Protocol Title: A Phase 2a, Multicenter, Randomized, Patient and Evaluator Blinded, Controlled Study Evaluating the Safety and Efficacy of NTX-001 Compared to Standard of Care in the Treatment of Acute Single Transected Peripheral Nerve Injury Occurring below the Distal Border of the Brachial Plexus Requiring Surgical Repair.

Protocol Number: NTx20201
Product: NTX-001
Study Phase: 2a

Sponsor Name and Address:
Neuraptive Therapeutics, Inc.
851 Duportail Road, Suite 200
Chesterbrook, PA 19087

IND#: 137375

DOCUMENT HISTORY	
Document	**Date**
Version 5.0	29Nov2023
Above Version Supersedes All Versions Listed Below	
Version 4.0	20Jun2022
Version 3.0	27Apr2021
Version 2.0	04Jun2020
Original 1.0	19Mar2020

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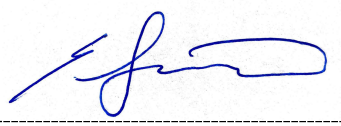
Protocol Title: A Phase 2a, Multicenter, Randomized, Patient and Evaluator Blinded, Controlled Study Evaluating the Safety and Efficacy of NTX-001 Compared to Standard of Care in the Treatment of Acute Single Transected Peripheral Nerve Injury Occurring below the Distal Border of the Brachial Plexus Requiring Surgical Repair.

I have read and approve this protocol. My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonisation Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from subjects who provided consent, using a previously approved consent form.

Sponsor Signatory/Responsible Medical Expert

Evangelos L Tzanis Chief Operating Officer EVP of Research and Development		
 Digitally signed by Evan L. Tzanis Date: 2024.01.30 10:35:13 -05'00'		Date:
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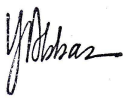 Digitally signed by Vicki J Abbas DN: cn=Vicki J Abbas, o=Neuraptive Therapeutics inc., ou=Clinical Operations, email=vicki.abbas@neuraptive.com, c=US Date: 2024.01.08 13:31:41 -07'00'		Date:

SIGNATURE PAGE

Protocol Title: A Phase 2a, Multicenter, Randomized, Patient and Evaluator Blinded, Controlled Study Evaluating the Safety and Efficacy of NTX-001 Compared to Standard of Care in the Treatment of Acute Single Transected Peripheral Nerve Injury Occurring below the Distal Border of the Brachial Plexus Requiring Surgical Repair.

I have read the foregoing protocol NTx20201 V5 and agree to the following:

The protocol contains all necessary details for carrying out this study; I will conduct the study as detailed in the protocol and will abide by all its provisions; I will conduct the study in compliance with the most current versions of International Conference on Harmonisation of Technical Requirements for registration of Pharmaceuticals for Human Use (ICH) Guidelines for Good Clinical Practice (GCP), all applicable government regulations and the requirements of the IRB that approved the study. I will train and supervise all individuals delegated to assist me in conducting this study, including providing copies of the protocol and all pertinent information and discussing the material with them to ensure they are fully informed regarding the investigational drug, the protocol and their responsibilities and obligations. I will use only the informed consent form (ICF) approved by Neuraptive Therapeutics Inc. (Neuraptive or their designee) and by the IRB responsible for this study. I will fulfill all requirements for submitting pertinent information to the IRB and to Neuraptive, including reportable serious adverse events (SAEs). I will provide Neuraptive (or their designee) with access to any source documents from which case report form information may have been generated. I understand that the information in this protocol and the referenced Investigator's Brochure (IB) is confidential and that its disclosure to any third parties (other than those involved in approving or conducting the study) is prohibited. I will take the necessary precautions to protect this information from loss, inadvertent disclosure, or access by third parties. I will complete the study within the time designated. My signature, in conjunction with the signature of Neuraptive, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the ICH Guideline for GCP, the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki. Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

Principal Investigator:

Print Name: _____

Signature: _____ Date: _____

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1. Abbreviations

2PDm or s	2 Point Discrimination (moving or static)
AE	Adverse Event
BUN	Blood Urea Nitrogen
CAP	Compound Action Potential
CAP	College of American Pathologists
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CISS	Cold Intolerance Symptom Severity
CLIA	Clinical Laboratory Improvements Amendments
CMAP	Compound Muscle Action Potential
Cr	Serum Creatinine
CRA	Clinical Research Associate
CRC	Clinical Research Coordinator
CRF	Case Report Form
CRO	Contract Research Organization
COVID-19	SARS-CoV-2
CTA	Clinical Trials Agreement
IPAR	Investigational Product Accountability Records
DCT	Decentralized Clinical Trials
DMC	Data Monitoring Committee
DMCP	Data Monitoring Committee Plan
EDC	Electronic Data Capture
EDx	Electrodiagnostic
EHR	Electronic Health Record
EP	Electrophysiology
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
β-HCG	Human chorionic gonadotropin
Δ	Change
H_0	Null Hypothesis
H_1	Alternative Hypothesis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization

IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IFU	Instructions for Use
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
IP	Investigational Product
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MHQ	Michigan Hand Questionnaire
MITT	Modified Intent-to-Treat
mN	Marking number
MMRM	Mixed Model Repeated Measures
MRCCs/m	British Medical Research Council Classification Sensory/Motor
NCV	Nerve Conduction Velocity
NDA	New Drug Application
NPRS	Numeric Pain Rating Scale
NSR	Non-Significant Risk (usually refers to device research)
PGIC	Patient Global Impression of Change
PD	Pharmacodynamics
PI	Principal Investigator
PNI	Peripheral Nerve Injury
prn	As Needed
PRO	Patient Related Outcome
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SoA	Schedule of Activities
SQV	Site Qualification Visit
SIV	Site Initiation Visit
Tbili	Total Bilirubin
WBC	White Blood Cell Count
WOCBP	Women of Child-Bearing Potential
WHO	World Health Organization

