PROTOCOL TITLE: Sciatic Block in Contralateral Limb for Treatment of Refractory Phantom and Residual Limb Pain; a Triple-Blind Randomized Crossover Controlled Trial

PRINCIPAL INVESTIGATOR:
David Walega, MD, MSCI
Division of Anesthesiology
312-695-2500
d-walega@northwestern.edu

VERSION DATE:
Version 1.0 07/14/2021

STUDY SUMMARY:

Investigational Agent(s) (Drugs or Devices)	Lidocaine 2%
IND / IDE / HDE #	NA
Indicate Special Population(s)	NA
Sample Size	20
Funding Source	Internal
Indicate the type of consent to be obtained	Written
Site	Single
Research Related Radiation Exposure	Yes
DSMB / DMC / IDMC	No

OBJECTIVES:
Participants with chronic, refractory phantom limb pain (PLP) or residual limb pain (RLP) for more than 6 months will be enrolled in this clinical trial.

Aim: Define the attributable pain relief and functional improvement in participants with PLP/RLP after contralateral limb sciatic nerve block. Also, contribute to the basic science understanding of the crossed-withdraw reflex by demonstrating a known animal model phenomenon in human participants.

Hypothesis: Contralateral limb sciatic nerve anesthetic block with 2% lidocaine provides immediate clinically meaningful pain reduction, defined as the proportion of patients with at least 50% improvement in NRS pain score in PLP/RLP when compared to sham.

BACKGROUND:
RLP and PLP affect most amputees at some point in their life[1]. The incidence of PLP has been estimated to range between 50 – 80% [2-8]. The prevalence of RLP has been estimated to be approximately 40%[9]. RLP is more common in the first year after amputation, with PLP becoming the predominate amputee pain complaint after one-year post-amputation[10].

Both RLP and PLP fall under the umbrella term "post-amputation pain." While these conditions are frequently found in combination, their clinical features are distinct and may share a common pathophysiological mechanism with neuroma formation[9,11]. PLP is a painful sensation in the distribution of the missing limb. Following amputation, abnormalities at multiple levels of the neural axis have been implicated in the development of PLP; changes include cortical reorganization, reduced inhibitory processes at the spinal cord, synaptic response changes and hyperexcitability at the dorsal root ganglion, retrograde peripheral nerve shrinkage, and neuroma formation[12-14].

RLP may be caused by a number of conditions, including skin pathologies (i.e. stump edema, verrucose hyperplasia, epidermoid inclusion cysts, contact dermatitis, Marjolin's ulcers, squamous cell carcinoma), positive pressure areas from a poor socket fit, bony nociceptive pain, adventitial bursitis, and neuroma formation[15]. Neuromas may form as early 6-10 weeks after nerve transection and are thought to produce ectopic neural discharges resulting in severe residual limb pain [16,17]. A diagnostic block can help isolate a neuroma as the source of pain[15].

Evidence suggests that RLP and PLP commonly co-occur, and patients may struggle to differentiate these pain types[18]. Risk factors for these painful conditions include female sex, pre-amputation pain, longer duration of time since amputation, residual pain in the still-intact contralateral limb, and upper extremity amputation[10,19].

Current treatments of PLP and RLP are often inadequate for controlling patients' symptoms. In addition to significant pain and disability, individuals with PLP and RLP also experience a higher incidence of indecisiveness, suicidal ideation, and thoughts of self-harm compared to pain-free health survey participants[8,20]. Treatments include pre-operative analgesia, mirror therapy [13,21-23], guided motor imagery [21,23,24], acupuncture[25], medications such as tricyclic antidepressants (TCAs) [26-28], selective serotonin reuptake inhibitors (SSRIs) [26], gabapentinoids [26,29,30], sodium channel blockers[27], ketamine[26], opioids [27], and non-steroidal anti-inflammatories drugs (NSAIDs)[5], transcranial magnetic stimulation [31], radiofrequency neurotomy[32], cryoablation[33], and neuromodulation (deep brain stimulation [35], dorsal root ganglion stimulation[34], spinal cord stimulation[35] and percutaneous peripheral nerve stimulation[3]). Additionally, various agents have been injected into and/or in close proximity to neuromas in attempt to mitigate pain symptoms, including local anesthetic [36], phenol[37], alcohol[38], and botulinum toxin[36]. In general, these treatments have been associated with modest outcomes at best.

