EA). Within each group, a subject will receive 2 acupuncture sessions – one in Week 1, the other in Week 2, in random order either to the median or to the ulnar nerve. This separation into 2 sessions is necessary as there may be residual post-acupuncture effects on the first treated nerve, interfering with isolating the true effects of acupuncture on the subsequently treated nerve.

Acupuncture will be applied by an experienced licensed acupuncturist (Annette Fallian or Yunpeng Luo), using sterile single-use acupuncture needles (DBC Spring Ten 0.25x30 mm, 0.25x40 mm, DongBang Corp, Korea). In all 3 intervention groups, a DeQi sensation will be elicited after penetration of the skin in a depth of 3-5 mm. In the **manual acupuncture** group, a second stimulation will be given midway through the session by manual rotation/manipulation of the needles.

In the **electroacupuncture groups** (LF-EA and HF-EA) such manipulation will not be possible, however electrical stimulus intensity will be adjusted so that the subjects continues to feel the electricity-caused paresthesias/DeQi throughout the treatment period. In both electroacupuncture modalities pulse duration will be 60 microseconds, on a continuous frequency. Electroacupuncture will be was performed by using an electrical device (Electrostimulator 6c.Pro, Pantheon Research, Venice, CA – **See Figs 6, 7**) with insulated cable clamps connected to the acupuncture needles.

For **LF-EA,** a frequency of 2 Hz will be used and **for HF-EA**- frequency of 100 Hz. Stimulus intensity will be increased and re-adjusted, so that the patient feels the stimulation strongly, but not painfully (2–8 mA). This will be done as each 5 minutes the patients will be asked to rate the intensity of the electrical sensation on a scale from 1-10, with desired range 6-7/10. Adjustments to stimulus intensity will be done so that it is perceived at 6-7/10 throughout the course of electroacupuncture treatment. Each acupuncture treatment will last 20 minutes.

Fig.6. Electroacupuncture delivery using Pantheon 6c Electrostimulator

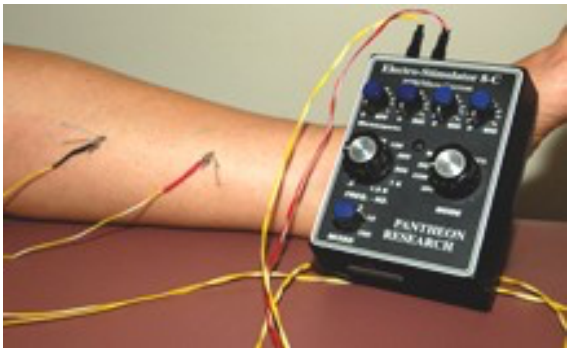
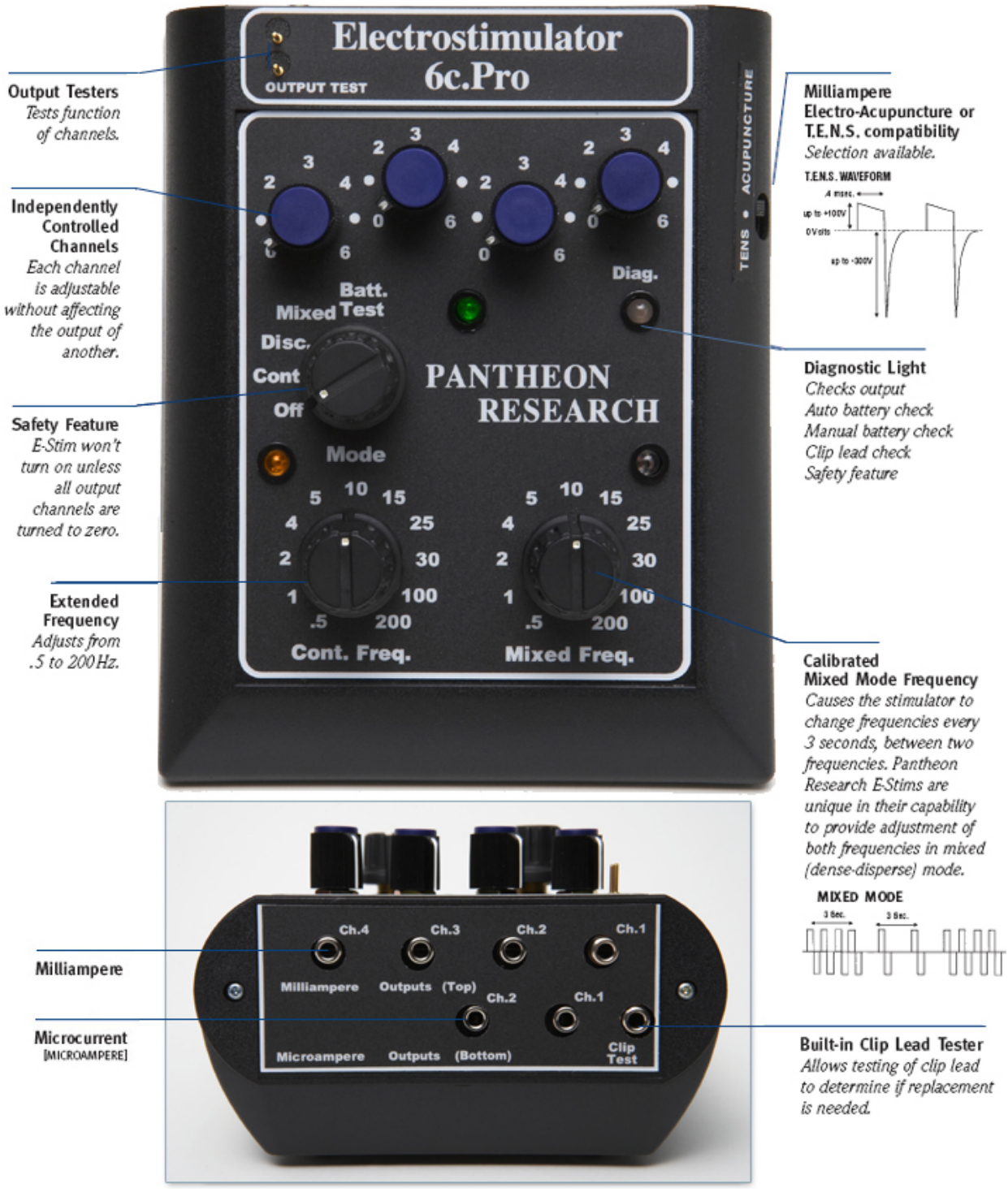


Fig. 7. Pantheon 6c Pro Electrostimulator



For the median nerve acupuncture treatment (MA, LF-EA or HF-EA) the insertion points will be on the Pericardium Channel (PC3 and PC5), which are used to stimulate the channel

(Water-Metal point) according to traditional 5-element acupuncture theory **(see images below).** PC3 and PC5 are closely anatomically associated with the median nerve (**see Figure 5**).