1. Protocol Summary

1.1. PROTOCOL SYNOPSIS

Protocol Title:	A Phase 2a, Multicenter, Randomized, Patient and Evaluator Blinded, Controlled Study Evaluating the Safety and Efficacy of NTX-001 Compared to Standard of Care in the Treatment of Acute Single Transected Peripheral Nerve Injury Occurring below the Distal Border of the Brachial Plexus Requiring Surgical Repair.
Study Number:	NTx20201
Development Phase:	Phase 2a
Clinical Trial Model	• The study will be conducted using a hybrid model of on-site and remote visits to meet FDA expectations for safety oversight when conducting clinical studies. It has been determined that alternative methods for conducting the study will only be allowed if the health emergency restrictions are in affect at the time of a visit or per subject request due to their concerns about the restrictions. A physician will be available to provide oversight of the remote assessments and/or to answer questions by phone during the visit. • On-site visits when deemed necessary by Investigator. • "In-home" research visits (rRV) conducted by study staff for subject follow-up assessments. • Week 12 is considered a critical visit and is to be conducted onsite. • The institutional procedures for individual safety will be followed during on-site visits if there is a COVID-19 health emergency. • Remote site qualification (rSQV) visits via web meetings.
Sponsor:	Neuraptive Therapeutics, Inc. 851 Duportail Road, Suite 200 Chesterbrook, PA 19087
Study Center(s):	This study will be conducted in approximately 15 centers in the US. The surgical component of the study will be either conducted at a standalone ambulatory surgical center where the principal investigator has privileges or at the facility of initial presentation. The locations where the repair and clinical follow-ups are performed are considered the clinical sites.
Study Objectives:	***Primary Objectives:*** • To assess the safety of NTX-001 across 48 weeks (12 Months) following the surgical repair of a peripheral nerve injury occurring below the distal border of the brachial plexus**.**

	● To assess functionality using MHQ Total Score at Week 12 following the surgical repair of a peripheral nerve injury occurring below the distal border of the brachial plexus. ***Exploratory Secondary Objectives:*** ● To assess electrophysiologic (EP) continuity after NTX-001 treatment; stratified by injury location. ● To assess improvement from baseline in the following assessments when NTX-001 is used in conjunction with standard suture neurorrhaphy: o British Medical Research Council Classification (MRCC) sensory scale, and/or the MRCC motor scale (based on location of injury) o Semmes Weinstein Monofilament Test (SWMT) o Grip/Pinch Strength o Michigan Hand Questionnaire (MHQ) o Cold Intolerance Symptom Severity (CISS) o Patient Global Impression of Change (PGIC) o Numeric Pain Rating Scale (NPRS)
Endpoints:	(Baseline values are required assessments obtained at any time from fully executed consent up to and including the Week 1 Visit) **Primary Endpoints:** o Safety analysis will be based on the comparison of adverse events and other safety data (i.e., vital signs, clinical labs, physical exam) across 48 weeks following surgical repair. o Change from baseline of MHQ Total Score at Week 12. **Exploratory Secondary Endpoints:** The following will be evaluated intraoperatively and percutaneously at Weeks 12 and 48. Weeks 12 and 48 are considered a critical visits and are conducted onsite. Facility and individual infection control policies will be followed during the visit. o Percent of responders from these parameters; • Compound Muscle Action Potential (No Contralateral Assessments) • Nerve Conduction Velocity (Contralateral assessment is done)

	The following will be evaluated at weeks 4, 8, 24 and 48 using the following measure. o Change from baseline of MHQ Total Score The following will be evaluated at Weeks 4, 8, 12, 24, 36 and 48 using the following measures: o Change from baseline of MRCC Motor Scale o Change from baseline of MRCC Sensory Scale o Change from baseline of SWMT Assessment o Change from baseline of Grip/Pinch Strength o Change from baseline of NPRS Score The following will be evaluated at Weeks 4, 8, 12, 24 and 48 using the following measures: o Change from baseline of CISS Score o Change from baseline of PGIC Score
Study Design:	A Phase 2a, Multicenter, Randomized, Patient and Evaluator Blinded, Controlled Study to be conducted in approximately 15 centers in the United States as described above. Subject follow-up evaluations will occur at Baseline, at Weeks 4, 8, 12, 24, 36 and 48 following surgical repairs. All sensory and/or functional assessments will be performed by the same qualified evaluator (if possible) blinded to treatment assignment.
Blinding:	Because of the nature of the surgery, it impossible to blind the surgeon and surgical staff to which treatment is being administered, to maintain blinding, the unblinded surgeon and surgical staff will not be involved in the other study procedures and assessments including the assessments for adverse events. Each site will have a blinding plan in place that is specific to their resourcing. • Any records generated during the surgery will be maintained separate from the study files and will not be accessible by other study personnel. • An unblinded site monitor (CRA) will review the surgical records and be responsible for NTX-001 accountability and application (IP Administration) compliance.
Product:	NTX-001 is used in conjunction with standard suture neurorrhaphy of severed peripheral nerve(s). The investigational components of NTX-001 are: • Solution #1 - Sterile calcium-free hypotonic saline (priming);

	• Solution #2 - Sterile 3.35 kDa polyethylene glycol, 50% in water (fusogen); • Solution #3 Sterile Lactated Ringer's for Injection (irrigation). • Device - Isolation Chamber Medical Device for focal application of Solution #2; The solutions are applied topically in sequence: 1. Trim the nerve stumps as needed; 2. Immediately apply Solution #1 to prime the injured nerve stumps for fusion; 3. Immediately suture; 4. Place isolation chamber under sutured nerve site; 5. Apply Solution #2 via isolation chamber for ~ 90 – 120 seconds of exposure; 6. Aspirate Solution #2 from isolation chamber as needed; 7. Remove isolation chamber; 8. Apply Solution #3 to irrigate, dilute and flush the surgical field; 9. Close wound Control: The control group is standard of care (SOC) consisting of standard suture neurorrhaphy.
Number of Subjects:	A total of 40 evaluable subjects will be enrolled in a 1:1 randomization schema (20 subjects to NTX-001; 20 subjects to the SOC). Additional subjects may be enrolled to account for early withdrawal (protocol deviations, withdrawal of consent, noncompliance, etc.). Subjects will be stratified by two locations of injury; • Distal border of brachial plexus to wrist crease; • Distal border of wrist crease to fingertip. Approximately 48 consented subjects will be randomized to meet the study goal of 40 evaluable subjects. An interim analysis is planned after approximately 20 (approximately10 per group) evaluable subjects have completed 12 weeks of treatment with a demonstrable balance between sites and injury location. If the balance between the sites and the injury location is significantly different, an interim