Pain improvement following mirror therapy suggests that the contralateral (intact) limb has an important role in PLP, and possibly RLP, resolution. This was further demonstrated in a randomized control trial[39] that compared anesthetic and saline trigger point injections in participants' intact limb (contralateral to the residual limb that experienced PLP). Contralateral

limb anesthetic trigger points provided greater pain relief than placebo, supporting the exploration of contralateral limb interventions to reduce PLP. An animal study established the pathophysiologic basis for this via the crossed-withdraw reflex[40].

The crossed-withdraw reflex occurs when an individual withdraws a limb with an injured nerve after a stimulus is applied to the contralaterally equivalent healthy nerve (i.e., right and left median nerve). Animal studies have proposed the following reflex mechanism: activated dorsal horn neurons on the uninjured side either directly, or indirectly, activate ventral horn neurons on the injured side[40]. This phenomenon occurs within 2 weeks of nerve injury and is likely due to plastic changes in the spinal cord. Furthermore, it appears that an injured nerve generates a greater proportion of wide-dynamic range (WDR) neuron activation on the contralateral limb nerve, when compared to contralateral WDR activation with two intact limb nerves[41]. This forms the basis for the current understanding of central nervous system changes following amputation that may contribute to PLP/RLP.

While studies have evaluated ipsilateral sciatic nerve block for PLP, myofascial injections in the contralateral (intact) limb, and transcutaneous electric nerve stimulation (TENS) in the contralateral limb, no study to date has evaluated the efficacy of contralateral limb sciatic nerve block for the treatment of PLP/RLP[32,39,40]. The present study aims to define the attributable effects of contralateral sciatic nerve block on pain and function in participants with post-amputation PLP/RLP.

We hypothesize that contralateral sciatic nerve block with 2% lidocaine will demonstrate superior clinical pain outcomes compared to sham in PLP/RLP. If this hypothesis proves correct, the study findings would fundamentally change the limb loss pain treatment paradigm. This would allow clinical teams to pursue more advanced contralateral procedures including perineural steroid injection and peripheral nerve stimulation. This could improve physical and psychological function, quality of life, and reduce overall healthcare utilization and cost in a substantial portion of the limb loss population.

We also believe that previous exploration into the basic science of the crossed-withdraw reflex and WDR neuron activity requires further validation with human subjects and clinical scenarios. A better understanding of this area will directly inform limb loss, pain, spinal cord, and neurology research.

STUDY ENDPOINTS:

Primary Outcome

Comparison of the proportions of participants reporting ≥ 50% improvement in NRS pain score from baseline at 15 minutes in treatment and sham groups

Secondary Outcomes (between and within-group comparisons will be used for each outcome):

1) Mean and standard deviation (SD) of change in NRS pain score at 1, 2, 3, 4, 5, 6, 24, 48, 72, 96, 120 hours post-saline and lidocaine injections

2) Mean and SD of average daily steps recorded at 24, 48, 72, 96, 120 hours post-saline and lidocaine injections (via Modus StepWatch™ or Evolution EvoWalk™)

3) Mean and SD of change in Orthotics and Prosthetics User's Survey (OPUS) score immediately post-injection and conclusion of washout (5 days) in saline and lidocaine groups
4) Mean and SD of change in Groningen Activity Restriction Scale (GARS) score immediately post-injection and conclusion of washout (5 days) in saline and lidocaine groups
5) General linear model analysis of the interaction between crossover sequence
6) Demographic factors associated with large improvement in NRS pain score
7) Complications associated with the procedures

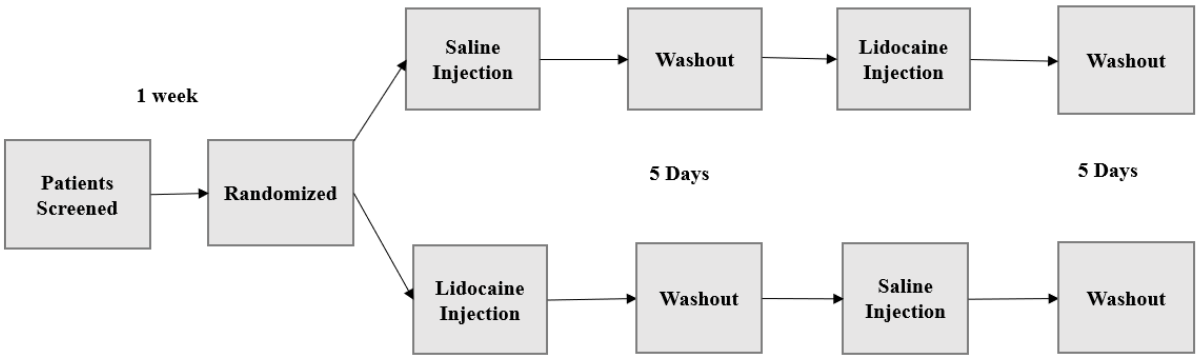
STUDY INTERVENTION(S) / INVESTIGATIONAL AGENT(S):
Image guided injection of the sciatic nerves with 2% lidocaine, 10 mL
vs.
Image guided injection of the sciatic nerves with preservative-free saline, 10 mL

