Study Name	Randomized Controlled Clinical Trial of Non-invasive Device to Alleviate Carpal Tunnel Syndrome
Short Title	Non-invasive CTS Device Clinical Trial
Study ID	PPS-CTS-SBIR2
Ver. / Date	3 / 2018 December 20
Sponsor	**Pressure Profile Systems (PPS)** 5757 W Century Blvd, Ste 600, Los Angeles, CA 90045
Funded By	National Institute of Biomedical Imaging and Bioengineering (NIBIB) SBIR, R44 EB024713-01

Approvals

Name	Title	Signature and Date
Jae Son	CEO/Founder, PPS	**Feb 5, 2018**
Pauline Luong	Clinical Research Manager	 signed 5/9/19 but protocol v3 IRB-approved 1/2/19

Study Name	Randomized Controlled Clinical Trial of Non-invasive Device to Alleviate Carpal Tunnel Syndrome
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INVESTIGATOR'S SIGNATURE PAGE

I agree to:

1. Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations.

1. Maintain all information in confidence and, when this information is submitted to an Institutional Review Board (IRB), Independent Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety and I agree to all aspects.

_____	_____	_____
Investigator Printed Name	Signature	Date
_____	_____	_____
Investigator Printed Name	Signature	Date
_____	_____	_____
Investigator Printed Name	Signature	Date
_____	_____	_____
Investigator Printed Name	Signature	Date

Acknowledged By:

_____	_____	_____
Sponsor Representative, Printed Name	Sponsor Representative, Signature	Date

Send signed/dated Investigator's Signature Page to Sponsor

TABLE OF CONTENTS

1. Personnel & Facilities

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2. Protocol Summary

2.1. Study Synopsis

Title	Randomized Controlled Clinical Trial of Non-invasive Device to Alleviate Symptoms of Carpal Tunnel Syndrome
Study Description	Sham-controlled, multi-center and remote patient-centered randomized controlled clinical trial to investigate the efficacy of a novel non-invasive, unobtrusive study device in reducing symptoms of carpal tunnel syndrome (CTS). Daily wear of the study device is expected to significantly reduce symptom severity (evaluated by the Boston Carpal Tunnel Questionnaire) in mild to severe CTS-diagnosed patients. Subjects are randomized into the active device group or sham group for 8 weeks, then followed for 12 weeks post-treatment.
Objectives	Primary: Investigate whether daily wear of the study device significantly reduces patient-reported CTS symptom severity. Secondary: Determine whether there is a difference between the active device group and sham group. Investigate whether changes in symptoms are sustained or continue post-treatment.
Endpoints	Primary: BCTQ-SSS of the treatment group at 8 weeks compared to Baseline. Secondary: BCTQ-SSS at 8 weeks and at post-treatment timepoints between the treatment and sham groups
Study Population	Sample size: 102 (51 in each arm) Adults diagnosed with mild to severe CTS, ages 21-65 of any gender Any geographic location within the United States
Phase	Confirmatory/pivotal
Sites	At least 3 physical sites located in the United States (national enrollment)
Study Device	Stiffness-optimized thermoplastic curved band that has a strong biocompatible adhesive in the center of the concave side of the device. Device is designed to decompress the median nerve and thus relieve symptoms of carpal tunnel syndrome.
Study Duration	Approximately 12 months
Participant Duration	5 months

2.2. Schedule of Events (SOE)

Schedule of Events Table – Active Device Group

	Treatment Period (8wk)					Post-Treatment Period (12wk)					
Wks Into Study	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**
Enrollment[1]	X*										
NCS[2]	X*										
BCTQ[3]	X*	X*	X*	X*	X*		X*		X		X
Follow-up[4]		X*	X*	X*	X*		X*		X		X
Usage Diary[5]		X*	X*	X*	X*						
User Survey[6]					X*						
Day	**0**	**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**

Schedule of Events Table – Sham Device Group

	Treatment Period (8wk with Sham Device)					Post-Rx Period		Treatment Period (8 wk with Active Device)			
Wks Into Study	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**
Enrollment[1]	X*										
NCS[2]	X*										
BCTQ[3]	X*	X*	X*	X*	X*		X*	X	X	X	X
Follow-up[4]		X*	X*	X*	X*		X*	X	X	X	X
Usage Diary[5]		X*	X*	X*	X*			X	X	X	X
User Survey[6]					X*						X
Day	**0**	**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**

** = required*

1 - Enrollment includes completing ICF and baseline questions (eligibility check, CTS diagnosis/history, randomization, demographics, medical history)

2 - NCS within 24 months required to enroll

3 - BCTQ incorporated into Follow-up Surveys

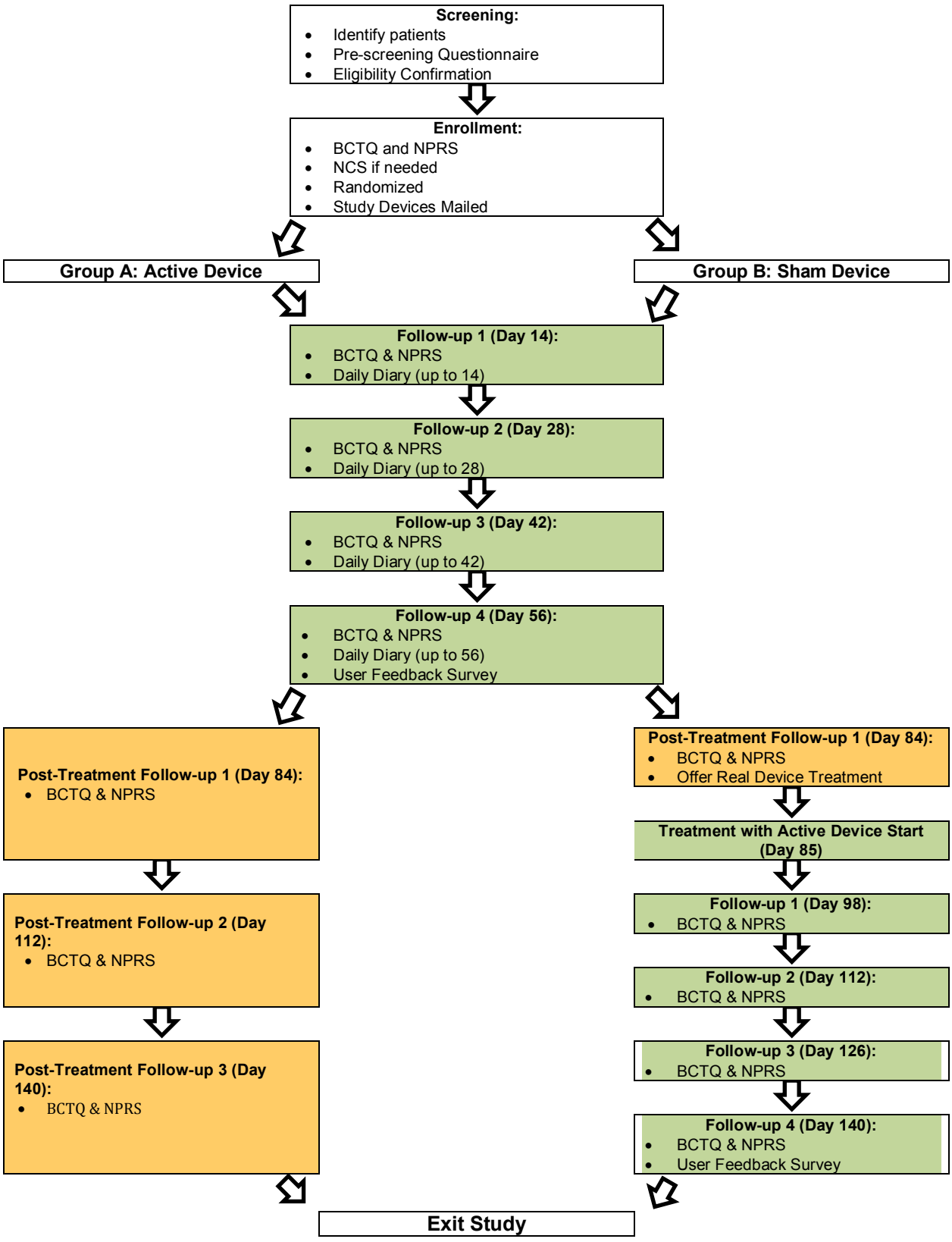
4 - Follow-up Surveys completed by patient online