	analysis will be performed with additional subjects to get an approximate balance. This study will utilize an Independent Data Monitoring Committee (DMC) to adjudicate/review safety and efficacy outcomes for the interim analysis.
Study Population:	Subjects who are between the ages of 16 and 80, have experienced an acute single transected peripheral nerve injury occurring below the distal border of the brachial plexus requiring surgical repair presenting and able to undergo surgery within 48 hours of injury.
Entry Criteria:	**Inclusion:** 1. The subject has voluntarily agreed to participate in this study and has signed an Institutional Review Board (IRB) approved informed consent form. 2. The subject is at least 16 years of age and not older than 80. 3. The subject has sustained a confirmed (intra-op assessment) single transected peripheral nerve injury; a. Involves injury to motor and/or sensory function of the radial, median, or ulnar nerve with injury localized distal to the brachial plexus cord level to the fingertip; b. Multiple transected digital nerves of the hand are allowed; with each digital repair which will follow the randomization assignment resulting from upper extremity trauma meeting the following criteria. 4. The subject's nerve injury is classified as Sunderland's Fourth and Fifth Degree (Class III). 5. The subject's nerve injury is amenable to minimal or acceptable tension, in direct, end-to-end repair. 6. The surgical repair will occur within 48 hours of injury. 7. The subject is willing to comply with all aspects of the treatment and evaluation schedule over the active study period. **Exclusion:** 1. The subject has a PNI with a segmental loss (gap) that cannot be repaired with minimal or acceptable tension. 2. The subject has documented history or clinical signs on either upper extremity within the past 6 months of: a. Clinically significant peripheral neuropathy in the upper extremities from any cause i.e., medications, chemotherapy, diabetes;

	b. Significant burns to the upper extremities that may inhibit sensory or functional assessments; c. A clinically significant neuromuscular disease; d. Clinically significant local or systemic neurological deficit; e. Clinically significant carpal tunnel syndrome defined as an alteration in normal 2PD or motor function; f. Raynaud's or other disorder known to compromise circulation or sensation of the affected area; g. Or other treatments known to affect the growth and/or physiology of the neural and vascular system; The nerve injury has vascular damage that cannot be repaired to provide adequate perfusion of the injured site. 3. The subject requires chronic use of systemic glucocorticosteroids (daily throughout active study period or has had a "Burst and Taper" regimen within 14 days prior to the nerve repair). 4. The subject requires chronic opioid therapy (daily use within 14 days of nerve repair and may be required through 12 Week Assessment except for surgical repair pain or other acute reason). 5. The subject has a known allergy to polyethylene glycol (PEG). 6. If any of the assessments cannot be done on the contralateral side (CL) or the MRCC sensory 2PD value is > 10 mm on the CL side during baseline period, the subject is a screen failure. However, if a subject is missing the contralateral arm due to an amputation or has sustained an injury on the contralateral arm that makes it impossible to measure MRCC, this subject may be considered for enrollment. This assessment is done based on location of injury and is not performed on subjects with motor or mixed motor injury. 7. The subject is pregnant and/or breastfeeding. 8. The subject has a significant medical comorbidity precluding immediate repair. 9. The nerve injury has vascular damage that cannot be repaired to provide adequate perfusion of the injured site. 10. The subject is not able to strictly adhere to the rules of the current clinical protocol, e.g., significant mental health issues, homelessness, incarceration, intellectually or developmentally challenged without proper legal representation. 11. The subject is currently enrolled in another investigational study or has participated in an investigational study within 30 days prior to screening.

Study Procedures:	Study procedures, frequency, and timing are provided in Schedule of Activities (SoA). Subjects will be screened and will complete an informed consent prior to study-specific procedures being performed. Eligible subjects will be randomized to one of two a treatment groups and surgery must be performed within 48 hours of the PNI. Follow-up visits and examinations that are included in standard of care for nerve repair plus study designated visits and assessment requirements. The Investigator will determine, based on the subject's condition, if a clinic visit is required, however the clinical labs, pregnancy test (if applicable), and EP for the Weeks 12 and 48 visits must be done in the clinic.
Criteria for Evaluation:	Primary Evaluation(s): • Adverse Events • MHQ Total Score Exploratory Secondary Evaluation(s) • Electrophysiologic Assessments • MRCC Sensory Scale • MRCC Motor Scale • SWMT • Grip/Pinch Strength Patient Related Outcomes • NPRS • MHQ • CISS • PGIC
Statistical Methods:	**Sample Size Estimation:** ***Primary Endpoint of MHQ Score:*** A sample size of 20 patients per group can provide 90% power to detect a difference of 5.0 with a standard deviation of 5.3 in the primary endpoint of change from baseline of MHQ total score between NTX-001 and SOC at week 12, assuming that the change from baseline MHQ total score is 7.0 and 2 for each of the NTX-001 and SOC, respectively. The following hypothesis will be tested: $H_0: \Delta \geq 5.0$ vs. $H_1: \Delta < 5.0$ Where Δ is the difference in the change from baseline of MHQ total score between NTX-001 and SOC at Week 12. A one-sided significance level of 0.05 is considered.

Analysis Populations:

Intent-to-Treat (ITT) Population:
The ITT population will include all subjects who successfully pass screening criteria and randomized for study treatments.

Modified Intent-to-Treat (mITT) Population:
The mITT population will include all subjects who received or were exposed to at least one application of the topical study product and who provide at least up to week 4 of evaluable data for the primary endpoint. All subjects will be analyzed according to the treatment that they actually received. The mITT population data set will be used for all the efficacy analyses. All the subjects who meet mITT criteria are considered evaluable subjects.

Per Protocol (PP) Population:
The PP population will include all subjects who received or were exposed to at least one application of the topical study product, with no significant protocol deviations, and who provide at least up to week 4 of evaluable data for the primary endpoint.

Safety Population:
The safety population will include all subjects who received or were exposed to at least one application of the topical study product. All subjects will be analyzed according to the treatment that they actually received. The Safety population data set will be used for all the safety analyses.

Interim Analysis and Sample Size Re-estimation:
An interim analysis will be performed to re-assess the adequacy of the study sample size based on the primary efficacy endpoint of interest, the change from baseline MHQ total score at week 12 after the first approximately 20 (about 10 subjects in NTX-001 group and about 10 subjects in SOC group) randomized subjects have completed 12 weeks of treatment with a demonstrable balance between sites and injury location. If the balance between the sites and the injury location is significantly different, interim analysis will be performed with additional subjects to get an approximate balance.