IND exemption criteria for 2% lidocaine:

- The drug is lawfully marketed in the United States: Yes, 2% lidocaine is used as a standard local anesthetic in many medical offices throughout the United States.
- The research is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug: Correct, our study is not evaluating the efficacy of lidocaine. Rather, it is evaluating a procedural technique that requires analgesia. Analgesia is well established property of 2% lidocaine.
- The research is not intended to support a significant change in the advertising for the product: Correct. Lidocaine will be used to deliver analgesia. This is not a novel application of this medication.
- The research does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product: Correct, we will be using a volume and concentration that is well within standard sodium channel blocker safety limits. Furthermore, we will use ultrasound guidance to deliver the medicine and effectively avoid intravascular administration of the medication, further reducing its risk.
- The research is conducted in compliance with the marketing limitation described in 21 CFR §312.7: Correct, we will not be promoting an investigational new drug in this study. Rather, we will be using a drug with well-established analgesic properties in a novel procedural technique.

PROCEDURES INVOLVED:
Study Design
We aim to conduct a single-site, prospective, randomized, triple blind, sham-controlled, cross-over trial of consecutive participants.to determine the efficacy of contralateral sciatic nerve block in treating chronic, refractory PLP/RLP.

Figure 1: Study Crossover Design



Methods

Twenty participants will be recruited from the Northwestern-affiliated practices of the PI and the Co-I, the Shirley Ryan Ability Lab, the University of Chicago, and local prosthetic clinics.

Pre-visit: Candidates will be screened by authorized research personnel via chart review to determine candidacy for the study. If the participant meets eligibility criteria, they will be scheduled for a clinic visit.

Visit 1 – Consent, inclusion screening, and prosthetic step counter placement

All participants will present to the Pain Clinic (259 E. Erie, Suite 1400, Lavin Pavilion) and undergo an informed consent process with authorized research personnel. Eligibility criteria will be reviewed and confirmed. Dr. Walega will meet with the participant, explain the treatment block procedure, will review the medical history and perform a brief physical examination (focusing on residual limb point of maximal tenderness, review of prior imaging studies if available, and lower extremity musculoskeletal examination). Participants will provide baseline outcome measures and demographic data. Participants will be asked to complete the OPUS and GARS survey and provide demographic information. They will be given the option of completing these either on paper or on an iPad.

Devices

During initial evaluation (visit 1), participants' prostheses will be fit with a Modus StepWatch™ or Evolution EvoWalk™. This will be tested in clinic by a research coordinator to ensure proper step count. The device will remain on participant's prosthesis until study completion. Participant kinematic and gait data will be recorded by Modus StepWatch™ or Evolution EvoWalk™ and uploaded via Bluetooth to secure a de-identified, Health Insurance Portability and Accountability Act (HIPAA) compliant cloud-based storage application and extracted by research coordinator to an encrypted, HIPAA-compliant, Northwestern research database (REDCap).

Participants will also be instructed to maintain a daily pain log through My Pain Diary smartphone application or paper log depending on participant preference. They will be asked to log daily pain scores during their treatment. Data will be extracted by a researcher to an encrypted, HIPAA-compliant, Northwestern research database (REDCap).

Visit 2 (procedure 1)– Randomization and Study Intervention

Eligible participants will return to the Lavin 14th floor Pain clinic within 2 weeks of the initial visit. Participants will be randomized to treatment or sham group. Participant pre-procedure 1 NRS pain score will be collected. Individual pain log will start 15 minutes after procedure. Participant will log pain score every hour until asleep. The next day, participant will record daily NRS pain score for 5 days.

Randomization

A computer-generated 1:1 block randomization scheme (https:// www.randomizer.org) will be used to assign participants to receive a peri-sciatic nerve injection with either 10 mL of 2% lidocaine or 10 mL of preservative-free saline (compounded by the 11th floor Lavin pharmacy and labeled with a "1" or "2" to ensure adequate blinding). Randomization will be performed by a research assistant by opening an opaque envelope to reveal the participant number and group assignment printed inside of the envelope. This will instruct authorized study personnel to draw up either 2% lidocaine or saline (labeled "1" or "2" by compounding pharmacy per above). The blinded injectionist will be provided an unlabeled syringe of injectate immediately before the injection procedure. Participants, injectionist, and study personnel who collect outcomes data will be blinded to group assignment.