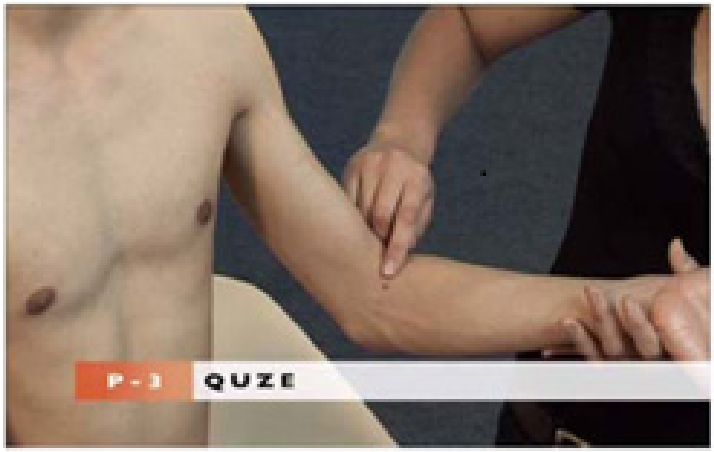


Fig.8. Acupuncture point PC3 (Pericardium 3)

Fig.9. Acupuncture point PC5 (Pericardium 5)

For the **ulnar nerve acupuncture treatment** (MA, LF-EA or HF-EA) the insertion points will be on the Heart Channel (HT3 and HT4), which are used to stimulate the channel (water-metal points) according to traditional 5-element acupuncture theory (**see images below**). HT3 and HT4 are closely anatomically associated with the ulnar nerve (**Figure 5**).

Fig.10. Acupuncture point HT3 (Heart 3)

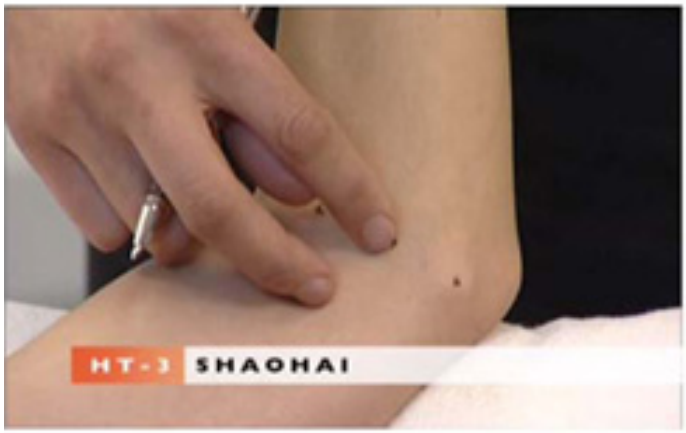


Fig 11. Acupuncture point HT4 (Heart 4)

5.2. Experimental Procedure Timeline (Figure 1)

During Week 1, enrolled and consented subjects will come to the lab for Week 1 Baseline QST and NCS testing as outlined above. During this baseline testing subjects will be introduced to the QST equipment and will undergo assessment of baseline cold detection threshold (CDT) and vibration detection threshold (VDT), as well as baseline NCS as outlined above. This would take approximately 1.5 hours and both procedures are non-invasive.

Following assessment of Baseline QST and NCS, subjects will be screened for Secondary Exclusion criteria, which relate to their CTS diagnosis and ability to tolerate NCS and QST (**Figure 1**). Subjects who do not pass the Secondary Exclusion Criteria will exit the study, with proper documentation of why they were ineligible.

Those who pass the Secondary Exclusion Criteria will be randomized to MA, LF-EA and HF-EA, as well as undergo random treatment assignment of median (PC3, PC5) or ulnar (HT3, HT4) nerve. Following randomization a subject will undergo acupuncture for 20 minutes involving 2 needles as outlined in detail above.

Following acupuncture, Week 1 Post-acupuncture QST (CDT and VDT) and NCS will be obtained in a manner analogous to the Week 1 Baseline QST and NCS testing outlined above. QST will be obtained first, with the needles retained in position, followed by needle removal and conduction of NCS. This will conclude Week 1. Total estimated time of Week 1 procedures is 4-4.5 hours. Subjects will be provided with water, bathroom break/other breaks as needed and a healthy snack.

Week 2 procedures will occur exactly one week after Week 1, as close to the same time of day as possible. Week 2 will start with Week 2 Baseline QST and NCS testing, following the same methodology as the Week 1 Baseline QST and NCS outlined above, although subjects will not be screened for inclusion/exclusion criteria at Week 2. A second baseline is necessary because in our experience even a single intervention to PC3, PC5 or HT3, HT4 may alter NCS and QST parameters or the median and ulnar nerves, respectively.

Once Week 2 Baseline QST and NCS testing is obtained, acupuncture will be delivered to the nerve not treated during Week 1. For example, if a given subjects is randomized to LF-EA and randomly assigned to ulnar nerve acupuncture in Week 1, the same subject will be administered LF-EA to the median nerve in Week 2, following Week 2 Baseline QST and NCS (**Figure 1)**.

After the acupuncture intervention, Week 2 Post-acupuncture QST (CDT, VDT) and NCS will be obtained in a manner analogous to those obtained in Week 1. Following completion of Week 2 NCS, subjects will complete and exit the study. Total testing time for Week 2 is estimated to be 3.5-4 hours.

Data will be recorded using the study *Data Form* (Appendix A).

5.3. Adherence Assessment

We do not anticipate problems with adherence as acupuncture will be delivered in the lab during both study visits. It is possible that some subjects will exit the study after Week 1, in which case we will include their results from Week 1 in the analysis.

6. STUDY PROCEDURE/EVALUATION SCHEDULE

Procedure	SCREENING (in EMG Lab or Neuromuscular Clinic)	WEEK 1	WEEK 2
Medical Record Screening	x		
EMG/NCS review of prior study (up to 2 yrs old)	x		
Prospective Subject Interview	x		
Study Screening by PI	x		
Screening Form	x		
Enrollment and OHSU Consent-and-Authorization Form	x		
Lay Language Protocol Summary form	x		
Baseline QST and NCS		x	x
Screening for Secondary Exclusion Criteria by PI		x	
Randomization and Random Treatment Assignment		x	
Data Form		x	x
Acupuncture Intervention		x	x
Post-acupuncture QST and NCS		x	x
Study Completion and Exit			x
Adverse Events		X	X

7. SAFETY ASSESSMENTS

Acupuncture holds the risk of minor bleeding/ecchymoses, especially in coagulopathic patients or those taking anti-platelet agents. Placing needles in the area of the median or ulnar nerves may lead to nerve damage by the needles, however the acupuncture points described above (PC3,5 and HT3,4) are commonly used and well established as safe over centuries of acupuncture practice. Furthermore, the needle used in acupuncture is 30G and solid (non-hollow), which minimizes underlying tissue damage. Electroacupuncture causes small, rapid muscle contractions surrounding the needles, which can feel unpleasant, but is not painful or harmful. In clinical practice patients routinely undergo acupuncture without any need for follow-up, unless a problem arises.

NCS testing is unpleasant to most patients, however holds no health risk. QST is widely considered safe and non-invasive.

7.1. Adverse Events and Serious Adverse Events

Assessment of acupuncture's safety is typically observation based. Adverse events typically occur as a result of treatment or in the few days immediately post-treatment. There are no lab values or other parameters, which could assure acupuncture safety.

An **adverse event (AE)** is defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. Adverse events will be recorded regardless of their relationship to the study intervention.