Sample size adjustment is based on the primary endpoint, the change from baseline of MHQ total Score. However, the sample size will not be reduced regardless of the results of the interim analysis. At the end of the study, the

	data will be analyzed using the Cui-Hung-Wang (Cui-Hung-Wang 1999) method to reflect the fact of the sample size adjustment. The interim analysis will be performed by an external independent statistician. Details of the interim analysis will be provided in a Statistical Analysis Plan (SAP). **Efficacy Analyses:** All the efficacy analyses will be the comparisons of the NTX-001 group with the SOC group for all the primary and secondary efficacy end points. Baseline efficacy endpoints are the results obtained at any time from fully executed consent to before or at Week 1 Visit. **Primary Efficacy Analysis:** The Primary efficacy analysis will be performed using Mixed Model Repeated Measures (MMRM) analyses for the primary endpoint of change from baseline of MHQ total Score at Week 12. The model will include treatment and visit as fixed effects and baseline MHQ total score as covariate. **Exploratory Secondary Efficacy Analysis:** The Cochran-Mantel-Haenszel test will be used for the secondary endpoint of comparison of percentage of patients responding to Electrophysiologic Assessments at Week 12 between NTX-001 and SOC. If a patient withdraws from the study, this patient will be counted as a non-responder for endpoints after withdrawal. All the remaining secondary efficacy analyses will be performed using Mixed Model Repeated Measures (MMRM) analyses similar to the primary end point analysis. Summaries for the absolute and change from baseline values for all these secondary endpoints will be provided by treatment group and time point. **Safety Analyses:** The safety analysis will include reported AEs and other safety information (i.e., clinical laboratory evaluations, vital signs, physical examination). A summary of safety results will be presented for each treatment group.

1.2. Table 1 – Schedule of Activities (SoA)

Study Visit	V0	V1a	V1b	V1c	V2	V3	V4	V5	V6	V7	V8
	Baseline Period										
	Screen	Pre-Op	Intra-Op	Post-Op	W 1 +4/- 2 D	W 4 +/- 5D	W 8 +/- 5D	W 12 +/- 5D	W 24 +/- 7D	W 36 +/- 7D	W 48 +/- 7D
Informed Consent[1]	X										
Demographics	X										
Inclusion/Exclusion	X	X	X[2]								
Smoking History	X										
Class of Injury			X[2]								
Type-Nerve Injury	X										
Medical History[11]	X										
Concurrent Injuries	X										
Physical Exam	X							X			X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X
Labs (Pregnancy, Chem7, CBC)	X							X			
Randomization			X								
Urine Pregnancy								X	X	X	X
Date-Time Injury	X										
EP								X			X[12]
CheckPoint® Stimulator			X								
MRCC Sensory [3, 4, 5, 6, 9]	X					X	X	X	X	X	X
MRCC Motor [3, 4, 6]	X					X	X	X	X	X	X
MHQ [8]	X					X	X	X	X		X
Grip/Pinch Strength [3, 4, 6, 7]	X					X	X	X	X	X	X
SWMT [3, 4, 6, 10]	X					X	X	X	X	X	X
CISS [4, 6]	X					X	X	X	X		X
PGIC [4, 6]	X					X	X	X	X		X
NPRS [4, 6]	X					X	X	X	X	X	X
PT/OT Compliance until DC					X	X	X	X	X	X	X
Splint Evaluation until DC					X	X	X	X	X	X	X
Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X

1. No study related procedures conducted prior to obtaining ICF.
2. Intra-operative assessment, if the peripheral nerve injury does not meet Sunderland's, Fourth and Fifth Degree (Class III), the subject is considered a screen fail.
3. Assessments are conducted on the affected and contralateral sides; however, contralateral assessments are only done at Baseline, Weeks 8, 12 and 48. An additional CL assessment is done at Week 24 week for Pinch/Grip strength.
4. Baseline values (except for Grip/Pinch Strength) are required assessments obtained at any time from fully executed consent to before or at Week 1 Visit.
5. If any of the assessments cannot be done on the contralateral side (CL) or the MRCC sensory 2PD value is > 10 mm on the CL side during baseline period, the subject is a screen failure. However, if a subject is missing the contralateral arm due to an amputation or has sustained an injury on the contralateral arm that makes it impossible to measure MRCC, this subject may be considered for enrollment. This is assessed based on location of injury and is not performed on subjects with motor or mixed motor injuries. The subject will be a screen failure or early termination if done post-repair.
6. The sequence of assessments will be standardized to mitigate questionnaire fatigue.
7. The Grip/Pinch Strength test is conducted based on location of injury. Grip/Pinch strength testing is done on motor or mixed motor injuries only. These assessments are done after splint removal (as applicable) and only with investigator approval.
8. The screening/baseline assessment of the MHQ should reflect the subject's functional ability 7 days prior to their injury.
9. The MRCC Sensory Scale includes 2 point discrimination measurements and is assessed based on location of injury. Both static and moving assessments are to be done on the ulnar and radial sides on the affected digits only (palmar crease to fingertip). The exam is not performed on subjects with motor or mixed motor injuries.
10. The SWMT is assessed based on location of nerve injury. For sensory nerve injuries (digital), the ulnar and radial sides on the affected digits are tested (palmar crease to fingertip). For motor or mixed motor injuries, the ting is done based on the regions of the hand affected by the ulnar, radial, or medial nerve injuries.
11. Medical history is collected within six (6) months prior to screening visit.
12. EP assessment done at Week 48 has a defined window of plus or minus four (4) weeks.

2. Introduction

2.1. Study Rationale

Peripheral nerve transections from trauma commonly occur in civilian and military populations and often result in prolonged or permanent significant loss of sensation and neuromuscular function (Brushart 2011; Fishman 2000; Bittner et al. 2015; Ghergherehchi et al. 2016; Fox 2010). Recovery from peripheral nerve transection requires surviving proximal stumps to extend outgrowths (an innate action), limited to growth rates of ~1mm/day, that often slowly, partially, and non-specifically reinnervate distal target tissues. The rate of regeneration may vary depending on location along the neuron in which proximal segments may see an increase of 2-3mm/day while more distal segments may progress at a rate of 1-2mm/day (Menorca, 2013).