.

Treatment block of sciatic nerve in contralateral limb: Procedure planning will be based on the participant's indication of residual limb point of maximal pain (measured by distance from posterior superior iliac spine (PSIS) to most painful point [in cm]). Note that this point may beyond the anatomic end of the residual limb. The block will be performed at the exact same distance from PSIS on the contralateral side. If the block cannot be performed at this site due to anatomic or technical considerations (such as proximity to vascular structures), a more cephalad site along the sciatic nerve course will be selected for the procedure. During the block procedure, the participant will be positioned prone. Standard American Society of Anesthesiologists (ASA) procedure monitoring will be used (pulse oximetry, ECG, blood pressure, and heart rate). The participant's skin will be prepared with chlorhexidine. A sterile ultrasound probe will be placed on the participants' residual limb at a transverse angle in order to view the nerve in short-axis. The skin will be anesthetized with 1-2 mL of 1.0% lidocaine. The ultrasound probe (in plane) will be advanced to the intact limb's sciatic nerve equidistance to that of the residual limb point of maximal pain. A 22-gauge standard echogenic needle will be placed adjacent to the sciatic nerve with ultrasound guidance. At the site of the nerve, 10mL of 2% lidocaine will be injected through the needle in the intervention group and 10ml of saline will be injected in the sham group.

In treatment group: At the site of the nerve, 10mL of 2% lidocaine will be injected through the needle

In control group: At the site of the nerve, 10ml of saline will be injected through the needle

Following injection, participants will be kept in recovery area and monitored for 30 minutes. They will also complete a pain log starting 15 minutes post-injection. After the first pain score is recorded, the participants will dress and exit procedure area. Participants will be required to arrange transportation as the block may impair lower extremity motor function.

Both saline and local anesthetic will be administered to all subjects with a crossover design as described above. Participants will undergo 5-day washout between injections.

Visit 3 – Crossover for both groups
Eligible participants will return to the Lavin 14th floor Pain clinic within 5 days of visit 2. Participant pre-procedure 2 NRS and OPUS will be collected. Note that this will serve as post-procedure 1 washout and pre-procedure 2 intervention data point.

Both groups: will cross over and undergo treatment as described in V*isit 2.* Participant pain log will start 15 minutes after procedure 2. Participant will log pain scores every hour until asleep. The next day, participant will record daily NRS pain score for 5 days.

Telephone call 1,2,3: participant will be called at 1- and 5-days post-procedures for NRS, OPUS survey and safety monitoring by research coordinator (see Safety Monitoring below).

SAFETY MONITORING Participants will be contacted one day following both interventions to assess for any adverse events or side effects.

DATA
We will obtain socio-demographic and clinical variables:

- Age (years)
- Sex
- Height (cm)
- Weight (kg)
- Level and side of amputation
- Duration of pain (weeks)
- Date of amputation
- Etiology of amputation
- Baseline NRS score for both PLP/RLP (worst, least, average, current)
- Site of residual limb maximal pain (measured by distance from posterior superior iliac spine (PSIS) to most painful point [in cm])
- Analgesic medication log: dose and frequency of each medication participant currently taking
- OPUS: Lower-Extremity Functional Status Measure Subsection Score
- GARS

POWER ANALYSIS
Power and sample size calculations for this clinical trial were performed based on the data from a small cross-over study (N = 8) by Casale et al[39]. The primary outcome variable will be achievability of ≥ 50% pain relief (dichotomous variable with yes/no), calculated from pre- and post-inject NRS in each of the lidocaine and sham conditions (i.e., pre-injection NRS – post-injection NRS). Based on the data from Casale et al., along with our expected, overall success rate of 75% by lidocaine injection, we calculated the difference in two proportions of discordant pairs to be 0.625 and the overall proportion of discordant pairs to be 0.875. Using these values and binomial enumeration (1,500 enumerations), along with an

alpha level of 0.05, a power of 0.80, a two-sided t-test, and a dropout rate of 10%, the sample size was estimated as 20.

STATISTICAL PLAN

Data for the primary outcome variable, proportion of participants reporting ≥ 50% immediate pain reduction from baseline, will be reported as the mean and standard deviation (or median and interquartile range if not normally distributed) of the lidocaine and sham groups. Mean change in pain score, will be examined using an unpaired t test (NCSS) (or Mann-Whitney U test if not normally distributed). The median difference and its 95% CI will be calculated. The criterion for rejection of the null hypothesis will be $P < 0.05$.