5 - Usage Diary completed online by patient DAILY

6 - User Feedback Survey (feedback on design and use of device) completed by patient online.

2.3. Study Procedures Flow-chart

See next page


Screening:
Identify patients
Pre-screening Questionnaire
Eligibility Confirmation
Enrollment:
BCTQ and NPRS
NCS if needed
Randomized
Study Devices Mailed
Group A: Active Device
Group B: Sham Device
Follow-up 1 (Day 14):
BCTQ & NPRS
Daily Diary (up to 14)
Follow-up 2 (Day 28):
BCTQ & NPRS
Daily Diary (up to 28)
Follow-up 3 (Day 42):
BCTQ & NPRS
Daily Diary (up to 42)
Follow-up 4 (Day 56):
BCTQ & NPRS
Daily Diary (up to 56)
User Feedback Survey
Post-Treatment Follow-up 1 (Day 84):
BCTQ & NPRS
Post-Treatment Follow-up 2 (Day 112):
BCTQ & NPRS
Post-Treatment Follow-up 3 (Day 140):
BCTQ & NPRS
Post-Treatment Follow-up 1 (Day 84):
BCTQ & NPRS
Offer Real Device Treatment
Treatment with Active Device Start (Day 85)
Follow-up 1 (Day 98):
BCTQ & NPRS
Follow-up 2 (Day 112):
BCTQ & NPRS
Follow-up 3 (Day 126):
BCTQ & NPRS
Follow-up 4 (Day 140):
BCTQ & NPRS
User Feedback Survey
Exit Study

3. INTRODUCTION

3.1. Background & Rationale

Carpal tunnel syndrome (CTS) is one of the most common peripheral neuropathies and the most well-known workplace repetitive stress injury.[1-4] The carpal tunnel is located at the wrist and is composed of the eight carpal bones and the transverse carpal ligament. The median nerve travels through the carpal tunnel at the wrist and may become entrapped due to inflammation, awkward wrist postures, repetitive hand motions, or other causes. Compression impairs normal median nerve function, which leads to paresthesia, pain, numbness, and other symptoms in the distribution of the median nerve. Chronic compression may lead to irreversible nerve damage, significant impairment of hand function, and muscle atrophy.[1,4]

Commonly, CTS is first addressed with conservative treatment options, including wearing wrist braces or splints, lifestyle changes, or the use of oral non-steroidal anti-inflammatory agents (NSAIDs).[3-6] Although wrist splints are prescribed at night and as much as possible during the day, fulltime compliance is poor.[7] Patients may elect to receive a steroid injection into the wrist, but the procedure is hazardous[3] and the effects are short-term. Repeat injections are not recommended.

Severe cases of CTS are often referred directly to surgery to prevent further nerve damage. Approximately 70-90% of carpal tunnel release (CTR) surgeries have good to excellent long-term outcomes,[4] but, like all operations, there are risks associated with CTR surgery. Some of these risks include injury to the median nerve, its branches, vessels or tendons; infection; and scar sensitivity.[8] In a review of 186 CTR cases, about 24% of patients experienced mild residual symptoms and 8% experienced recurrent or persistent problems.[3]

The shortcomings of current conservative treatment options and the fear of invasive procedures, scarring, or return of symptoms after surgery motivate several patients to explore other conservative, non-invasive treatment options.

3.2. Study Device

The study device is a stiffness-optimized thermoplastic curved band that has a strong biocompatible adhesive in the center of the concave side of the device. Similar to other non-invasive devices for CTS, the study device is a Class I device that requires Food and Drug Administration (FDA) registration but does not require 510(k) clearance.

Unlike the majority of traditional and dynamic splints, the study device was developed to decompress the median nerve without excessive applied force and cumbersome usage requirements. The design of the study device allows for free movement of the wrist with minimal impediment of daily activities.

The study device is indicated for people who have been diagnosed with mild to severe carpal tunnel syndrome. It is fit to the subject based on the criteria in the Instructions for Use.

The sham device is similar to the active study device but with a conformable cushion attached to the underside to prevent the main mechanism of action. Neither the sham nor the active study device contain any medicinal substances or electromagnetic properties that could affect human tissue.

The active study device and the sham device should be stored at room temperature.

3.3. Potential Risks & Benefits

3.3.1. Known Potential Risks

Immediate risks related to the device include skin irritation or reaction to the adhesive used on the device, and discomfort related to any forces that the device applies to the wrist.

Previous studies have found the study device can be worn for over 12 hours with little to no discomfort and minor to no redness.[9]

The sham device is the same as the active device but with a cushion on the underside. This cushion is similar to sponges used for make-up or healthcare applications.

3.3.2. Known Potential Benefits

Prolonged wear (anywhere from 1 week to 4 weeks) of the study device may reduce symptoms of CTS.[9]

The sham device may cause a placebo effect and reduce symptoms of CTS as well.

4. Objectives & Endpoints

Objective	Endpoints	Explanation
Primary		
Investigate whether daily wear of the study device significantly reduces patient-reported CTS symptom severity.	Symptom Severity Score (SSS) of the Boston Carpal Tunnel Questionnaire (BCTQ) in the treatment group at 8 weeks compared to Baseline.	The SSS is a validated combined measure of the patient's perception of the level and frequency of pain, numbness, tingling caused by CTS. 8 weeks is the end of the treatment period.
Secondary		
Determine whether there is a difference between the active device group and sham group.	Comparing SSS at 8 weeks and between the active device group and sham group.	Between group comparison conducted for the primary outcome variable at the primary endpoint (8 weeks).