Examples of unanticipated adverse events involving acupuncture are: infection at the acupuncture needling site, moderate-severe bruising and bleeding at the acupuncture site, moderate-severe pain and discomfort after acupuncture, new onset of weakness or numbness, permanent worsening of carpal tunnel syndrome symptoms.

A **serious adverse event (SAE)** is defined as any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or results in persistent or significant disability/incapacity.

7.2. Subject Follow up and Protection against Risk

All subjects will be given Dr. Dimitrova's contact number and encouraged to report any concerns and complications during the 8-day study period and following completion of the study. In the unlikely event that acupuncture causes lasting discomfort, bothersome ecchymoses, worsening of carpal tunnel and neuropathy symptoms, Dr. Dimitrova will be available for urgent assessment and treatment. If the patient needs further neurologic or other care, they will be referred to Dr. Dimitrova's clinic or to one of the other providers in the neuromuscular division or another appropriate clinician within OHSU. The informed consent will clearly state that a subject may discontinue participation in the study at any time.

As with all human subject investigations at OHSU, any adverse events will be reported to the IRB and there is a Data and Safety Monitoring Plan in place (see details below).

7.3. Adverse Event Tracking and Reporting - Data and Safety Monitoring Plan

There is a Data and Safety Monitoring Plan (DSMP) in place for the IRB-approved study "Local effects of acupuncture on the Median and Ulnar nerves in patients with Carpal Tunnel Syndrome", in accordance with OHSU IRB's recommendations and guidelines.

According to this IRB-approved DSMP, an independent study safety monitor has been appointed – Dr. Tessa Marburger. The independent monitor is a neuromuscular expert and has no conflict of interest and no direct involvement in the study. The research staff will report any unanticipated problems and adverse events to the PI and the independent monitor. The PI will be responsible that the study procedures follow the approved protocol.

The independent monitor will receive a monthly safety report prepared by Dr. Dimitrova. The report will include information on any adverse events, unanticipated problems and protocol

deviations that have occurred each month. Reportable unanticipated adverse events include: infection at the acupuncture needling site, moderate-severe bruising and bleeding at the acupuncture site, moderate-severe pain and discomfort after acupuncture, new onset of weakness or numbness, permanent worsening of carpal tunnel syndrome symptoms and any other adverse events. Additionally, serious adverse events such as death, life-threatening adverse events, inpatient hospitalization, persistent or significant disability/incapacity will be immediately reported to Dr. Marburger and to the IRB. Unanticipated adverse events, as well as inability to tolerate experimental procedures will result in immediate exit from the study.

Unanticipated problems will be reported in accordance with the OHSU procedures and timeframes - within 7 calendar days in case of death and life-threatening events or within 15 calendar days for all other adverse events or unanticipated problems.

8. INTERVENTION DISCONTINUATION

A subject may withdraw consent at any point in the study, as stated in the OHSU Consent-and-Authorization Form. Other reasons for exiting the study include inability to comply with QST due to a cognitive problem, inability to tolerate QST or NCS, inability to tolerate acupuncture or electroacupuncture.

In general, since this is a brief study with only 2 visits, we do not anticipate that many subjects will exit the study. Should a subject exit the study, his/her data will be included in the analysis.

9. STATISTICAL CONSIDERATIONS

9.1. Sample Size Calculation

A mechanistic study of acupuncture, which examines its local, nerve-specific effects using Quantitative Sensory Testing (QST) and Nerve Conduction Studies (NCS) as outcome measures has not been attempted before. Therefore, we estimated acupuncture's effects based on larger studies drawn from the literature. Changes in acupuncture-associated sensation were derived from Lang et al (42) - an evaluation of manual and electroacupuncture- induced analgesia in the legs, using 24 healthy subjects, 12 men and 12 women, in a cross-over design. Effect sizes in Median nerve conduction velocity (NCV) were calculated as clinically relevant changes from the mean NCV reported by Kimura et. al (52) and Di Guglielmo et. al (53). Both studies were NCS characterizations specifically in CTS with 105 and 198 patients respectively and publicized in the AAEM summary statement on electrodiagnostic parameters in CTS (54).

QST testing from the Lang et al (42) acupuncture intervention was observed to be a significant predictor of Cold Detection Threshold (CDT), with a 0.2°C change (-3.6 ± 0.9 °C to -3.4 ± 0.4 °C) seen in the low-frequency-acupuncture treated legs. As this study was conducted in healthy subjects, we expect to see a greater effect of acupuncture on patients with neuropathy, especially as the acupuncture will be administered locally, with greater potential to affect the underlying nerve. Sample size estimation assumed the variance of the change in QST outcomes due to local acupuncture delivery over the Median and Ulnar nerves will be comparable to the variance in QST observed by Lang after acupuncture in healthy nerves ($\sigma^2_{CDT} = 0.696\ (°C)^2$). Under these assumptions, a minimum QST change of 0.35°C, considered reasonable as an on-treatment effect

size in CDT, would be observed as statistically significant at a significance level of α=0.05 with 80% power with 20 subjects per arm.

The pooled parameters of the studies by Kimura et al (52) and Di Guglielmo et al (53) observed a mean Median nerve motor NCV of 47.5 ± 5.76 m/s in their combined cohort of 303 CTS patients. At minimum and assuming the same variance as seen historically (σ^2_{NCV} = 33.2 $(m/s)^2$), an 8% change in NCS (corresponding to a clinically feasible 3.7 m/s change post-intervention) would be considered significant with the same arm size of 20 subjects and at the same significance of α=0.05 and 80% power.

Although estimated from the literature, these on-treatment effect sizes are considered reasonable based on previously collected pilot data in three subjects. When treatment and testing location were matched, a 0.337°C increase in CDT was observed in the Median nerve compared to the Ulnar nerve. Similarly, a Median nerve motor NCV improvement of 3.3 m/s was observed in the wrist. These initial pilot values are encouraging as they agree well with projected on-treatment effect size estimates from the literature.

Specific Aim 1: We expect that the proposed sample size of 20 per acupuncture modality will enable us to see significant treatment-dependent changes in the NCS and QST (CDT, VDT) of the diseased Median nerve within each of the 3 intervention systems (MA, LF-EA, HF-EA).

Specific Aim 2: For the current study, the Ulnar nerve is serving as a healthy control to allow for comparison to the diseased Median nerve post-intervention. Historic studies measuring the local, direct effect of acupuncture on a healthy nerve or studies comparing the local effects of acupuncture on a healthy versus a diseased nerve are not available. With respect to our Specific Aim 2 hypothesis, the Ulnar nerve is serving as a disease-free control condition, wherein acupuncture-dependent change in QST and NCS in the Ulnar nerve is anticipated to be largely negligible as the nerve is already functioning at optimal physiologic parameters. Due to this expectation of negligible treatment effect in the Ulnar nerve, the proposed sample size from Specific Aim 1 (20 subjects per acupuncture modality) is expected to be sufficient for these comparisons within each type of acupuncture. Further, we plan to carry out the Median/Ulnar nerve comparisons separately for each of the 3 intervention modalities. The use of both Median and Ulnar nerves lets the treatment as well as control conditions of interest come from the same subjects, allowing them to serve as their own controls. However, this repetition design warrants the use of mixed-model analysis so the random-effects portion can account for the intra-subject serial correlation expected with repeated measurements.