Participant data and secondary variables that are characterized by nominal data will be summarized as the number of participants in each category and the percentage of all participants in the group that they represent. These variables will be compared between the groups using the Pearson $\chi 2$ test, or when at least one of the cells of the contingency table had an expected number less than five, the Fischer exact probability test. The Miettinen-Nurminem score will be used to calculate 95% CIs for differences in percentages where indicated.

Variables that are characterized by ordinal data and non-normally distributed continuous data (e.g., procedure time) will be summarized as median and interquartile range. These variables will be compared between the groups using the Mann-Whitney U test. Median differences and their 95% CIs will be calculated where indicated.

Variables that are characterized by normally distributed continuous data (e.g., age and body weight) will be summarized as mean and standard deviation. These variables will be compared between the groups using the unpaired t test (NCSS). Mean differences and their 95% CIs will be determined.

In case there were significant differences in the demographic variables, multivariate logistic and linear regression analyzes will be conducted to examine the binary and continuous outcome variables by group, while accounting for the statistically significant demographic variables analysis will be used to determine if any demographic or clinical variables (age, BMI, duration of pain, etc.) are independently associated with successful pain (NRS) outcomes.

Lastly, Pearson’s correlation coefficients will be computed to assess the relationships among various demographic and procedural covariates.

DATA AND SPECIMEN BANKING
NA

SHARING RESULTS WITH PARTICIPANTS
Results will not be shared with participants or their medical providers.

STUDY TIMELINES
- IRB submission and approval process: 2 months
- Recruitment: 12 months
- Statistical analysis and manuscript: 2 months
- Duration of participation for each participant is approximately: 3 weeks

INCLUSION AND EXCLUSION CRITERIA
INCLUSION CRITERIA
1. Age greater than 18 years of age at day of enrollment
2. Lower extremity amputation performed more than 12 months before study enrollment
3. PLP/RLP in affected amputated limb > 4 on NRS26
4. Pain duration of more than 6 months despite a trial of conservative therapies for at least 2 months, including oral medications, topical medicines, physical therapy, and physical modalities (i.e., heat, cold, transcutaneous electrical nerve stimulation, phonophoresis)
5. Willingness to undergo image guided diagnostic nerve block

EXCLUSION CRITERIA
1. Refusal / inability to participate or provide consent
2. Contraindications to diagnostic nerve block
3. Non-neurogenic source of PLP/RLP
4. Current opioid use > 50 morphine milligram equivalents per day
5. Any interventional pain treatment in the residual limb within the last 30 days
6. Severe uncontrolled medical condition (i.e., hypertensive crisis, decompensated hypothyroidism)
7. Use of investigational pain drug within past 30 days or other concurrent clinical trial enrollment

VULNERABLE POPULATIONS
NA

PARTICIPANT POPULATION(S)

Accrual Number:	Category/Group: (Adults/Children Special/Vulnerable Populations)	Consented: Maximum Number to be Consented or Reviewed/Collected/Screened	Enrolled: Number to Complete the Study or Needed to Address the Research Question
Total:	1 Adult Group	20	20

RECRUITMENT METHODS
Participants will be recruited from the Northwestern-affiliated practices of the PI, the Shirley Ryan Ability Lab, the University of Chicago, and local prosthetic clinics. The trial will be posted on clinicaltrials.gov. IRB approved flyers will also be used.

COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES
None

WITHDRAWAL OF PARTICIPANTS
Participants may withdraw from the study at any time. Participants may be withdrawn from the research without their consent if they are non-compliant with providing outcome measures or study visits.

RISKS TO PARTICIPANTS
Ultrasound-guided perineural anesthetic injection is a commonly performed procedure in the U.S. and is considered safe and effective in treating chronic pain. It is considered very safe when performed with image guidance and by an experienced injectionist. The major complication (permeant nerve injury) rate following peripheral nerve block is estimated to be 1.5 / 10,000[42].