Additionally, we will determine if this difference continues post-treatment.	Comparing SSS 1 month post-treatment (12 weeks) between the active device group and sham group.	Single timepoint at 12 weeks compared between groups for post-treatment analysis.
Exploratory		
Does CTS symptom improvement occur before 8 weeks?	Significant reduction in SSS compared to Baseline at any time point before 8 weeks.	Identification of significant SSS reduction before 8 weeks suggests a shorter minimum duration of wear.
Do unilateral and bilateral CTS patients respond differently to treatment?	Change in SSS at 4 and 8 weeks in a unilateral subgroup compared to a bilateral subgroup.	Unilateral patients showed significant SSS improvement in the pilot study, whereas bilateral patients seemed to show none.[9] Both 4- and 8-week timepoints compared in case a difference is seen before the end of treatment.
Do patients respond differently based on Baseline severity?	Change in SSS at 4 and 8 weeks in mild, moderate, and severe subgroups.	AANEM guidelines categorize CTS into 3 severity groups.
Describe the effect of study device treatment on patients with hormonal-induced CTS, such as pregnancy.	Change in SSS at or within 8 weeks in a subgroup of pregnant women.	The study device is hypothesized to work primarily for repetitive stress induced CTS. Pregnant women often develop CTS due to swelling of the tissue.
Demonstrate high subject compliance.	Diary wear time responses. Number of dropouts due to non-compliance.	Compliance is measured by adherence to daily wear and actual vs advised wear time.
Obtain user feedback on the comfort, use, and design of the study device.	User Feedback Survey responses at the end of Treatment Period	Collects qualitative data on practical aspects of the device.

5. Study Design

5.1. Overall Design

It is hypothesized that daily wear of the study device will result in significant improvements in patient-reported symptom severity. It is also hypothesized that the effects from active study device treatment will be significantly greater than effects from sham treatment. In both cases, it is hypothesized that improvements will be sustained post-treatment.

This study is designed as a randomized, double-blind, sham-controlled, two-arm trial consisting of an eight-week treatment period (active study device or sham), followed by one required follow-up four weeks later (at week 12). After the required follow-up evaluation, the active device group can optionally continue to report symptom changes for an additional 8 weeks. The sham group participants can elect to wear the active study device for 8 weeks after completing their week 12 follow-up evaluation of the sham device. For both groups, completion through the optional follow-ups results in a 5-month patient duration.

There are two study groups: the active device group receiving the active study device and the sham group receiving a non-active sham device. Subjects will be informed that they have a 50:50 chance of receiving treatment or a sham. They will also be informed that if they receive sham device, they will be offered the active device 4 weeks into the post-treatment period. However, all subjects will not know what treatment they are on until the conclusion of the trial. Study devices are shipped directly to enrolled subjects from the Sponsor's designated shipping associate, which blinds site staff to group assignment.

There are (at minimum) three physical research sites but subjects are primarily enrolled remotely. The physical research sites are clinics that local subjects can physically go to if needed (e.g., medical concern, AE). Enrolled subjects are assigned to the PI of the geographically closest physical site.

Subjects are enrolled following confirmation of CTS in one or both wrists via a recent Nerve Conduction Study (NCS) and are asked to wear the assigned device daily for 8 weeks. The NCS is an electrodiagnostic technique used to confirm clinical diagnosis of CTS, with a 56% to 85% sensitivity and at least 95% specificity for CTS.[15] The primary outcome measure, Symptom Severity Score (SSS) of the Boston Carpal Tunnel Questionnaire (BCTQ), is evaluated at:

- Baseline
- Once every 2 weeks during the 8-week treatment period
- 4 weeks after the end of treatment (at week 12)

After week 12, the active device group can continue to complete follow-ups every 4 weeks for another 8 weeks. At the end of week 12, the sham group will be given the opportunity to wear the active study device for 8 weeks. These subjects will be evaluated once every 2 weeks during an 8-week treatment period with the active study device (similar to the initial treatment period).

For visual representation of the study design, see Section 2.2 Schedule of Events (SOE).

5.2. Scientific Rationale

The study device was used in a pilot clinical trial (PPS-CTMD-15-001, ClinicalTrials.gov ID NCT02534493) that finished in October 2016 with promising results. Participants showed an average improvement in symptom severity scale (SSS) score of the Boston Carpal Tunnel Questionnaire (BCTQ) of 0.59 ± 0.68 points at 4 weeks (end of treatment period) compared to baseline SSS scores. After the 4-week treatment period, symptoms continued to improve for a total of 0.79 ± 0.74 points lower SSS compared to Baseline at 12 weeks.[9] These results motivate the primary objective of this study.

The pilot study investigated the effects of the study device up to 4 weeks, but the trajectory of SSS did not indicate that improvement plateaued by 4 weeks. Thus, the treatment period is extended to 8 weeks in this study to determine if improvements continue with longer-term wear.

Analysis of the unilateral vs bilateral CTS patients showed a stark contrast in response. SSS of the unilateral patients improved 0.9 ± 0.5 points at 4 weeks and up to 1.2 ± 0.5 points at 12 weeks. In contrast, the bilateral patients appeared to show no improvement; however, the pilot study was not powered to detect differences in unilateral and bilateral subgroups. This difference is being explored as an exploratory objective in this study.

Most participants described the study device as being very comfortable and easy to wear. However, there were occasional comments about discomfort from the edges of the device. In Aim 1 of the NIBIB grant R44 EB024713-01, a series of experiments were conducted to investigate the applied pressures on wrists using tactile pressure sensors, the changes in median nerve dimensions using magnetic resonance imaging (MRI), and the changes in carpal tunnel or median nerve compression pressures in cadavers when the study device was applied to the wrist. This allowed the study device to be re-designed to fit a wider range of people and to reduce uncomfortable pressure points. A user feedback survey is incorporated in the present study to improve user satisfaction, which is critical for any practical application and success.