Reinnervation occurs over months-to-years post-operatively (Post-Op) in large mammals such as humans (Spaeth et al. 2012; Brushart 2011). Severed distal axonal segments in mammals always degenerate within three (3) days (Brushart 2011; Bittner et al. 2015; Fishman 2000; Spaeth et al. 2012; Brushart 2011). Degeneration of the distal stump of the nerve results in denervation of target tissues that may severely and permanently atrophy before innate regeneration can occur.

Improving the rate and quality of mammalian axonal regeneration has been a major goal for neuroscientists and peripheral nerve repair surgeons, with repair strategies to date (e.g., nerve growth guides, nerve coaptation protection appliances, microsutures) relying on guiding axonal outgrowth to increase reinnervation success. Such techniques sometimes improve recovery of sensation and function, but do not affect the rate of axonal outgrowth, improve the time course of recovery, nor prevent Wallerian degeneration of severed distal axons (Riley et al. 2015; Bittner et al. 2015; Ghergherehchi et al. 2016; Bittner et al. 2016; Birch 2011; Kalbermatten et al. 2009; Kawasaki et al. 2000; Lago et al. 2007; Welin et al. 2009).

Due to the direct costs of acute care, rehabilitation, loss to the workforce and long-term disability, the aggregate economic impact to the US healthcare system secondary to PNI has been estimated at >$150 billion (Brattain 2015). These staggering statistics coupled with the current lack of medical technologies to improve the speed and quality of recovery from PNI underscore the significance of the need for better therapeutic alternatives.

2.2. Background

More than 1.4 million traumatic injuries that include peripheral nerve injuries (PNI) occur in the US each year. There are immediate and long-term consequences to PNIs. Immediately after a PNI the patient experiences complete loss of sensation and function in the distal area innervated by the severed nerve. Soon thereafter (within days of injury), the distal segments of all axons within the severed nerve always undergo obligate degeneration (“Wallerian degeneration”) (Brushart, 2011), (Bittner, 2015), (Fishman, 2003), (Spaeth, et al., 2011). Subsequent recovery

from PNI is only possible by natural regrowth of the axons from the proximal end of the nerve. This process is slow (~1 mm/day) and imperfect (Grinsell, 2014). The protracted recovery period results in prolonged denervation of distal targets such as muscle, neuromuscular junctions and neurosensory organs causes atrophy, which is often irreversible even after reinnervation. Contemporary standard of care for transected PNI involves surgical reattachment of the proximal and distal stumps of the injured nerve using microsutures ("neurorrhaphy"). Unfortunately, neurorrhaphy does not address the underlying problem of obligatory degeneration of all distal axonal segments of the severed nerve. More importantly, no technology in clinical practice nor in development has been shown to increase the speed nor the quality of natural regeneration, which remains the only possible route to sustained recovery. Long-term clinical outcomes from PNIs include partial to near-complete loss of sensation and/or function manifesting in some degree of disability, which is many times permanent in nature (Grinsell & Keating, 2014).

Polyethylene glycol (PEG) mediated axonal fusion ("PEG-fusion") embodied into NTX-001, holds considerable promise for improving clinical outcomes for patients with PNIs. By reconnecting (fusing) a substantial number of axons within a severed nerve, the degeneration-regeneration cycle and subsequent atrophy is substantially reduced or prevented for those axons and their targets, respectively. PEG-fusion has the potential to avoid the consequences of protracted denervation of distal target tissues by eliminating the period of total denervation, reducing the time to stable recovery, and providing substantially greater innervation to affected tissues.

Preclinical studies utilizing the PEG-fusion technology have shown that PEG-fusion increases the speed and quality of recovery from PNI. Additionally, two (2) investigator sponsored INDs have been sanctioned by the FDA at WellSpan York Hospital, York, PA, led by Richard Trevino MD (ClinicalTrials.gov Identifier: NCT03236064) now closed and at Vanderbilt University, Nashville, TN, led by Wesley Thayer MD (ClinicalTrials.gov Identifier: NCT02359825). Ten (10) pilot clinical cases of PEG-fusion in patients with upper extremity severed nerves have been identified, two (2) by Ravinder Bamba (Bamba 2016), four (4) by Thayer and four (4) to date by Trevino. These seem to confirm that the PEG fusion procedure may produce a safe and similar effect in humans.

2.3. Benefit/Risk Assessment

There are no known risks associated with NTX-001. There are assumptions of risk based on the clinical understanding of the standard of care procedure currently used in PNI repair. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of NTX-001 may be found in the Investigator Brochure (IB).

2.3.1. Benefit Assessment

Any known potential benefits are reflected in the non-clinical animal testing conducted by Neuraptive and discussed in the IB. Two (2) investigator sponsored INDs have been sanctioned by the FDA and the results provide supportive human validation of the surgical approach and while acknowledging these case studies, no generalization related to benefit in larger populations can be made.

2.3.2. Overall Benefit: Risk Conclusion

The concept of risk is generally understood to refer to the combination of the probability and magnitude of some future harm. According to this understanding, risks are considered "high" or "low" depending on whether they are more (or less) likely to occur, and whether the harm is more (or less) serious. This study presents minimal risk as the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of itself than those ordinarily encountered in peripheral nerve injury repair. For additional information on risk, see the Investigator Brochure.

3. Endpoint and Objective(s):

All the primary and secondary efficacy end points will be used for the comparisons of the NTX-001 group with the SOC group. The treatment comparisons of safety endpoints will be summarized by treatment using the descriptive statistics. Baseline efficacy endpoints are the results obtained at any time from fully executed consent to before or at Week 1 Visit.

3.1.1. Primary Endpoint(s):

Safety:

Safety endpoints include adverse events and other safety data (vital signs, clinical labs, physical exam) across 48 weeks following operative repair. Safety assessments are done during each interaction with the patient, including required study visits and any ad hoc communications or visits where the patient describes any of their experiences following the surgical repair. There is no difference in the way safety information is gathered and documented between the NTX-001 or the SOC care groups as those assessments will be done by evaluators blinded to treatment assignment.