RISKS RELATED TO NEEDLE PLACEMENT
- Temporary bruising or swelling at the site of the injection
- Hematoma (pocket of blood caused by bleeding from a broken blood vessel)
- Infection of the tissues of the leg surrounding the area of injection

RISKS RELATED TO INJECTION OF MEDICATIONS
Lidocaine Risks
Infrequent
- Bradycardia
- Hypotension
- Drowsiness
- Dizziness
- Muscle twitching
- Nervousness
- Paresthesia
- Sensation of feeling cold
- Anxiousness

Rare
- Allergic reaction to lidocaine
- Skin injury including ulceration at the site of the injection
- Methemoglobinemia
- Diplopia
- Cardiac manifestations: Bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation, asystole, wide / premature QRS, bundle branch block, II to III AV block, ST changes, ventricular ectopy
- Respiratory depression
- Unconsciousness

- Seizure
- Nausea
- Apprehension

Normal Saline Risks
- Hypernatremia

Loss of confidentiality

POTENTIAL BENEFITS TO PARTICIPANTS
Individual participants may experience short- or long-term improvements in pain as a result of participation in this research.

DATA MANAGEMENT AND CONFIDENTIALITY
All data will be de-identified and recorded in duplicate on electronic study-specific case report forms (CRFs). Data will be entered utilizing REDCap. Participants will be given a study identification number that will be reported on all CRFs and source documents. Only the PI and authorized staff, according to the list of Authorized Study Personnel, are entitled to make entries on the CRF. Personal participant data will be kept confidential. Participant documentation will identify a participant by initials and study number. Only the PI will keep in his file a Participant Identification and Enrollment List. To allow compliance with GCP principles, each participant will be asked for consent regarding the access to source documents for monitoring, audits, and inspections. Data both electronic and paper will be destroyed 5 years after manuscript completion using current vendors and department protocol. Paper documents will be stored in the Arkes 10th floor Anesthesiology Administrative Office which is key card controlled in a locked research closet.

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS
A data safety monitoring board consisting of the Department of Anesthesiology Director of Research, a pain medicine attending physician, a statistician, and study research personnel will periodically evaluate the data collected to determine whether participants remain safe. Safety data and adverse event data will be reviewed using the medical record and data collection form. It will be reviewed every 10 subjects or if one of the study subjects experiences a rapid response team intervention. Data will be compared between groups using the $\chi 2$ statistic or the Fisher's exact test. A p-value < 0.05 will be required to reject the null hypothesis.

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS
Data will be de-identified and given a study identification number. The PI will keep in his file a subject identifier log. To allow compliance with GCP principles, each participant will be asked for consent regarding the access to source documents for monitoring, audits, and inspections. During the consent process they will be reassured that their data will be de-identified and personal participant data will be kept confidential.

COMPENSATION FOR RESEARCH-RELATED INJURY

None

ECONOMIC BURDEN TO PARTICIPANTS
The patient will not be responsible for these healthcare services or medications.

CONSENT PROCESS
Participants will be consented in the NMH Pain Clinic (259 East Erie Street, Suite 1400) by authorized research staff. Authorized research staff will explain the consent document. Each section of the form will be discussed, taking time to highlight the purpose of the study, procedures, risks, confidentiality measures taken to protect the participant, and how to revoke/withdraw consent, if desired, and to answer any questions the participate may have. They will also be informed that participation in this study is completely optional and regardless of their participation their care will not be negatively impacted. Subjects will be given ample time as they need to make their decision. The participants will receive a signed copy of the consent.

NON-ENGLISH SPEAKING PARTICIPANTS
NA

WAIVER OR ALTERATION OF CONSENT PROCESS
NA

PROTECTED HEALTH INFORMATION (PHI AND HIPAA)
HIPPA Authorization will be obtained from all research subjects through the consent document. Subjects will give us the permission to use personal health information that includes health information in the medical records and information that can identify them. Personal health information may include the subjects name, address, or phone number. Health information we collect and use for this research includes:

• All information in a medical record
• Results of physical examinations
• Medical history
• Lab tests, or certain health information indicating or relating to a particular condition as well as diaries and questionnaires
• Records about study medication or drugs
• Records about study devices

QUALIFICATIONS TO CONDUCT RESEARCH AND RESOURCES AVAILABLE
There is a large volume of chronic pain patients treated annually at NMH, ensuring the participant sample projections can be achieved. In addition, a co-investigator serve as faculty at the Shirley Ryan AbilityLab, the nation's largest amputee rehabilitation program. The principal investigator has 22 years of clinical experience performing ultrasound-guided nerve blocks in both a clinical and research setting. He has authored several peer reviewed articles on the topic of perineural injections for pain indications.

All research team members have completed the necessary regulatory training. We anticipate 1-2 cases per week. Authorized research personnel will have dedicated time to recruit participants. All authorized research personnel are informed about the protocol and their duties and functions.