6. STUDY POPULATION

The study population includes adults ages 21 to 65 of all races and ethnicities and of both genders who meet the inclusion/exclusion criteria below. We expect to recruit at least twice as many women as men because studies have found that approximately 3 times as many women are affected by CTS as men.[10,11]

6.1. Inclusion Criteria

1. Ages 21-65
2. Clinically diagnosed with mild to severe carpal tunnel syndrome (CTS)
3. CTS diagnosis confirmed by a nerve conduction study (NCS) performed within the past 24 months OR at enrollment/baseline visit
    a. CTS severity determined via AANEM criteria[13]
    b. Bilateral CTS accepted (worse wrist via NCS and/or BCTQ is designated as the study wrist)

4. BCTQ SSS $\geq$ 2
5. Reliable access to and ability to use Internet, Wi-Fi, or mobile data through computers, mobile devices, laptops, and/or tablets
6. Willing to abstain from any other treatment or therapies for CTS throughout the study
7. Ability to read and write English, or has a reliable person to assist with reading and writing English

6.2. Exclusion Criteria

1. Other upper extremity neuropathies (e.g., epicondylitis, radial nerve neuropathies, ulnar nerve neuropathies)
2. Double crush syndrome
3. Cervical stenosis
4. Brachial plexopathy
5. Wrist fractures or cysts
6. Prior wrist surgeries, especially carpal tunnel release surgery
7. Injection of corticosteroid/cortisone into the wrist or hand within the past 6 months
8. Thyroid disease
9. Rheumatoid arthritis
10. Diabetes
11. Systemic diseases
12. Connective tissue diseases
13. Fibromyalgia or chronic pain syndrome
14. Diabetic neuropathy
15. BMI $\geq$40
16. Participation in other research studies or clinical trials currently or within the past 2 weeks.

6.3. Prior/Concomitant Medications or Therapies

1. No other therapies for carpal tunnel syndrome may be undertaken during the study (e.g., hand therapy, wearing wrist brace/splint, corticosteroid/cortisone injection to the wrist, carpal tunnel release surgery).
2. Hand stretching exercises and stretches indicated for carpal tunnel syndrome are allowed.
3. Yoga, tai chi, and other fitness programs often associated with helping with carpal tunnel syndrome are allowed but should be reported.
4. No narcotics, opioids, or other prescription painkiller or pain medication may be taken during the study and must not have been taken for 3 months prior to enrollment.
5. Over-the-counter low-dose NSAIDs or painkillers (e.g., Advil, Tylenol) are allowed if taken only as needed (e.g., to relieve pain caused by injuries, migraines, period cramps, menstrual pain) and taken no more than the recommended doses on the medication's label (e.g., no more than 6 tablets in 24 hours).
6. Pain creams should not be applied to the wrist where the device is applied.

6.4. Enrollment Determination

Subjects that pass the inclusion/exclusion criteria, have provided or completed a NCS report confirming mild to severe CTS diagnosis, and have signed the Informed Consent Form (ICF) are considered enrolled in the study.

6.5. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical trial (i.e., sign the ICF) but are not subsequently randomized to a study intervention or enrolled. Some reasons for not enrolling after signing the ICF include the subject deciding not to participate or the discovery of disqualifying criteria after signing the ICF.

In certain cases, a subject may need an NCS performed under their primary care provider after having signed the ICF. If the NCS report does not meet the inclusion criteria, the subject is not enrolled and is categorized as screen failure.

6.6. Strategies for Recruitment & Retention

Each site will advertise and recruit subjects per each site's best practices and following applicable GCP, HIPAA, and all local to federal laws. Recruitment may be supplemented with IRB-approved physical advertisements such as flyers or cards and with IRB-approved digital advertisements on webpages and social media. Sponsor may supply advertising and marketing materials at Sponsor's discretion or as needed by the sites.

Sites may identify eligible subjects from their patient or volunteer databases or from their (electronic) medical records. Physicians at each site may identify eligible subjects during routine appointments, at which point the physician should offer information about the study to the patient. Sites may also obtain referrals from nearby or partner clinics.

Before enrollment, all subjects are informed that there is a 50/50 chance of receiving the real device or the sham device. However, the sham group will be given the opportunity to undergo treatment with the real device upon completion of the main part of the trial (after Week 12). This method seeks to increase fairness of participation and improve retention of sham group participants.

7. STUDY PROCEDURES

7.1. Screening, Informed Consent and HIPAA

Subjects that pass the pre-screening questionnaire and meet all inclusion/exclusion criteria will be asked to participate in the study. The study design, objective, procedures, schedule, and participation parameters/criteria will be provided to and/or discussed with subjects prior to enrollment. Subjects wishing to participate must read and complete the Informed Consent Form (ICF) and sign an "Authorization for Use and Disclosure of Health Information for Research" release as a component of the ICF (HIPAA authorization) prior to undergoing any study-related procedures.

The ICF/HIPAA Authorization may be sent electronically to the subject. Subjects and designated site staff may sign electronically or can physically sign but must provide a scanned signed copy ICF/HIPAA Authorization to the site for documentation.

Documentation of screening, eligibility confirmation, and reasons for ineligibility or non-participation will be kept in a Screening Log.

7.2. Enrollment, Baseline Assessment, and Randomization

7.2.1. Enrollment Procedures

After the subject has passed the pre-screening questionnaire, the subject will begin enrollment, which includes reading and signing the ICF/HIPAA Authorization, completing the Enrollment Form which includes the BCTQ and NPRS, and confirmation of CTS diagnosis via NCS. After confirming meeting all inclusion/exclusion criteria, the subject is considered enrolled. The subject will be randomized into either the active device group or the sham group and assigned a Subject ID.

Once the subject is enrolled, study devices are shipped (expedited) to the subject to begin treatment as soon after enrollment as possible. If a subject is bilateral, only the worse wrist (via NCS severity and/or SSS score) will be treated during the study. If NCS severity and/or SSS score are the same for both wrists, the dominant wrist will be treated. Standardized training and instructional materials will be provided to the subject on how to use the study devices, how and when to complete surveys, Diaries, etc.; how and when to report AE's/SAE's; and how to contact site staff or PI.

7.2.2. Subject ID Assignment

Subjects will be assigned a unique identification code (Subject ID). The subject ID is unique across all sites. After the subject is enrolled in the study, all forms will refer to the subject with the Subject ID and not the subject's name. Each site will maintain an Enrollment Log linking identity of study subjects to the Subject IDs.

7.2.3. Baseline Assessment

The Enrollment CRF captures Baseline assessment measures. These include:

- Date of birth/age
- Gender
- CTS severity (mild, moderate, or severe, from NCS)
- CTS diagnosis by hand (unilateral/bilateral, right/left/both)
- BCTQ and NPRS for affected hand(s)

7.2.4. Randomization

There are two treatment groups: active study device or sham device. Subjects will be equally randomized across all sites to ensure equal and equivalent active device and

sham groups. Randomization will occur using a Sponsor-supplied randomization tool or using the randomization module of the Electronic Data Capture (EDC) platform.