MHQ Total Score at Week 12:

This co-primary endpoint is the change from baseline of MHQ Total Score at Week 12. MHQ is a 37-item self-assessment instrument that measures disability along 6 domains: function, activities of daily living, pain, hand appearance, patient satisfaction, and work disability. (Chung 1998)

The screening/baseline assessment of the MHQ should reflect the subject's perception of functional ability seven (7) days prior to their injury. Change scores quantifying the amount of improvement for each domain were calculated for each participant by subtracting the score of the second administration of the MHQ from the score from the first (The range of MHQ Total Score is 0–100, with 100 being the "best" score). (Shauver, 2009)

3.1.2. Exploratory Secondary Endpoint(s):

Electrophysiologic Assessment

The electrophysiological endpoint includes the percentage of subjects responding to intraoperative nerve stimulation and an electrophysiology assessment at 12 and 48 weeks. Weeks 12 and 48 are considered critical visits and are conducted onsite. Facility and individual infection control policies will be followed during the visit. Contralateral testing is conducted in nerve conduction velocity only not EMG.

A CheckPoint® Stimulator will be used intra-operatively to detect immediate reconnection of severed peripheral nerves (axons).

- Intra-operative nerve stimulation will be performed in the NTX-001 group after microsuture and Solution #3 irrigation prior to surgical close.
- Intra-operative nerve stimulation will be performed in the SOC group after microsuture and standard rinse prior to surgical close.

The measures include in response of direct nerve stimulation, proximally and distally to coaptation site. Restoration of nerve conduction indicates the restoration of axon continuity, which is a prerequisite for the prevention for Wallerian degeneration, neuromuscular junction degeneration, muscle atrophy and functional recovery.

Medical Research Council Classification (MRCC) Sensory Scale

The MRCC Sensory assessment includes 2 point discrimination (2PD) measurements and is assessed based on injury location. Both static and moving assessments are done on the ulnar and radial sides on the affected digits only (palmar crease to fingertip). The nerve sensory endpoint

	Was there a Motor Response?	Amplitude	Pulse Duration
1. Distal Motor Response	☐ Yes ☐ No	☐ 0.5 mA ☐ 2 mA ☐ 20 mA	_____
2. Proximal to Coaptation: After Microsuture			
Motor Response	☐ Yes ☐ No	☐ 0.5 mA ☐ 2 mA ☐ 20 mA	_____
3. Proximal to Coaptation: After final Rinse			
Motor Response	☐ Yes ☐ No	☐ 0.5 mA ☐ 2 mA ☐ 20 mA	_____

includes the change from baseline of MRCC sensory scale scores at the visits 4, 8, 12, 24, 36 and 48 weeks. The scale is commonly used, by including 2PD for grading the sensory outcome after peripheral nerve surgery. This scale is categorized into S0-S4: S0 is the absence of sensibility; S1 is the recovery of deep cutaneous pain; S2 is the return of superficial cutaneous pain and some degree of tactile sensibility; S3 is the return of superficial cutaneous pain and tactile sensibility without over response; and S4 is the complete recovery. (MacKinnon and Dellon, 1990)

MRCC Research Council Classification (MRCC) Motor Scale

The MRCC Motor Scale is assessed based on location of injury. This assessment it is conducted on motor and mixed motor nerve injuries only. The nerve motor endpoint includes the change from baseline of MRCC sensory scale scores at the visits 4, 8, 12, 24, 36 and 48 weeks. The MRCC motor scale is commonly used to assess strength which can best be assessed by isolating an individual muscle group and comparing power with that of the patient. It can be conducted to assess larger muscles or muscle groups as well as intrinsic muscles of the hand. 0/5 is no muscle activation whatsoever; 1/5 is muscle activation without limb movement; 2/5 implies that the limb can be moved only when gravity is taken out of the equation; 3/5 means that the patient can overcome gravity but not resistance; 4/5 (or 4+ or 4-) implies weakness with enough strength to overcome varying degrees of physical resistance; 5/5 is full strength. (Brandsma 1995)

Semmes Weinstein Monofilament Test (SWMT)

The SWMT is assessed based on location of nerve injury. For sensory only (digital injuries), the ulnar and radial sides on the affected digits are tested (palmar crease to fingertip). For motor or mixed motor injuries, the testing is done based on the regions of the hand affected by the ulnar, radial, or medial nerve injury. The sense of touch endpoint includes the change from baseline of SWMT cutaneous pressure threshold values at the visits 4, 8, 12, 24, 36 and 48 weeks. SWMT is used to assess perception of cutaneous pressure threshold, which reflect reinnervation of peripheral targets. Tactile gnosis is the capability of the hand to recognize the character of objects, such as shapes, textures, and is a prime marker of functional recovery. (Bell-Krotoski 1987)

Grip/Pinch Strength

The Grip/Pinch Strength test is conducted based on location of injury. Strength testing is done on motor or mixed motor injuries only. These assessments are done after splint removal (as applicable) and with investigator approval. Grip/pinch endpoint include the change from baseline of grip/pinch strength values at the visits 4, 8, 12, 24, 36 and 48 weeks. Assessment of grip/pinch strength using dynamometry equipment are common methods to assess functional motor outcome. The tests are used initially and in periodic retests to demonstrate improvement in the strength available to grasp or pinch. (Geere 2007)

Numeric Pain Rating Scale (NPRS)

The pain endpoint includes the change from baseline NPRS scores at the visits, 4, 8, 12, 24, 36 and 48 weeks. The NPRS is used to assess for pain and to determine pain intensity. The evaluation of pain using the NPRS will be analyzed as change from baseline as compared to each score obtained at each visit over the 48 week period. (McCaffery 1989) (Wang 2013)

MHQ

The secondary MHQ endpoint included the change from baseline MHQ Total scores at the visits, 4, 8, 24, and 48 weeks.

Cold Intolerance Symptom Severity (CISS)

The cold sensitivity endpoint includes the change from baseline of CISS questionnaire score at the visits, 4, 8, 12, 24, and 48 weeks. Cold sensitivity is a complex symptom, which may present as pain, numbness, stiffness, weakness, swelling and change in skin color. The Cold Intolerance Symptom Severity (CISS) is used to evaluate sensitivity of cold intolerance during daily life. (Ruijs 1996)

Patients' Global Impression of Change (PGIC)

The patient reported outcome endpoint includes the change from baseline of PGIC questionnaire score at the visits, 4, 8, 12, 24, and 48 weeks. This scale evaluates all aspects of patients' health and assesses if there has been an improvement or decline in clinical status. (Guy 1996)

4. Study Design

4.1. Overall Design

The hypothesis of the study is that subjects that experience an acute single transected peripheral nerve injury occurring below the distal border of the brachial plexus to the fingertip requiring surgical repair will have outcomes that reflect improved quality and time to restoration of motor function and sensation with the adjunct use of the NTX-001. Multiple transected digital nerves of the hand are allowed. Each digital repair will follow the randomization assignment and, if randomized to NTX-001, will require a separate NTX-001 IP Kit.