MULTI-SITE RESEARCH
This is a single-site study

References

1. Richardson C, Glenn S, Nurmikko T, Horgan M. Incidence of phantom phenomena including phantom limb pain 6 months after major lower limb amputation in patients with peripheral vascular disease. *The Clinical journal of pain.* 2006;22(4):353-358.
2. Richardson C, Glenn S, Horgan M, Nurmikko T. A prospective study of factors associated with the presence of phantom limb pain six months after major lower limb amputation in patients with peripheral vascular disease. *The journal of pain : official journal of the American Pain Society.* 2007;8(10):793-801.
3. Cohen SP, Gilmore CA, Rauck RL, et al. Percutaneous Peripheral Nerve Stimulation for the Treatment of Chronic Pain Following Amputation. *Military medicine.* 2019.
4. Ephraim PL, Wegener ST, MacKenzie EJ, Dillingham TR, Pezzin LE. Phantom pain, residual limb pain, and back pain in amputees: results of a national survey. *Archives of physical medicine and rehabilitation.* 2005;86(10):1910-1919.
5. Hanley MA, Ehde DM, Jensen M, Czerniecki J, Smith DG, Robinson LR. Chronic pain associated with upper-limb loss. *American journal of physical medicine & rehabilitation.* 2009;88(9):742-751; quiz 752, 779.
6. Kooijman CM, Dijkstra PU, Geertzen JH, Elzinga A, van der Schans CP. Phantom pain and phantom sensations in upper limb amputees: an epidemiological study. *Pain.* 2000;87(1):33-41.
7. Dijkstra PU, Geertzen JH, Stewart R, van der Schans CP. Phantom pain and risk factors: a multivariate analysis. *Journal of pain and symptom management.* 2002;24(6):578-585.
8. Yin Y, Zhang L, Xiao H, et al. The pre-amputation pain and the postoperative deafferentation are the risk factors of phantom limb pain: a clinical survey in a sample of Chinese population. *BMC anesthesiology.* 2017;17(1):69.
9. Desmond DM, Maclachlan M. Prevalence and characteristics of phantom limb pain and residual limb pain in the long term after upper limb amputation. *International journal of rehabilitation research Internationale Zeitschrift fur Rehabilitationsforschung Revue internationale de recherches de readaptation.* 2010;33(3):279-282.
10. Schley MT, Wilms P, Toepfner S, et al. Painful and nonpainful phantom and stump sensations in acute traumatic amputees. *The Journal of trauma.* 2008;65(4):858-864.
11. Hsu E, Cohen SP. Postamputation pain: epidemiology, mechanisms, and treatment. *Journal of pain research.* 2013;6:121-136.
12. Flor H, Nikolajsen L, Staehelin Jensen T. Phantom limb pain: a case of maladaptive CNS plasticity? *Nature reviews Neuroscience.* 2006;7(11):873-881.
13. Ramachandran VS, Brang D, McGeoch PD. Dynamic reorganization of referred sensations by movements of phantom limbs. *Neuroreport.* 2010;21(10):727-730.
14. Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. *The Lancet Neurology.* 2010;9(8):807-819.
15. Pascale BA, Potter BK. Residual Limb Complications and Management Strategies. *Current Physical Medicine and Rehabilitation Reports.* 2014;2(4):241-249.