Specific Aim 3: With regards to the proper sample size for comparison among the 3 types of acupuncture – we based the sample size calculation for each study arm in part on the effect sizes observed by Lang et al (42), who enrolled 24 healthy subjects in 6 groups involving a cross over between manual, low-frequency and high-frequency acupuncture and were able to observe significant differences in QST (CDT) between the 3 acupuncture modalities, p=0.0034. In our current study, the cross-over design is based on the comparisons of Median and Ulnar nerves; however, the individual methods of acupuncture will be populated by different cohorts. For this reason, the random-effects blocking of our mixed- models will have the nerve dependence

grouped by subject but the modality contrasts will be inter-subject and not require a serial correlation correction. With a significant difference observed by Lang et al with groups of n=6, the proposed sample size of 20 per intervention group should be more than sufficient to observe differences among the modalities, even without the explicit cross-over design. Please see statistical analysis plan for further details.

As the goal is to recruit 20 subjects per arm, for a total of 60 study completers, we anticipate the need to screen and enroll approximately 75 subjects, including with baseline nerve conduction studies to confirm the diagnosis of mild-moderate CTS and assure that the electrodiagnostic inclusion criteria for this study are met.

9.2. Stratified Randomization – See section 4.4

9.3. Outcome Measures and Statistical Hypotheses, as outlined in the Specific Aims

Specific Aim 1: Characterize the effects of acupuncture on QST (cold and vibration sensation thresholds) and nerve conduction parameters in the Median and Ulnar nerves.
Hypothesis: Acupuncture will cause decrease in cold and vibration detection thresholds (improve sensation) in the underlying nerve sensory distribution only. Acupuncture will cause NCS changes, characteristic of improved nerve function.
The outcomes generated in this aim will be the baseline and post-acupuncture values of CDT and VDT from Week 1 and Week 2, as well as baseline and post-acupuncture nerve conduction study data from both weeks, consisting of: distal motor/sensory latencies, CMAP and SNAP amplitudes, CMAP area and duration, nerve conduction velocities.

Specific Aim 2: Compare the effects of acupuncture on a diseased nerve (Median) to those of a healthy nerve (Ulnar), using QST (cold and vibration sensation thresholds) and NCS parameters.
Hypothesis: There will be greater change in cold and vibration detection thresholds and NCS parameters in the median nerve compared to the ulnar, due to the lower functional baseline of the median nerve.
The outcomes generated in this aim consist of statistical comparison of acupuncture-induced CDT, VDT and NCS changes in the Median nerve to those in the Ulnar nerve. The Post- minus Pre-acupuncture differences will be compared for the Median and Ulnar nerves in pooled data from all 3 groups, using independent sample t-testing.

Specific Aim 3: Compare the effects of manual acupuncture to those of low-frequency and high-frequency electroacupuncture.
Hypothesis: High-frequency electroacupuncture will have greater effect on NCS, QST followed by low-frequency electroacupuncture and manual acupuncture, in accordance to traditional practices.
Acupuncture-induced changes in CDT, DVT and NCS parameters will be compared among the 3 groups (Post- minus Pre- changes), using ANOVA.

9.4. Statistical Analysis Plan
Primary statistical analysis for all 3 Specific Aims will use linear mixed-effect models to evaluate the effects of treatment group and intervened nerve location on the outcome measures described above. A mixed-model design will be used to create an intention-to-treat framework

and allow for any missing data. Principal assessment will be on the change in outcomes resulting from acupuncture intervention, calculated as the difference in outcomes before and after treatment. These outcomes will include CDT and VDT, distal motor/sensory latencies, CMAP and SNAP amplitudes, CMAP area and duration, nerve conduction velocities (Specific Aim1). Acupuncture characterization will be carried out first in the Median and Ulnar nerves of the arm (Specific Aims 1, 2). In both Median and Ulnar nerve interventions, group will be a three level factor based on the type of acupuncture - MA, LF-EA and HF-EA (Specific Aim 3).

Specific Aims 1 and 2:
As a principal independent variable, location of the intervention will be a four-level factor encompassing the possible combinations of treated and evaluated nerves. For Specific Aims 1 and 2, these levels will be: MM – Median treated and tested, MU – Median treated and Ulnar tested, UM – Ulnar treated and Median tested, and UU – Ulnar treated and tested. A time variable (Week 1, Week 2) will also be included to test for any effects due to order of the treated nerves. Additional covariates known to be associated with QST and NCS outcomes such as age and gender will be corrected for as well. Secondary analysis will include treatment evaluations of outcomes within each location of intervention and additional contrasts between the four time points (pre and post treatment for both Week 1 and Week 2). Persistence of the acupuncture effects will specifically be assessed by comparing changes in outcomes after the first treatment but before the second session.

Another way to characterize the wash-out effect of acupuncture is to compare baseline data from Week 1 and Week 2. We will perform an exploratory analysis to assess for an interaction between location and time, in a mixed linear model. We will incorporate nerve location, evaluation time and the location-time interaction to check for dependencies between Week 1 and Week 2. As stated, the dependent outcomes of all models are the change in QST and NCS from baseline to post-acupuncture. This will allow for a full assessment of washout and carry-over effects with respect both to the nerve location (healthy Ulnar vs diseased Median), time (Week 1 vs Week 2) as well as the order of nerve assessment (the interaction). However, with the repeated nerve measures, it will still be necessary to utilize a mixed-model approach so that the random-effects blocking (nerve location dependent on subject) will allow for the intra-subject serial correlation. For the final model, although exploration of the wash-out effect will be critical, it will pose to be impractical to keep all these covariates in the final model. Only significant time-dependent interactions will be included since the model would otherwise suffer from overfitting due to too many covariates and the limited sample size.

Specific Aim 2: Following completion of Specific Aim 1, we expect to see significant acupuncture effect on the Median nerve (within each acupuncture group). In our proposed mixed linear model for Specific Aims 1 and 2 this would represent MM on the level of each individual group (MA, LF-EA, HF-EA). Conversely, we do not expect to observe a significant effect of acupuncture on the healthy Ulnar nerve as it is already functioning at optimal physiologic level. This would be the UU at the level of each individual group and corresponds to a clinical control. We will conduct direct contrasts between MM and UU as part of the mixed linear model with nerve location, time dependencies and random-effects grouping following the same design as in Specific Aim 1.

Specific Aim 3: We will revise the linear mixed model and focus on the MM factor from Specific Aims 1 and 2 (Median nerve treated and tested). In this revised model we will incorporate acupuncture modality as a 3-factor covariate (MA, LF-EA, HF-EA). Incorporating both the 4-factor sets of nerve intervention/assessment combinations and the 3-factor acupuncture modality would create a very complex model with over 15 variables. As described in the washout analysis, this will lead to overfitting of the model and cause it to be underpowered at 60 subjects. We could run a similar revised mixed liner model analysis substituting UU, UM or MU for MM, although this would be beyond the scope of Specific Aim 3.