7.3. Treatment Period

The Treatment Period begins the first day that the subject begins wearing the device. Electronic Diaries are sent to subjects every day from the first day of treatment for 56 days. Subjects should be reminded if (s)he does not complete an entry. If 3 or more consecutive diary entries are missed, the site should contact the subject to remind them to complete entries or they could be withdrawn from the study. No more than 3 consecutive Diary entries and no more than 25% of total entries should be missed (14 out of 56 diary entries), but withdrawal due to missed Diary entries will be up to Sponsor after evaluating the situation

Follow-up surveys are electronically sent to subjects every 2 weeks from the subject's first day of device wear up to 8 weeks. The subject should complete the surveys within 3 days and reminders should be sent if the subject does not complete the survey. If the subject does not complete the survey within 3 days, the site should follow up with the subject to remind them to complete the survey and address any issues preventing the subject from completing the survey. All subject correspondences and contact attempts should be documented.

On the last day of treatment, the subject will complete a User Feedback Survey. This should be completed within 5 days.

7.4. Post-Treatment Period (Active Study Device Group)

After the 56th day of treatment (end of Week 8), subjects will stop wearing the device. A post-treatment follow-up will then occur 4 weeks after the last day of treatment (Week 12). Survey completion and reminder timelines are the same as for the Treatment Period Follow-up Surveys above.

Subjects in the treatment group will be exited after the last day of the Post-Treatment Period (end of Week 12) and after they have completed all required surveys and follow-ups. See Section 7.6 Exit Procedures.

7.5. Post-Treatment Period (Sham Device Group)

After the 56th day of treatment (end of Week 8), subjects will stop wearing the device. A post-treatment follow-up will then occur 4 weeks after the last day of treatment (Week 12). The sham group will be offered the active study device at this point. If the subject agrees, then (s)he will wear the active study device daily for an additional 8 weeks and complete Follow-up Surveys biweekly and Diary entries daily. On the last day of treatment (Week 20), the subject will complete a User Feedback Survey.

If the subject decides not to test of the active study device, then the subject will be Exited from the study.

7.6. Exit Procedures

Exit procedures will only occur after the assigned site has ensured the subject has completed all required assessments and follow-ups. The assigned site staff member will complete the Exit CRF.

An Exit CRF must be completed for any subject that has signed the ICF and is being withdrawn for any reason.

7.7. Subject Withdrawal

Potential reasons for withdrawal or removal of subjects are outlined below:

- Subject decides it is in his/her best interest to withdraw
- Principal investigator decides it is in the subject's best interest to withdraw
- Subject is noncompliant during the 12-week treatment period (i.e., Sponsor deems subject has missed too many Diary entries or Follow-ups).
- Subject is lost-to-follow-up at any point (more than 5 documented attempts to contact and ask to complete follow-ups with no response after 3 weeks)
- Subject fails to refrain from other CTS treatments or therapies.

If the subject is withdrawn, the PI or designated staff member must fill out the Exit Form and document the reason for withdrawal or removal of the subject from the study. Unless the subject requests removal of their data, any data or information collected from the subject will remain in the database and analyzed at the sponsor's discretion.

8. Study Supplies

8.1. Study Device Supply

A designated Sponsor employee independent from the clinical trial will be delegated authority for shipping supplies to enrolled subjects (heretofore referred to as "Shipping Associate"). This individual will not reveal any PHI or PII to the other Sponsor employees involved in the clinical trial.

Once a subject is enrolled, the Shipping Associate will be informed of the type of devices to ship (active device or sham), quantity, and the name and address to ship to. The Shipping Associate will expedite the package to the newly enrolled subject.

If subject has not received devices by the expected delivery date, site staff must contact the Shipping Associate to re-send the package. Shipment and Confirmation Logs will be kept by the sites.

8.2. Study Device Reconciliation and Destruction

Subjects are asked to retain all used and unused study devices throughout the Treatment Period. At the end of the Treatment Period, or otherwise determined by the Sponsor, subjects will be asked to return all used and unused study devices by mailing the devices using supplied shipping materials.

Number of lost, used, and unused devices will be reconciled for each subject.

The Sponsor will retain devices. Device destruction or disposition is at the discretion of the Sponsor.

8.3. Other Study Supplies

Study-related documents, investigator binders, study subject binders, and project trial binders will be provided by the sponsor. Other supplies will be supplied as needed and negotiated by site.

9. SAFETY ASSESSMENTS

9.1. Specification of and Methods for Collecting Safety Parameters

Subjects will be able to report safety concerns on their surveys and Diaries. Subjects may also contact their assigned site staff directly with safety concerns. Subjects will be instructed to report any safety concern or medical event including injury, sickness, hospitalization or other adverse event that occurs during their involvement in the study.

9.2. Adverse Events and Serious Adverse Events

An adverse events (AE) is any unexpected medical problem experienced by the subject that occurs during treatment or during the study that may or may not be associated with the treatment.

A serious adverse event (SAE) is any AE that results in a life-threatening situation, inpatient or prolonged hospitalization, significant incapacity or disruption of normal life functions, abnormal birth defect, or death. Any major medical event that may jeopardize the subject and may require medical or surgical intervention may be interpreted as SAEs.

9.3. Reporting Procedures

Site staff and Sponsor's Clinical Research Manager will regularly monitor survey and Diary responses (e.g., daily for Diaries and as they come in for other surveys) for any safety concerns. Severity and relatedness of patient-reported safety concerns will be assessed by the PI or appropriately qualified site staff member. If determined to be the level of an adverse event or serious adverse event, the safety concern will be recorded in the AE/SAE Log within the IRB's reporting timeframe. The PI or appropriately qualified site staff member will determine the necessary follow-up medical response.

Minor AEs such as minor injuries (e.g., sprains, cuts, bruises) or minor illnesses (e.g., colds, flus, food poisoning) that are clearly not associated with device do not need to be reported to the Sponsor or IRB. AEs that result in injury to the affected wrist area or in discontinuation of device use should be reported to the Sponsor.

SAEs are to be recorded as soon as possible from the discovery of the SAE and both the PI, sponsor, and IRB notified promptly. The Sponsor should notify all sites of an SAE. AEs/SAEs should be reported within the timeframes from IRB and GCP guidelines.

9.4. Follow-up for Adverse Events

Site staff should contact subjects that report an AE within 3 days of learning of the AE, unless the AE is minor (see above).

For subjects with a reported and recorded AE, site staff should contact the subject at each subsequent Follow-up (i.e., every 2 weeks during Treatment Period, every 4 weeks during Post-Treatment Period) to obtain an update on the status of the AE/SAE. The AEs should be followed until resolved, considered stable, or the subject is exited from the study.

10. STATISTICAL CONSIDERATIONS

10.1. Statistical Hypotheses

10.1.1. Primary Efficacy Endpoint

H_0: Daily wear of the study device does not improve symptom severity.

H_1: Daily wear of the study device improves symptom severity by at least 0.4 points.

10.1.2. Secondary Efficacy Endpoint

H_0: Daily wear of the study device does not improve symptom severity in comparison to sham treatment.

H_1: Daily wear of the study device improves symptom severity by at least 0.4 points more than the sham group.