16. Nystrom B, Hagbarth KE. Microelectrode recordings from transected nerves in amputees with phantom limb pain. *Neuroscience letters.* 1981;27(2):211-216.
17. Wall R, Novotny-Joseph P, Macnamara TE. Does preamputation pain influence phantom limb pain in cancer patients? *Southern medical journal.* 1985;78(1):34-36.
18. Sherman RA, Sherman CJ. Prevalence and characteristics of chronic phantom limb pain among American veterans. Results of a trial survey. *American journal of physical medicine.* 1983;62(5):227-238.
19. Subedi B, Grossberg GT. Phantom limb pain: mechanisms and treatment approaches. *Pain research and treatment.* 2011;2011:864605.
20. Fuchs X, Flor H, Bekrater-Bodmann R. Psychological Factors Associated with Phantom Limb Pain: A Review of Recent Findings. *Pain Res Manag.* 2018;2018:5080123.
21. MacIver K, Lloyd DM, Kelly S, Roberts N, Nurmikko T. Phantom limb pain, cortical reorganization and the therapeutic effect of mental imagery. *Brain : a journal of neurology.* 2008;131(Pt 8):2181-2191.
22. Brodie EE, Whyte A, Niven CA. Analgesia through the looking-glass? A randomized controlled trial investigating the effect of viewing a 'virtual' limb upon phantom limb pain, sensation and movement. *European journal of pain (London, England).* 2007;11(4):428-436.
23. Chan BL, Witt R, Charrow AP, et al. Mirror therapy for phantom limb pain. *The New England journal of medicine.* 2007;357(21):2206-2207.
24. Herrador Colmenero L, Perez Marmol JM, Marti-Garcia C, et al. Effectiveness of mirror therapy, motor imagery, and virtual feedback on phantom limb pain following amputation: A systematic review. *Prosthet Orthot Int.* 2018;42(3):288-298.
25. Trevelyan EG, Turner WA, Summerfield-Mann L, Robinson N. Acupuncture for the treatment of phantom limb syndrome in lower limb amputees: a randomised controlled feasibility study. *Trials.* 2016;17(1):519-519.
26. Alviar MJ, Hale T, Dungca M. Pharmacologic interventions for treating phantom limb pain. *The Cochrane database of systematic reviews.* 2016;10:Cd006380.
27. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *European journal of neurology.* 2010;17(9):1113-e1188.
28. Robinson LR, Czerniecki JM, Ehde DM, et al. Trial of amitriptyline for relief of pain in amputees: results of a randomized controlled study. *Archives of physical medicine and rehabilitation.* 2004;85(1):1-6.
29. Nikolajsen L, Christensen KF, Haroutiunian S. Phantom limb pain: treatment strategies. *Pain management.* 2013;3(6):421-424.
30. Spiegel DR, Lappinen E, Gottlieb M. A presumed case of phantom limb pain treated successfully with duloxetine and pregabalin. *General hospital psychiatry.* 2010;32(2):228.e225-227.
31. Nardone R, Versace V, Sebastianelli L, et al. Transcranial magnetic stimulation in subjects with phantom pain and non-painful phantom sensations: A systematic review. *Brain research bulletin.* 2019;148:1-9.
32. Sperry BP, Cheney CW, Conger A, Shipman H, McCormick ZL. Cooled Radiofrequency Ablation of a Large Sciatic Neuroma at the Infrapiriformis Foramen for Recalcitrant Phantom Limb Pain in a Below-Knee Amputee: A Case Report. *Submitted to AAPM&R.* 2020.

33. Moesker AA, Karl HW, Trescot AM. Treatment of phantom limb pain by cryoneurolysis of the amputated nerve. *Pain practice : the official journal of World Institute of Pain.* 2014;14(1):52-56.
34. Eldabe S, Burger K, Moser H, et al. Dorsal Root Ganglion (DRG) Stimulation in the Treatment of Phantom Limb Pain (PLP). *Neuromodulation.* 2015;18(7):610-616; discussion 616-617.
35. Viswanathan A, Phan PC, Burton AW. Use of spinal cord stimulation in the treatment of phantom limb pain: case series and review of the literature. *Pain practice : the official journal of World Institute of Pain.* 2010;10(5):479-484.
36. Wu H, Sultana R, Taylor KB, Szabo A. A prospective randomized double-blinded pilot study to examine the effect of botulinum toxin type A injection versus Lidocaine/Depomedrol injection on residual and phantom limb pain: initial report. *The Clinical journal of pain.* 2012;28(2):108-112.
37. Gruber H, Glodny B, Kopf H, et al. Practical experience with sonographically guided phenol instillation of stump neuroma: predictors of effects, success, and outcome. *AJR American journal of roentgenology.* 2008;190(5):1263-1269.
38. Lim K-B, Kim Y-S, Kim J-A. Sonographically guided alcohol injection in painful stump neuroma. *Ann Rehabil Med.* 2012;36(3):404-408.
39. Casale R, Ceccherelli F, Labeeb AA, Biella GE. Phantom limb pain relief by contralateral myofascial injection with local anaesthetic in a placebo-controlled study: preliminary results. *J Rehabil Med.* 2009;41(6):418-422.
40. Won R, Lee BH. Contralateral Metabolic Activation Related to Plastic Changes in the Spinal Cord after Peripheral Nerve Injury in Rats. *Neural Plast.* 2015;2015:438319-438319.
41. Siegfried J, Zimmermann M, Baumgartner R, Gesellschaft zum Studien des Schmerzes für Deutschland ÖudS. *Phantom and stump pain.* Berlin; New York: Springer-Verlag; 1981.
42. Jeng CL, Torrillo TM, Rosenblatt MA. Complications of peripheral nerve blocks. *BJA: British Journal of Anaesthesia.* 2010;105(suppl_1):i97-i107.