Because of the exploratory nature of our analyses, no adjustment for multiple testing will be undertaken. Raw *P* values 0.05 will be regarded as statistically significant. Regardless, the multiple assessments inherent in the exploratory analysis will be discussed in future publications. Statistical analysis will be performed using SAS 9.1 (SAS Institute, Cary, NC).

9.5. Interim Analyses and Stopping Rules

There are no plans to conduct any interim analyses of primary and secondary outcome data prior to study completion. Manuscript and abstract presentations will focus on methodological and descriptive aspects of the study. No final data and safety monitoring plan has been discussed in detail and approved by NCCIH. In the event that such a plan involves a DSMB we propose an adverse event listing report rather than an interim analysis.
Similarly, we do not plan to conduct any futility analyses prior to termination of the study. As this is not a treatment study, but a brief 2-session based mechanistic study futility in the sense of lack of symptomatic improvement of CTS does not carry the same implications because the study consists of 2 visits which are aimed to measure an immediate nerve-specific, local physiologic response, whereas a treatment protocol for CTS typically involves 2 sessions per week over a period of 6-8 weeks and needling of additional acupuncture points than the ones tested in this study.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1. Data Collection Forms and Participant Confidentiality

The research material obtained from all subjects consists of relevant medical history information as part of the screening process, physiologic data such as nerve conduction parameters and sensory threshold values. No research personnel will have access to individually identifiable private information about human subject. Privacy and anonymity will be assured by replacing names and other identifying information with encoded identifiers, with the encoding key kept in a separate secure location. The PI will fill out the Study Screening Form (Appendix A) during screening in the EMG lab or in Neuromuscular clinic. For subject confidentiality, from the time of screening, only a 5-letter name code will be used to identify the subject. No study forms (beside the consent form) will contain a subject's name. A key to 5-letter codes and subject identities will be kept in a password protected document on OHSU's database, which requires network and workstation login. All methods to maintain subject confidentiality will adhere to HIPAA standards. HIPAA Authorization is part of the study consenting process.

All stored electronic data will be kept in password-protected documents, on computers protected by OHSU network password. Paper data will be stored in a locked secure cabinet, away from public access. Data storage will be compliant with all HIPAA and OHSU IRB regulations. All research materials will be used for research purposes only.

Experimental data from Week 1 and Week 2 will be recorded by a blinded investigator – Tabatha Memmott, using the study Data Form (Appendix A). As Ms Memmott will be blinded to the intervention, the acupuncture data – acupuncture points used and modality (MA, LF-EA or HF-EA) will be filled out by the acupuncturist at the end of the study session.

10.2. Data Management

This is a small pilot mechanistic study involving a sample size of 60 subjects. We will not be needing a data management organization or coordinating center. Data entry will be performed by Diana Dimitrova or a trained volunteer, who will not be involved in outcome measure assessment in any other way. They will use the data recorded in the *Data Form* (Appendix A). Data will be stored in a password-protected Excel spreadsheet. Once a subject completes the study, the PI will verify that the Data Form contents are entered correctly as PI will bear ultimate responsibility for data. This Excel spreadsheet be used by the statistician Charles Murchison, MS to conduct study data analysis as outlined above.

10.3. Quality Assurance and Training

All study staff are trained in Protection of Human Subjects, Responsible Conduct of Research and Conflict of Interest as mandated by OHSU's IRB. Staff will be familiar with this study protocol and trained in study procedures in lab practice sessions.

Over the past 1.5 years we have achieved lab consistency and reproducibility and have successfully performed the protocol on 3 pilot subjects. Dr. Dimitrova has undergone training in NCS and QST under the direction of Dr. Jau-Shin Lou, MD, PhD, who was director of the EMG lab during Dr. Dimitrova's fellowship.

10.4. Protocol Deviations

Protocol deviations will be reported to Dr. Dimitrova and recorded. When appropriate, these will be reported to OHSU's IRB and included in DSMP.

10.5. Monitoring

Study monitoring will be performed by NCCIH, who will have access to all study records upon request.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

Subjects can withdraw consent from the study at any point, as outlined in the *OHSU Consent-and-Authorization Form* (Appendix A).

11.1. Institutional Review Board (IRB) Review

This study will be overseen by OHSU's IRB and run in concordance with all IRB regulations and procedures including but not limited to informed consent, HIPAA release authorization,

protection of human subject, responsible conduct of research, conflict of interest and adverse event documentation, reporting and monitoring.

11.2. Informed Consent Forms – see Appendix A and section 4.3

11.3. Inclusion of Women and minorities

Both genders and all ethnicities are included in the study. All minorities are included in our recruitment pools. We anticipate that the ethnic distribution of the study will reflect that of OHSU's clinic population, which is a reflection of the population of Oregon and Southern Washington. So far 2 out of our 3 pilot subjects have been women and 1 of the 3 was Hispanic.

Children will be excluded from the study as Carpal Tunnel Syndrome is exceedingly rare in the pediatric population and children under a certain age cannot sustain attention and focus to be reliable QST reporters.

Patients without English proficiency will also be excluded from the study as QST reporting is a timed test, thus making translation impossible.

11.4. Participant Confidentiality – see 10.1

11.5. Study Discontinuation

This study may be discontinued at any time by the IRB, the NCCIH, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

12. PUBLICATION OF RESEARCH FINDINGS

Any presentation, abstract, or manuscript generated from this study will be made available for review by NCCIH prior to submission. Additionally, NCCAM and Dr. Dimitrova's K23 grant will be acknowledged in all publications.

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14. APPENDIX A – Study Forms

CONTENTS:

SUBJECT 5- LETTER CODE ___ ___ ___ ___ ___ **DATE**_____

Local Effects of Acupuncture and Nerve Conduction Studies
SUBECT SCREENING FORM

EMG Criteria: NEUROMUSCULAR DIVISION ONLY

INCLUSION CRITERIA:

☐ **Mild-moderate CTS - NCS within 2 years AND one of the following:**

- ☐ Prolonged Median distal sensory AND/OR motor latency
- ☐ Reduced Median SNAP amplitude ≥ 50%
- ☐ Median CMAP amplitude (from APB) > 50% of normal

☐ CTS symptoms for **at least 3 months**

☐ **Age 18-75**

EXCLUSION CRITERIA:

☐ **Isolated Median Motor neuropathy**

- ☐ Absence of sensory neuropathy on NCS AND
- ☐ Absence of sensory symptoms

☐ **Severe Carpal Tunnel Syndrome:**

- ☐ Absent SNAP recorded from the second digit AND/OR
- ☐ CMAP amplitude from APB < 50% of normal (< 2.5 mv)

☐ **Martin-Gruber anastomosis**

☐ **Ulnar neuropathy (ipsilateral to CTS)**

☐ **Severe neuropathy symptoms** – unable to tolerate acupuncture or QST

☐ **CTS release surgery**

☐ **Other surgery on the arm or shoulder**

☐ Change in opioid, benzodiazepines, SSRIs or other sedating medications in the **past 2 months**

SUBJECT 5- LETTER CODE ___ ___ ___ ___ ___ DATE_____

SUBJECT SCREENING FORM

Please list your current medications and the doses (if you know them):