If the surgeon is unable to address the nerve injury in the other digits using direct repair, they may use other methods to coapt the nerve such as conduits, auto and allografts. This data will not be analyzed with the primary efficacy endpoint.

- Phase 2a
- The Investigational Product under study is called NTX-001.
- Patient and Evaluator Blinded, Randomized-Controlled, Multi-Center Study
- The study will be executed in such a way as to minimize bias in the conduct of the postoperative evaluations of study subjects by the following methods:
    - Subjects will be randomized into one of two groups using a blinded method provided by an independent statistician.
    - Any records generated during the surgery will be maintained separate from the study files and will not be accessible by other study personnel.
    - Subjects will not be informed as to which study arm; they have been assigned until after the study is completed.
    - Subjects will be blindfolded, or actual testing obscured to the subject during assessment for items 3 and 4 as noted below.
    - Postoperative evaluations such as functional motor and sensory assessments will be performed by the same qualified evaluator (if possible), blinded to treatment assignment.
    - An unblinded site monitor (CRA) will review the surgical records and be responsible for NTX-001 accountability and application (IP Administration) compliance.
    - Functional motor and sensory assessments will be done according to instructions for that assessment, in an attempt to prevent questionnaire fatigue, and if possible, standardize the assessment sequence as follows and conduct on contralateral (CL) side as noted:

1. NPRS-Pain
2. Vital Signs
3. MRCC Sensory and/or Motor based on location of injury
    a. CL is done during the baseline period and at Weeks 8, 12, 48 only.
    b. MHQ Patient Related Outcome
4. Semmes Weinstein Monofilament Test based on injury location
    a. CL is done during the baseline period and at Weeks 8, 12, 48 only.
5. Grip/Pinch Strength based on injury location
    a. CL is done during the baseline period and at Weeks 8, 12, 24, 48 only.
6. Cold Intolerance Symptom Severity (CISS)
7. Patient Global Impression of Change (PGIC)
8. PT/OT/Splint Compliance
9. EP - CMAP and NCV will be the last test conducted if all others are done on the same day or it can be done on another day within the allowable window before or after the scheduled visit.

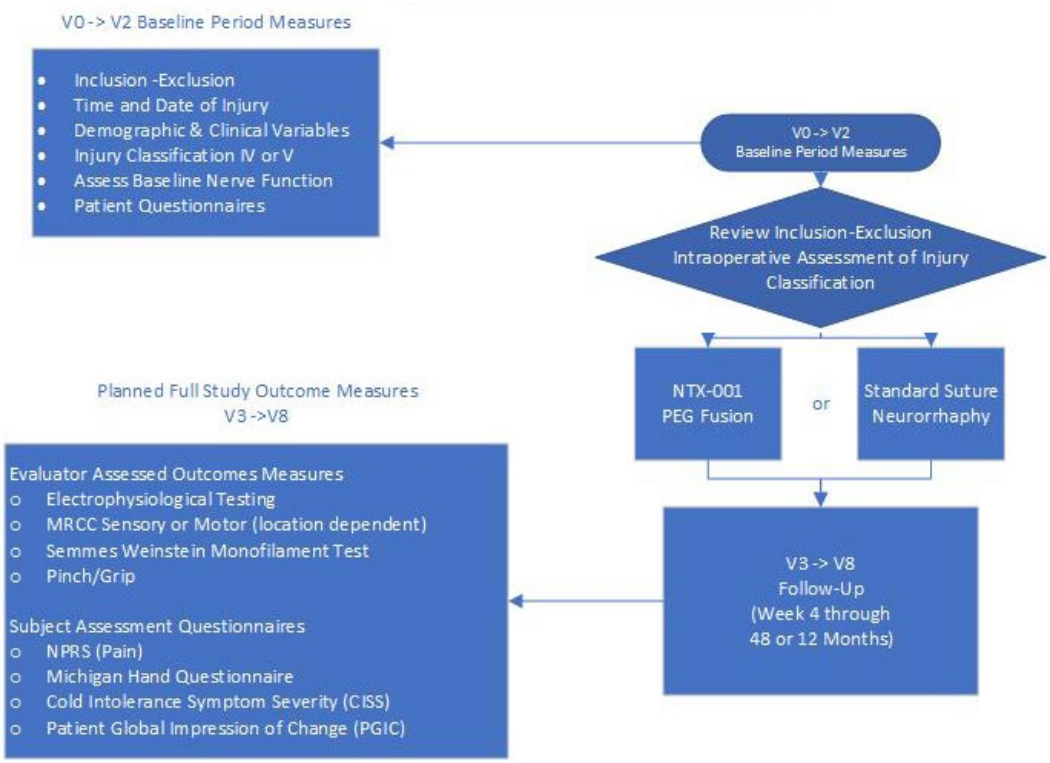
- There will be two groups under study, 20 randomized to the NTX-001 Product and 20 into the Control (SOC) group. Subject follow-up will be at weeks 4, 8, 12, 24, 36 and 48 weeks post repair.

    - An interim analysis will be performed to re-assess the adequacy of the study sample size based on the primary efficacy endpoint of interest, the change from baseline

- MHQ total score at week 12 after the first approximately 20 (about 10 subjects in NTX-001 group and about 10 subjects in SOC group) randomized subjects have completed 12 weeks of treatment with a demonstrable balance between sites and injury location. If the balance between the sites and the injury location is significantly different, interim analysis will be performed with additional subjects to get an approximate balance. Subjects will be studied for 48 weeks after surgical repair of the affected peripheral nerve.