H_0: Changes in symptom severity are not sustained after stopping treatment.

H_1: Changes in symptom severity are sustained or continue after stopping treatment.

10.2. Sample Size Determination

A total of 102 subjects are required for this study, with 51 in each group.

The outcome measure used for calculations in the SSS of the BCTQ, which ranges from 1 to 5 with 1 being no symptoms (improved) and 5 being the worst symptoms (worsened).

A moderate effect size of 0.4 was chosen, assuming that study device efficacy is 0.4 greater than sham.

The pilot study experienced a drop-out rate of 20% (2 out of 13 total). With the longer treatment and follow-up times of this study, a higher drop-out is expected. Therefore the sample size calculation is modified by an estimated attrition rate of 25%.

The primary objective examines the 8 week vs baseline within-active group SSS change. Sample size determination explanation. The power analysis using the above results in a significance level of 0.05 and a power of 0.94*.

The secondary objective examines the change in SSS after 8 weeks between the active study device and sham groups. Sample size calculation is based on a parallel, one-sided t-test power analysis to identify an effect size of 0.4, standard deviation of 0.7 (based on the pilot study PPS-CTMD-15-001), significance level of 0.05, power of 0.8, and an estimated attrition rate of 25%.

The sample size was chosen to meet both the primary and secondary objectives.

10.3. Randomization and Blinding Procedures

A simple randomization scheme is used to allocate subjects into the treatment group or the sham group. Site staff will be blinded to the randomization list and the Sponsor clinical research team blind to the allocation of each subject.

Blinding will be broken for each sham group participant at his/her first post-treatment follow-up (Week 12) so that the site can offer the sham group participant the opportunity to try the active study device. Complete blinding will be broken at the end of the study when all data has been entered and validated and the database has been locked.

Blinding may be broken if a subject experiences a SAE and if knowledge of the device is necessary for proper medical treatment of the SAE. Due to the low risk and minimal side effects associated with the device from previous studies, unblinding in most cases is not deemed necessary for medical treatment.

The subject's assigned site must obtain approval from the Sponsor to break the blind. After approval, the Shipping Associate responsible for randomization will provide the assignment for the subject in question. After a subject's treatment has been revealed, this must be noted along with reasons for breaking the blind in the subject's records and in the Deviation/Violation Log.

10.4. Population for Analyses

Statistical analyses will be based on a per protocol analysis - i.e., performed only on the SSS scores for subjects that have completed the full 8 week treatment period.

10.5. Statistical Analyses

The primary efficacy endpoint is the improvement (reduction) in SSS of the treatment group at 8 weeks after the first day of device wear. The primary efficacy endpoint will be analyzed using a paired, one-sided t-test.

The secondary efficacy endpoint is the improvement (reduction) in SSS of the treatment group compared to the sham group at T4 (8 weeks after the first day of device wear). The secondary endpoint will be analyzed using a two sample one-sided t-test.

A repeated measures analysis of variance will be used to evaluate changes over time in both the active and sham groups.

The exploratory endpoints will be analyzed using descriptive methods.

Safety analyses will be performed on all subjects that received treatment.

11. DATA COLLECTION AND QUALITY ASSURANCE

11.1. Data Collection Methods

Data for each subject at each site will be entered into an electronic data capture (EDC) system. Paper forms used as CRFs, during enrollment, or at other time points will be entered into

the EDC by site staff. Surveys are administered to subjects to collect baseline, follow-up, AE/SAE, user feedback, and exit data. Subjects use their own devices to complete these surveys and Diaries online. Forms will record the subject's ID, assigned site, date completed, and other relevant information. Subjects will be trained during or after enrollment on how to use and fill out these surveys. Support and re-training will be provided to subjects whenever requested.

Appropriate security and privacy settings in the EDC system, or procedures set up for use with the EDC system, will be put in place to meet minimum applicable regulations. These may include audit trails, unique log-ins, and custom user access. The EDC system will be set up and managed by the sponsor's Clinical Trials Manager or Clinical Trials Data Manager. Before study launch, the system will be tested and validated.

11.2. Data Management

The Sponsor Clinical Research (Data) Manager will control access to the EDC. Specific forms and functions will be granted to Sponsor and site staff based on their role in the study. The Clinical Research (Data) Manager will create the surveys and electronic workflow.

Site staff and the Clinical Research Manager will have access to subject responses in the EDC and will have the ability to correct data when necessary. Data correction may occur in instances where a subject enters the wrong information (e.g., puts in 2018 for their birth year) and the correction has been verified.

Once data collection is complete, the Clinical Research (Data) Manager will work with site staff to ensure accuracy and completeness of the data. Data will be exported, reviewed, cleaned as necessary, and then locked for statistical analysis.

Unlocking of the database requires justification and approval. Reasons for unlocking, date of unlocking, and date of re-locking the database will be documented.

11.3. Quality Assurance

11.3.1. Training

Training on the protocol, procedures, forms, and EDC system will be provided to the site prior to launch of the study. Training may be completed through teleconference or in-person, as determined between the Sponsor and the site. Training will be documented in Training logs.

11.3.2. Deviations/Violations

A deviation is an unplanned departure from protocol by the staff, participant, or investigator that does not cause significant consequences and is not intended to be a permanent or systematic change.

A violation is a divergence from protocol that reduces the quality or completeness of the data (e.g., missing or erroneous critical information on the surveys, I/E criteria not met), makes the Informed Consent Form inaccurate (e.g., ICF not fully signed), or impacts a subject's safety, rights, or welfare (e.g., unreported SAEs). Other violations include repeated subject non-compliance and intentional departures from protocol.

Site staff and PIs should be vigilant in identifying, recording, and addressing all deviations from and violations of the protocol. All deviations and violations should be recorded in the Deviations/Violations Log. The PI or appropriately delegated individual will determine if the Sponsor and/or IRB should be notified. Any deviation or violation performed to protect patient safety or confidentiality or otherwise impacting patient safety or confidentiality should be immediately reported to the IRB and Sponsor.

11.3.3. Monitoring

A staff member(s) at each site will be responsible for regularly monitoring subject responses in the EDC system. If a subject misses Diary entries or survey responses beyond the acceptable windows, the designated site staff member will contact subject to ensure completion of the documents.

The site staff member will also follow up with subjects to clarify entries that are or seem to be incorrect or questionable.

The Sponsor Clinical Trials Manager or Data Manager will similarly monitor subject compliance and safety across all sites weekly or biweekly. Any errors, discrepancies, missed entries, or other entries of concern will be queried to the respective site. The clinical research coordinators (CRC) or similarly designated staff member at each site is expected to respond to and resolve or help the Manager resolve the issue in a timely manner. Queries and resolution will be tracked by the Clinical Trials Manager.

The Clinical Trials Manager (or similarly designated staff member) will also check in regularly with each site to review items such as enrollment status, subject compliance and safety, supplies, and site questions or issues. These will be tracked in a Remote Monitoring Log.