_____

_____

_____

_____

_____

_____

_____

_____

_____

EXCLUSION CRITERIA

Check if you have any of the following medical problems/conditions:

☐ Wrist or elbow fracture, past arm trauma, loss of fingers, scarring

☐ Alzheimer's disease or other Mental Disability

☐ Epilepsy

☐ Other condition affecting sensation such as past stroke, Multiple Sclerosis or spinal cord disorder (Please specify) _____

☐ Cardiac Pacemaker

☐ Hospitalization for anxiety or depression in the past 3 months

☐ Other psychiatric condition you are being treated for (Please specify)

_____

☐ Bleeding/Clotting condition

☐ Pregnancy

SUBJECT 5- LETTER CODE ___ ___ ___ ___ ___ **DATE**_____

☐ Arthritis affecting the hands and fingers

☐ Thyroid problems

☐ Past chemotherapy treatment

☐ Use of any experimental medications within the **past 6 months**

☐ Any skin condition in the arm (dermatitis, bruises, weeping skin, skin lesions, infected skin, or necrotic skin)

☐ Have you had a change in your medications in the **past 2 months?**

☐ **Yes** – Please list specify below ☐ **No** (skip to next question)

_____

_____

_____

_____

☐ Have you used any illicit drugs, including marijuana **in the past month**

(Response will be strictly confidential) ☐ Yes ☐ No

☐ List how many (if any) drinks of alcohol you consume per week. List "0" if less than 1 per week.

_____ (Number) of drinks per week

OREGON HEALTH & SCIENCE UNIVERSITY
OHSU
Research Integrity Office
Mail code **L106-RI**
3181 S.W. Sam Jackson Park Road
Portland, Oregon 97239-3098
tel: 503 494-7887 | fax: 503 346-6808

Lay Language Protocol Summary

Principal Investigator: **Alexandra Dimitrova, MD** IRB#: **00008949**

Study/Protocol Title: **Local Effects of Acupuncture on the Median and Ulnar Nerves in Patients with Carpal Tunnel Syndrome**

1. The purpose of this study is to measure the effects of acupuncture on 2 of the large peripheral nerves in the forearm. It will yield data, which may improve our understanding of how acupuncture works.

2. We plan to recruit subjects with a diagnosis of Carpal Tunnel Syndrome from patients in the EMG lab and from the Neuromuscular clinic at OHSU.

3. The purpose of this study is to learn more about the way acupuncture works. Our goal is to apply acupuncture in traditionally used points in the forearm close to the Median Nerve and Ulnar Nerve. We will measure the effect of acupuncture on those nerves, using Nerve Conduction Studies. Nerve Conduction Studies are a non-invasive test, consisting of small electrical stimuli applied to the arm. In clinical practice Nerve Conduction Studies are the gold standard for diagnosing Carpal Tunnel Syndrome. No EMG (needle muscle testing) will be used in this research protocol.

   As another measurement of nerve function, we will use Quantitative Sensory Testing – a precise and non-invasive neurologic assessment of a subject's ability to sense vibration and cold temperature in the hand.

   Week 1:
   The first week's protocol will begin with Nerve Conduction Study and Quantitative Sensory Testing.

   Nerve Conduction Studies are the non-invasive part (with small electric stimulation, but no needles) of a larger test called EMG (electromyography). They consist of delivering small electrical stimuli over peripheral nerves and measuring the speed and magnitude of nerve conduction, so the health of the large peripheral nerves can be examined. Nerve Conduction Studies will be performed on the arm diagnosed with Carpal Tunnel Syndrome.

   Quantitative Sensory Testing is a non-invasive precise measurement of a person's ability to perceive cold and vibration, tested over a small patch of skin on the hand.

   Those subjects whose Nerve Conduction Studies and Quantitative Sensory Testing meet the study's criteria will proceed to acupuncture followed by repeat Nerve Conduction Study and Quantitative Sensory Testing.

Study participants will be randomly assigned to 3 groups - manual acupuncture group, low-frequency electroacupuncture group or high-frequency electroacupuncture group.

Acupuncture consists of the insertion of thin, sterile, single-use disposable needles in the body. Various sensations are experienced during treatment including a distended feeling around the needle site, itching, tingling, a dull ache, burning or heaviness. There is minor discomfort during needle insertion and manipulation. During electroacupuncture 2 acupuncture needles are connected to an electrostimulation machine and thus deliver a very small level electrical current to the tissues. The sensation of electroacupuncture are similar to the ones described above, but may also include painless muscle twitching.

The first visit is expected to last 1:30-2:30 hours, depending on a subject's ability to focus and sustain attention during the Quantitative Sensory Testing.

Week 2:
During the second week acupuncture (the same type as Week 1) will be applied to a different location in the forearm, again followed by Nerve Conduction Studies and Quantitative Sensory Testing.

This session will last 1-2 hours. At the end of the second visit the study will be complete and subjects will be compensated for your time and effort.

4. A 3-page screening form of inclusion/exclusion criteria will be used on enrollment in the study, which will ask questions about past and current medical conditions and medications.

5. All subject identifying information will be removed from the test results. Data from multiple subjects will be combined and analyzed together in order to assess the combined effect of acupuncture on the Median Nerve and the Ulnar Nerve. We will be testing for differences among the manual acupuncture, low-frequency electroacupuncture and high-frequency electroacupuncture groups in the data analysis. The testing results will not be used to guide clinical decisions about patient care.

OREGON HEALTH & SCIENCE UNIVERSITY

MED. REC. NO. _____
NAME _____
BIRTHDATE _____

IRB#: _____

Protocol Approval Date: _____

Clinical Research Consent Summary

Local Effects of Acupuncture on the Median and Ulnar Nerves in Patients with Carpal Tunnel Syndrome

You are being asked to join a research study because you have been diagnosed with Carpal Tunnel Syndrome – a condition affecting the median Nerve in the wrist and causing symptoms such as painful burning, tingling, numbness and sometimes weakness in the hand. You do not have to join the study. Even if you decide to join now, you can change your mind later.

If you decide to join, you will be asked to sign a consent form, which shows you give permission to be in the study, and an authorization form, which shows you give permission for us to use your health information for the study.

1. The purpose of this study is to learn more about acupuncture and its direct effects on the peripheral nerves.

2. In this study, we will learn how acupuncture needles affect 2 peripheral nerves in the arm – the median Nerve and the ulnar Nerve. We want to learn:

    a. Whether acupuncture needles placed in traditionally used acupuncture points have any direct effect on the nearly nerves.

    b. We will test the nerve's function by nerve conduction studies and quantitative sensory testing. Both of these are non-invasive tests and are generally considered safe.

    c. Acupuncture consists of the insertion of thin, sterile, single-use disposable needles in the body. Various sensations are experienced during treatment including a distended feeling around the needle site, itching, tingling, a dull ache, burning or heaviness. There is minor discomfort during needle insertion and manipulation. During electroacupuncture 2 acupuncture needles are connected to an electrostimulation machine and thus deliver a very small level electrical current to the tissues. The sensation of electroacupuncture are similar to the ones described above, but may also include painless muscle twitching.