After the first 3 subjects are enrolled at each site, the Clinical Trials Manager or Associate will check in with the site to ensure procedures are being conducted as expected and to address any problems early on. If refresher training is needed, the site may request virtual in-person training with the Clinical Trials Manager.

Interim monitoring visit(s) may be scheduled as needed.

11.4. Study Data & Records Retention

Study records will be maintained for at least 2 years after study close-out.

12. PARTICIPANT RIGHTS AND CONFIDENTIALITY

12.1. Institutional Review Board (IRB)

This protocol and the informed consent document (provided as a separate document) and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study.

12.2. Informed Consent Forms

The most recently approved version of the Informed Consent Form (ICF) will be used to obtain and document informed consent of study participants. The ICF is provided in English with no translations planned. If a new version of the ICF is approved during the study, previously consented and enrolled subjects will be re-consented using the newly approved ICF, only if the changes to the ICF are substantial and the IRB requires re-consent.

A signed ICF will be obtained from each participant. For participants who cannot consent for themselves, such as those with a legal guardian, the guardian must sign the ICF. The ICF will describe the purpose of the study, the procedures involved, the requirements to follow, the risks and benefits of participation, and compensation. A copy will be given to each participant or legal guardian.

12.3. Participant Confidentiality

During screening, prospective subjects agree to provide their name, email, phone number, and potentially general area of residence (such as zip code, for assignment to closest research site). This information is used to email the prospect introductory study information and send study surveys and forms. To protect the privacy of enrolled subjects, no personally identifiable information will be included in any material sent to the Sponsor (except in cases listed below). This includes: enrollment logs, patient names, phone numbers, fax numbers, patient addresses, Social Security numbers, local hospital medical record number.

The Sponsor employee responsible for shipping devices to enrolled subjects ("Shipping Associate") will be not be involved in any other clinical research and will only receive the minimum necessary information to ship the correct devices to the subject (i.e., name, address, treatment).

Compensation also requires that the name and address of the subject be provided to a Sponsor employee handling finances. In these cases, the name and address of the subject without the associated Subject ID will be sent to the designated employee to process and send compensation. The shipping and compensation employees will not be involved with any other component of the study and will not share any subject's personally identifiable information with Sponsor employees associated with the study.

13. PUBLICATION OF RESEARCH

Authorship will reflect joint cooperation between PPS and participating PI(s). Authorship responsibilities should be established prior to the writing of any manuscript.

No individual publications are allowed unless agreed upon, reviewed, and approved by the Sponsor before submission and/or publication. No individual publications are allowed prior to the completion of a final report for the study.

14. ABBREVIATIONS

AE	Adverse Event
BCTQ	Boston Carpal Tunnel Questionnaire
CFR	Code of Federal Regulations
CRA	Clinical research associate
CRC	Clinical research coordinator
CRF	Case report form
CTR	Carpal tunnel release
CTS	Carpal tunnel syndrome
EDC	Electronic data capture (usually followed by "system")
FDA	(U.S.) Food and Drug Administration
FSS	Functional Severity Scale (of the BCTQ)
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IRB/IEC	Institutional Review Board / Independent Ethics Committee
NCS	Nerve conduction study
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NIH	National Institute of Health
NPRS	Numeric Pain Rating Scale
NSAID	Non-steroidal anti-inflammatory drug
PPS	Pressure Profile Systems, Inc. (Sponsor)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SSS	Symptom Severity Scale (of the BCTQ)
Survey	Various questionnaires completed by patients and used to collect study data (includes Follow-up and User Feedback Surveys)

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REVISION HISTORY				
VER #	**Effective Date**	**Author**	**Signature**	**Notes**
3	12/20/2018	Pauline Luong		1. Revised NCS time limit from 12 months to 24 months 2. Corrected minor date errors, flowchart errors 3. Clarified blinding 4. Clarified re-consent with new ICF versions
2	8/16/2018	Pauline Luong		5. Study design updated to minimize drop-out. Duration reduce to minimum needed for evaluation of Sponsor goals. Changes implemented under Synopsis, Schedule of Events & flowchart (including new SOE chart and flowchart to improve clarity), Study Design, Objectives & Endpoints, and Study Procedures. 6. Replaced "COA" and "PRO" with the more accurate term "survey" 7. Updated language regarding Survey and Diary completion requirements 8. Corrected Daily Diary sent 56 days, not 28 days 9. Included brief NCS explanation and associated Works Cited 10. Updated example of withdrawal due to Sponsor's evaluation of subject's missing entries, rather than a flat number of missed entries. 11. Updated that EDC system does not need to be 21 CFR Part 11 compliant but will be integrated within a system of processes to ensure minimum security
1.1	02/21/2018	Pauline Luong		12. Moved PROs from Appendix to separate documents 13. Updated IFU and make separate document 14. Added BCTQ as Appendix I (added reference).
1.0	02/05/2018	Pauline Luong		1st release

APPENDICES

Appendix I: Boston Carpal Tunnel Questionnaire (BCTQ)
Appendix II: Nerve Conduction Study (NCS)

APPENDIX I: BOSTON CARPAL TUNNEL QUESTIONNAIRE (BCTQ)

The Boston Carpal Tunnel Questionnaire (BCTQ) is a patient-administered measure of symptom severity and functional impairment due to carpal tunnel syndrome. It has been shown to be "valid, reliable, responsive, and acceptable" tool to use as a primary outcome measure in carpal tunnel syndrome studies[13].

Each response has a value from 1 to 5. The average value of the responses to the first 11 questions provides the Symptom Severity Scale (SSS) score. The average value of the responses to the remaining 7 questions provides the Functional Severity Scale (FSS) score. The lowest value is 1 and represents no symptoms or functional impairment. The highest value is 5 and represents the worst possible symptoms and functional impairment.

Boston Carpal Tunnel Questionnaire (BCTQ)

The BCTQ is 2-part survey that quantifies the severity of your carpal tunnel syndrome. Thinking about your symptoms due to carpal tunnel syndrome for **a typical twenty-four (24) hour day during the past two (2) weeks**, please answer the following questions. (If you have bilateral CTS (both hands affected), answer for the wrist that is more severe based on the nerve conduction study (NCS) results. If difficult to tell, answer for your dominant hand.)

Part I - Symptom Severity Scale (SSS)

1. **How severe is the hand or wrist pain that you have at night?**

❑ I do not have hand or wrist pain at night
❑ Mild pain
❑ Moderate pain
❑ Severe pain
❑ Very severe pain

2. **How often did hand or wrist pain wake you up during a typical night in the past two weeks?**

❑ Never
❑ Once
❑ Two or three times
❑ Four or five times
❑ More than five times

3. **Do you typically have pain in your hand or wrist during the daytime?**

❑ I never have pain during the day
❑ I have mild pain during the day
❑ I have moderate pain during the day
❑ I have severe pain during the day
❑ I have very severe pain during the day

4. **How often do you have hand or wrist pain during the daytime?**

❑ Never
❑ Once or twice a day
❑ Three to five times a day
❑ More than five times a day

❑ The pain is constant

5. **How long, on average, does an episode of pain last during the daytime?**
❑ I never get pain during the day
❑ Less than 10 minutes
❑ 10 to 60 minutes
❑ Greater than 60 minutes
❑ The pain is constant throughout the day

6. **Do you have numbness (loss of sensation) in your hand?**
❑ No
❑ I have mild numbness
❑ I have moderate numbness
❑ I have severe numbness
❑ I have very severe numbness

7. **Do you have weakness in your hand or wrist?**
❑ No weakness
❑ Mild weakness
❑ Moderate weakness
❑ Severe weakness
❑ Very severe weakness

8. **Do you have tingling sensations in your hand?**
❑ No tingling
❑ Mild tingling
❑ Moderate tingling
❑ Severe tingling
❑ Very severe tingling

9. **How severe is numbness (loss of sensation) or tingling at night?**
❑ I have no numbness or tingling at night
❑ Mild
❑ Moderate
❑ Severe
❑ Very severe

10. **How often did hand numbness or tingling wake you up during a typical night during the last two weeks?**
❑ Never
❑ Once
❑ Two or three times
❑ Four or five times
❑ More than five times

11. **Do you have difficulty with grasping and use of small objects such as keys or pens?**
❑ No difficulty
❑ Mild difficulty
❑ Moderate difficulty

- ❑ Severe difficulty
- ❑ Very severe difficulty

Part II - Functional Severity Scale (SSS)

On a typical day during the past two weeks have hand and wrist symptoms caused you to have any difficulty doing the activities listed below? Please circle one number that best describes your ability to do the activity.

ACTIVITY	No Difficulty	Mild Difficulty	Moderate Difficulty	Severe Difficulty	Cannot do at all due to hand or wrist symptoms
Writing	1	2	3	4	5
Buttoning clothes	1	2	3	4	5
Holding a book while reading	1	2	3	4	5
Gripping a phone	1	2	3	4	5
Opening a jar	1	2	3	4	5
Household chores	1	2	3	4	5
Carrying grocery bags	1	2	3	4	5
Bathing and dressing	1	2	3	4	5

APPENDIX II: NERVE CONDUCTION STUDY (NCS)

An electrodiagnostic confirmation of carpal tunnel syndrome (CTS) in addition to clinical diagnosis of CTS is required for enrollment into the PPS-CTS-SBIR2 study. A nerve conduction study (NCS) must be performed and provided to the site before patients can be enrolled into the study. The objective of the examination is to determine the presence of nerve damage or destruction in study subjects and to classify CTS severity as mild, moderate, or severe (per AANEM criteria[13]). The following NCS tests are the minimum tests that must be performed to confirm CTS diagnosis and provided for reference.

Median and ulnar motor and sensory studies should have been performed on either (unilateral CTS) or both wrists (bilateral CTS) of each study subject to confirm CTS diagnosis.

Procedure

The study subject will be placed in a supine position and any clothing will be adjusted or removed to allow for exposure of the wrist and forearm. Electrodiagnostic testing will be performed with a Cadwell Sierra 2 EMG unit and a grounding pad will be used. Skin temperature will be measured and testing will be performed with skin temperatures in the 26–32°C range.

Four (4) separate sub-studies will be performed as part of the overall nerve conduction study (electrodiagnostic carpal tunnel testing) as follows:

Median nerve sensory distal latency study:

Orthodromic stimulation with active ring electrode placed at the base of the second finger and reference electrode placed distally 4 cm apart. Stimulation is performed 13 cm proximal to the active ring electrode over the median nerve between the tendons of the palmaris longus and flexor carpi radialis.

Normal values:
Amplitude: ≥ 20 μV
Conduction velocity: ≥ 50 m/sec
Distal peak latency: ≤ 3.5 msec

Ulnar nerve sensory distal latency study:

Ring electrodes are placed over the fifth digit 4 cm apart with the active electrode proximally at the base of the finger. Stimulation is performed 14 cm proximally radial to the flexor carpi ulnaris. Distal distance will be 11 cm.

Normal values:
Amplitude: ≥ 17 μV
Conduction velocity: ≥ 50 m/sec
Distal peak latency: ≤ 3.1 msec

Median nerve motor conduction velocity and latency study:

The active surface electrode is placed one half the distance between the metacarpophalangeal joint and the thumb and the midpoint of the distal wrist crease. The reference electrode is placed on the distal phalanx of the thumb.

Distal stimulation is performed 7 cm proximal to the active electrode over the median nerve between the tendons of the flexor carpi radialis and palmaris longus. Proximal stimulation is performed over the medial aspect of the antecubital space between the biceps tendon and brachial artery.

Normal values:
Amplitude: ≥ 4.0 mV
Conduction velocity: ≥ 49 m/sec
Distal latency: ≤ 4.4 msec

Ulnar nerve motor conduction velocity and latency study:
The active surface electrode is placed over the abductor digiti minimi on appointment between the distal wrist crease and the crease at the base of the fifth digit. The reference electrode is placed on the fifth digit. The elbow is flexed to 90°. Stimulation is performed 8 cm proximal to the active electrode just over the flexor carpi ulnaris tendon; a second stimulation just distal to the ulnar groove and a third stimulation proximal to the ulnar groove, with the cathode distally placed.

Normal values:
Amplitude: ≥ 6.0 mV
Conduction velocity: ≥ 49 m/sec
Distal latency: ≤ 3.3 msec

All amplitude, conduction velocity and latency values will be recorded in the subject's chart and results will be printed and attached to the subject's chart.

A one-sided (unilateral) nerve conduction study (electrodiagnostic carpal tunnel test) will take approximately 20 minutes to perform.

In the case that diagnosis is still uncertain after performing these four sub-studies, the following two (2) sub-studies may be performed:

Median/radial sensory study:
Antidromic stimulation with the active ring electrode placed at the base of the thumb and reference electrode placed distally 4 cm apart. Stimulation performed 10 cm proximal to the ring electrode over the radial nerve at the radial styloid process and over the median nerve at the wrist between the tendons of the flexor carpi radialis and palmaris longus.

A difference of ≥ 0.4 msec between the radial and median nerve peak latency, where the median nerve would be slower, will be considered abnormal.

Median versus ulnar sensory latencies to digit 4 study:
Ring electrodes are placed at the base of the 4th finger, active proximal, reference distal, 4 cm apart. Stimulation is performed over the medial and ulnar nerves at the wrist at identical distances from the proximal electrode (11-13 cm).

A difference of ≥ 0.5 msec will be considered significant.