CO1450

3. This study's investigators are funded by the National Institutes of Health and by OHSU.

4. We do not know whether acupuncture can help improve the function of the peripheral nerves or minimize your carpal tunnel syndrome symptoms.

5. If you join the study, you will have 2 visits at OHSU, 1 week apart. The first visit should last 4-4.5 hours and the second – 3.5-4 hours. At the end of the second visit the study will be complete and you will be compensated for your time and effort.

6. The risks involved in participating in this study are comparable to the general risks of receiving acupuncture, as described above.

7. You may withdraw your consent voluntarily at any point of the study and choose to not undergo further testing.

MED. REC. NO.:_____

NAME:_____

Epic CSN (if applicable):_____

OREGON HEALTH & SCIENCE UNIVERSITY

IRB#: _____

MED. REC. NO. ____
NAME ____
BIRTHDATE ____

Clinical Research Consent Form

TITLE: Local Effects of Acupuncture on the Median and Ulnar Nerves in Patients with Carpal Tunnel Syndrome

PRINCIPAL INVESTIGATOR: Alexandra Dimitrova, MD (503) 494-0744

SPONSOR: NIH/NCCIH

PURPOSE: You are being asked to join a research study because you have been diagnosed with Carpal Tunnel Syndrome – a condition affecting the Median Nerve in the wrist and causing symptoms such as painful burning, tingling, numbness and sometimes weakness in the hand.

The purpose of this study is to learn more about the way acupuncture works. Our goal is to apply acupuncture in traditionally used points in the forearm close to the Median Nerve and Ulnar Nerve and measure the effect of acupuncture on those nerves, using Nerve Conduction Studies, which are identical to the test you underwent when you were diagnosed with Carpal Tunnel Syndrome (consisting of small electrical shocks to the arm). No EMG (needle muscle testing) will be used in this research protocol.

As another measurement of nerve function, we will use Quantitative Sensory Testing – a precise neurologic assessment of your ability to sense vibration and cold temperature in the hand.

This study attempts to measure the effects of acupuncture on 2 of the large peripheral nerves in the forearm. It will yield data, which may improve our understanding on how acupuncture works.

While acupuncture has been shown to help certain patients with neuropathy, including Carpal Tunnel Syndrome, our experimental protocol is somewhat different from typically used acupuncture treatments for Carpal Tunnel Syndrome. It is possible that some of the study participants may feel improvement in their Carpal Tunnel Syndrome symptoms; specifically acupuncture may improve the speed and amplitude of nerve conduction and sensation in the hand. This would be an unintended benefit of the study and is by no means guaranteed. We do not know whether acupuncture applied to the forearm would affect the nerves favorably.

CO1450

This study requires 2 visits to OHSU, 1 week apart. We plan to enroll a total of 60 subjects, who meet the inclusion/exclusion criteria.

PROCEDURES:

Week 1:
The first week's protocol will begin with Nerve Conduction Study and Quantitative Sensory Testing. You have undergone Nerve Conduction Studies as part of your diagnosis of Carpal Tunnel Syndrome. Our procedure will be somewhat shorter. Nerve Conduction Studies are the non-invasive part (with small electric stimulation, but no needles) of the test you underwent when you were diagnosed with Carpal Tunnel Syndrome. Quantitative Sensory Testing is a non-invasive precise measurement of your ability to perceive cold and vibration, tested over a small patch of skin on the hand.

If the results of these tests meet the study inclusion criteria, you will proceed to acupuncture followed by repeat Nerve Conduction Study and Quantitative Sensory Testing. You may be given manual acupuncture, low frequency or high frequency electroacupuncture, depending on the randomization process.

The first visit should last 1:30-2:30 hours, depending on your ability to focus and sustain attention during the quantitative sensory testing.

Week 2:
During the second week acupuncture (the same type as Week 1) will be applied to a different location in the forearm, again followed by Nerve Conduction study and Quantitative Sensory Testing.

This session will last 1-2 hours. At the end of the second visit the study will be complete and you will be compensated for your time and effort.

This is a randomized study. Neither you nor the investigator can choose which modality of acupuncture group you will be assigned to – manual acupuncture, low frequency or high-frequency electroacupuncture.

Your medical record will be reviewed in order to obtain information needed for the study. Specifically, your nerve conduction studies/EMG and current medications will be reviewed, as well as a list of current and past medical conditions.

MED. REC. NO.:_____

NAME:_____

Epic CSN (if applicable):_____

If you have any questions regarding this study now or in the future, contact Dr. Dimitrova at (503) 494-0744. You will not be contacted with results after completion of this study as clinical decisions will not be made on the basis of any of the study results, as this is a study about the mechanism of acupuncture, rather than its treatment effects.

RISKS AND DISCOMFORTS:
Acupuncture delivered by an experienced practitioner is quite safe, however has small risks. These include infection (rare), bruising and bleeding into the tissues (usually small and self-limiting), pain and discomfort, weakness, tiredness, fainting, nausea, aggravation of existing symptoms for a short time. If at any time you experience a stinging, burning or any uncomfortable feeling please let the investigator know so the needle may be adjusted or removed.

There are no known side effects to nerve conduction studies, aside from momentary discomfort during testing. This test is painless and the cold temperatures cannot damage the skin in any way. Quantitative Sensory Testing requires focused attention, but is comfortable and safe, without any known side effects.

Confidentiality risks: Efforts will be made to keep your personal information confidential as described in the CONFIDENTIALITY section, but we cannot guarantee total privacy. There is a small chance that your information could be accidentally released.

BENEFITS:
You may or may not personally benefit from being in this study. However, by serving as a subject, you may help us learn how to benefit patients in the future.

ALTERNATIVES:
You may choose not to be in this study. If you are interested in trying acupuncture as a patient, you may visit OHSU's acupuncture clinic, within the Neurology department.

CONFIDENTIALITY:
We will not use your name or your identity for publication or publicity purposes. A code number will be assigned to you, as well as to information about you. Only the investigators named on this consent form will be authorized to link the code number to you. Other investigators who may be performing parts of the testing and data analysis will be given only the code number, which will not identify you.

Research records may be reviewed and copied by people involved in conducting or overseeing research including the OHSU Institutional Review Board and the Office for Human Research Protections (OHRP). All other parties including employers, insurance companies, and relatives will be refused access to your information unless you provide written permission or unless we are required by law to release it.

We may request your social security number in order to process any payments for participation.

MED. REC. NO.:_____

NAME:_____

Epic CSN (if applicable):_____

COSTS AND COMPENSATION: There will be no cost to you or your insurance company to participate in this study.

During Week 1, Baseline Nerve Conduction Study and Quantitative Sensory Testing will be obtained. If it is determined that you are not a candidate for the acupuncture session, you will exit the study and will be compensated $25 USD.

If you are determined to be a candidate for the acupuncture sessions on Week 1 and Week 2, you will be compensated a total of $75 at the end of your Week 2 visit. If you need to exit the study prior to completion at any other point prior to completion during Week 1 or Week 2, you will be compensated a total of $25.

LIABILITY:
If you believe you have been injured or harmed while participating in this research and require immediate treatment, contact Dr. Dimitrova at (503) 494-0744.

You have not waived your legal rights by signing this form. If you are harmed by the study procedures, you will be treated. Oregon Health & Science University does not offer to pay for the cost of the treatment. Any claim you make against Oregon Health & Science University may be limited by the Oregon Tort Claims Act (ORS 30.260 through 30.300). If you have questions on this subject, please call the OHSU Research Integrity Office at (503) 494-7887.

PARTICIPATION:
If you have any questions regarding your rights as a research subject, you may contact the OHSU Research Integrity Office at (503) 494-7887.

You do not have to join this or any research study. If you do join, and later change your mind, you may quit at any time. If you refuse to join or withdraw early from the study, there will be no penalty or loss of any benefits to which you are otherwise entitled.

You may be excluded from further participation in the study if after the initial testing on Week 1 your results do not meet the study criteria for acupuncture and/or if you are unable to participate in the Quantitative Sensory Testing.

SIGNATURES:
Your signature below indicates that you have read this entire form and that you agree to be in this study.

We will give you a copy of this form.

MED. REC. NO.:_____

NAME:_____

Epic CSN (if applicable):_____

_____
Name of Subject, Printed

Signature of Subject Date

_____
Name of Person Obtaining Consent, Printed

Signature of Person Obtaining Consent Date

MED. REC. NO.:_____

NAME:_____

Epic CSN (if applicable):_____

OREGON HEALTH & SCIENCE UNIVERSITY

MED. REC. NO. ____
NAME ____
BIRTHDATE ____

IRB#: _____

HIPAA CLINICAL RESEARCH AUTHORIZATION

Title of Study:	**Local Effects of Acupuncture on the Median and Ulnar Nerves in Patients with Carpal Tunnel Syndrome**
Name of Principal Investigator:	**Alexandra Dimitrova, MD**
Phone Number:	**(503) 494-0744**

We have already asked you for your consent to be in the research study. We are also required to seek separate permission to use your health information for the study. The Health Insurance Portability and Accountability Act (HIPAA) is a federal law designed to help protect the privacy of health information.

During this study, OHSU will use and disclose (release) health information about you. Under federal law, we may not use or disclose it unless you authorize us to do so by signing this form. This authorization is voluntary. You do not have to sign this form. If you choose not to sign it, you cannot join this study.

The health information we will collect, use, and disclose is described in the attached consent form. The consent form also describes why we will use the health information. Investigators, study staff, and others at OHSU who are involved in the research or overseeing the research may use and disclose your health information.

We may send your health information to others outside OHSU who are involved in the research or overseeing the research, including:

- The Office for Human Research Protections, which oversees research involving humans

When we send information outside of OHSU, it may no longer be protected under federal law. In this case, your information could be used and re-released without your authorization.

We may continue to use and disclose your health information indefinitely.

You have the right to withdraw this authorization at any time. To withdraw your permission for us to use information that identifies you, please send a written request or email to:

Alexandra Dimitrova, MD
Mail Code: CR 120

CO1450

3181 S.W. Sam Jackson Park Road
Portland, OR 97239-3098
Tel. (503) 494-0744
e-mail: dimitroa@ohsu.edu

The use and disclosure of your health information for this research will stop as of the date the principal investigator receives your request. However, the use and disclosure of information collected in good faith before your request arrives will continue. Withdrawing this authorization will not affect your health care or your relationship with OHSU.

Please ask the investigator or study staff if you have any questions about this HIPAA authorization.

We will give you a copy of this signed form.

_____
Name of Subject, Printed

Signature of Subject Date

_____
Name of Person Obtaining Authorization, Printed

Signature of Person Obtaining Authorization Date

MED. REC. NO.:_____

NAME:_____

Epic CSN (if applicable):_____

SUBJECT 5- LETTER CODE ___ ___ ___ ___ ___ **DATE**_____

__ **WEEK 1** ___**WEEK 2**

Local Effects of Acupuncture on the Median and Ulnar Nerves
DATA FORM

BASELINE **Temperature**_____

COLD Detection Threshold

MEDIAN	ULNAR
#1 _____	#1 _____
#2 _____	#2 _____
#3 _____	#3 _____
Average _____	**Average** _____

VIBRATION Detection Threshold **Temperature**_____

MEDIAN	ULNAR
#1 _____	#1 _____
#2 _____	#2 _____
#3 _____	#3 _____
Average _____	**Average** _____

NERVE CONDUCTION STUDIES **Temperature**_____

MEDIAN Motor

Supramax CMAP Amplitude WRIST _____ ELBOW_____
CMAP Area WRIST _____ ELBOW_____
NCV_____
Distal Motor Latency WRIST _____ ELBOW_____
Duration (Wrist) _____ (Elbow) _____

ULNAR Motor

Supramax CMAP Amplitude WRIST _____ ELBOW_____
CMAP Area WRIST _____ ELBOW_____
NCV_____
Distal Motor Latency WRIST _____ ELBOW_____

SUBJECT 5- LETTER CODE ___ ___ ___ ___ ___ **DATE**_____

__ **WEEK 1** ___**WEEK 2**

Duration (Wrist) _____ (Elbow) _____

MEDIAN Sensory 2nd Digit **Temperature**_____

Supramax SNAP Amplitude _____

SNAP Area _____

NCV Wrist _____

Distal Sensory Latency 1) _____ 2) _____

ULNAR Sensory 5th Digit

Supramax SNAP Amplitude _____

SNAP Area _____

NCV Wrist _____

Distal Sensory Latency 1) _____ 2) _____

ACUPUNCTURE SETTING **START TIME**_____ **Temperature**_____

ACUPUNCTURE POINTS _____

__ Manual

__ Low-frequency

__ High-frequency

POST-ACUPUNCTURE MEASUREMENTS **Temperature**_____

COLD Detection Threshold

MEDIAN	ULNAR
#1 _____	#1 _____
#2 _____	#2 _____
#3 _____	#3 _____
Average _____	**Average** _____

VIBRATION Detection Threshold **Temperature**_____

MEDIAN	ULNAR
#1 _____	#1 _____
#2 _____	#2 _____
#3 _____	#3 _____
Average _____	**Average** _____

SUBJECT 5- LETTER CODE ___ ___ ___ ___ ___ DATE_____

__ WEEK 1 ___WEEK 2

NERVE CONDUCTION STUDIES **Temperature_____**

MEDIAN Motor

Supramax CMAP Amplitude WRIST _____ ELBOW_____
CMAP Area WRIST _____ ELBOW_____
NCV_____
Distal Motor Latency WRIST _____ ELBOW_____
Duration (Wrist) _____ (Elbow) _____

ULNAR Motor

Supramax CMAP Amplitude WRIST _____ ELBOW_____
CMAP Area WRIST _____ ELBOW_____
NCV_____
Distal Motor Latency WRIST _____ ELBOW_____
Duration (Wrist) _____ (Elbow) _____

Median Sensory 2nd Digit **Temperature_____**

Supramax SNAP Amplitude _____
SNAP Area _____
NCV Wrist _____
Distal Sensory Latency 1) _____ 2) _____

Ulnar Sensory 5th Digit

Supramax SNAP Amplitude _____
SNAP Area _____
NCV Wrist _____
Distal Sensory Latency 1) _____ 2) _____