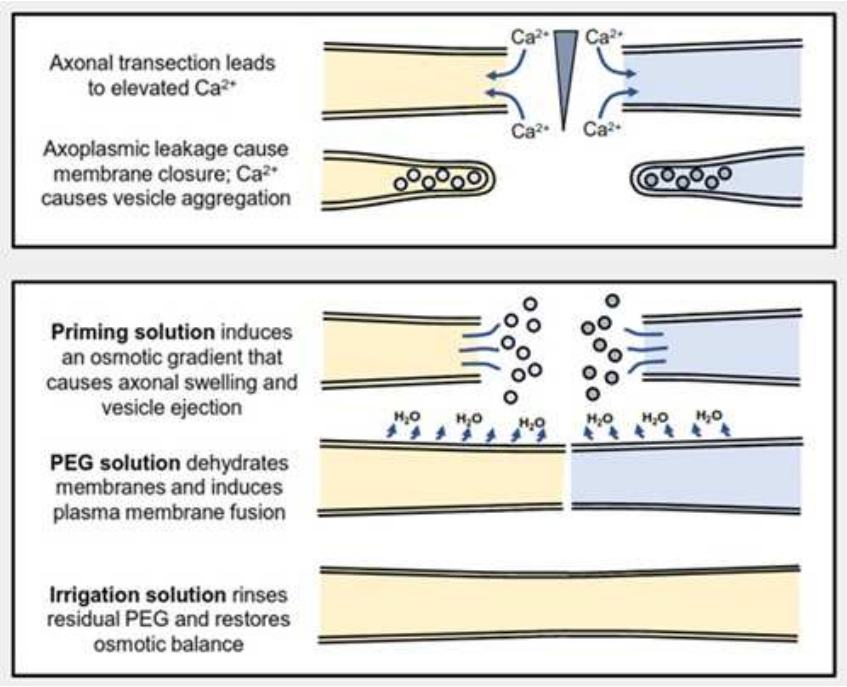
- The study will be conducted at approximately 15 sites in the United States.

4.2. Rationale for Study Design



4.3. Justification for NTX-001 Application

PEG-fusion: The mechanism of action of PEG-fusion is well published (Bittner 2016; Mikesh et al. 2018a; Mikesh et al. 2018b) and is based upon the use of a hydrophilic polymer that induces fusion of closely apposed axonal ends within a severed and microsutured nerve (Figure 1). Fusion immediately restores axonal continuity between the proximal and distal ends of the repaired nerve. Electrical signaling of fused axons can be intraoperatively detected within minutes. Fused axons with re-established connectivity to cell bodies located proximal to the injury and repair site are more likely to remain viable and not undergo WD and the target tissues enervated by those same axons do not undergo denervation-mediated atrophy. The fusing and stability of lipid bilayers including plasma membranes is dependent on several factors: 1) the cohesive forces between phospholipids and water molecules, 2) the electrostatic repulsive forces



between adjacent bilayers, and 3) the van der Waals attractions between the hydrocarbon chains. For synthetic lipid bilayers and natural plasma membranes, strong hydrostatic forces between the water molecules and phospholipids as well as membrane associated proteins are key in maintaining membrane stability. The induction of plasma membrane fusion by PEG is a biophysical phenomenon wherein the water molecules associated with phospholipids and plasma membrane proteins are temporarily sequestered by PEG molecules. This induces local dehydration of plasma membranes causing plasma membrane instability and subsequent fusion to proximal axonal membranes. For axonal plasma membrane fusion to occur, local dehydration is rapidly induced by high concentrations (25-50%) of low molecular weight PEG. The resulting membrane instability persists until fusion with other unstable plasma membrane segments occurs. Removal of PEG by aspiration as needed from the device and subsequent irrigation with excess isotonic calcium-containing solution dilutes residual PEG and restores transmembrane osmotic balance to the axons. Fusion is only possible when the axonal ends are in close approximation as created by standard suture neurorrhaphy.

It is important to note that the isolation chamber device performs no therapeutic action and only functions to temporarily contain Solution #2 in the sequence of application. The device is intended to only be in contact with the treated nerve for enough time to allow for prescribed PEG exposure during the procedure and is not left implanted in the body. The entire sequence of steps as well as the administration and function of each solution are described in an Instructions for Use (IFU) document.

4.4. End of Study Definition

A subject is considered to have completed the study if they have completed all phases of the study including the last visit shown in the SoA, Table 1, Study Procedure Frequency and Timing Overview. The end of the study is defined as completion of the last visit (V8 or Week 48).

Subjects will participate in the study for a total of approximately 48 weeks. Participation will consist of a screening visit, a treatment or surgical visit, week 1 visit (Baseline Period) and follow-up visits that will occur at weeks 4, 8, 12, 24, 36 and 48 weeks.

4.5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

4.6. Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. The subject has voluntarily agreed to participate in this study and has signed an Institutional Review Board (IRB) - approved informed consent form.
2. The subject is at least 16 years of age and not older than 80.
3. The subject has sustained a confirmed (intra-op assessment) single transected peripheral nerve injury resulting from upper extremity trauma meeting the following criteria:
    a. Involves injury to motor and/or sensory function of the radial, median, or ulnar nerve with injury localized distal to the brachial plexus cord level to the fingertip;
    b. Multiple transected digital nerves of the hand are allowed; with each digital repair which will follow the randomization assignment resulting from upper extremity trauma meeting the following criteria:
4. The subject's nerve injury is classified as Sunderland's, Fourth and Fifth Degree (Class III)
5. The subject's nerve injury is amenable to minimal or acceptable tension, in direct, end-to-end repair.
6. The surgical repair will occur within 48 hours of injury.
7. The subject is willing to comply with all aspects of the treatment and evaluation schedule over the active study period.

4.7. Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

1. The subject has a PNI with a segmental loss (gap) that cannot be repaired with minimal or acceptable tension.
2. The subject has documented history or clinical signs on either upper extremity of:
    a. Clinically significant peripheral neuropathy in the upper extremities from any cause i.e., medications, chemotherapy, diabetes;
    b. Significant burns to the upper extremities that may inhibit sensory or functional assessments;
    c. A clinically significant neuromuscular disease;

d. Clinically significant local or systemic neurological deficit;
e. Clinically significant carpal tunnel syndrome defined as an alteration in normal 2PD or motor function;
f. Raynaud's or other disorder known to compromise circulation or sensation of the affected area;
g. Or other treatments known to affect the growth and/or physiology of the neural and vascular system;

3. The subject requires chronic use of systemic glucocorticosteroids (daily throughout active study period or has had a "Burst and Taper" regimen within 14 days prior to the nerve repair).
4. The subject requires chronic opioid therapy (daily use within 14 days of nerve repair and may be required through 12 Week Assessment except for surgical repair pain or other acute reason).
5. The subject has a known allergy to polyethylene glycol (PEG).
6. If any of the assessments cannot be done on the contralateral side (CL) or the MRCC sensory 2PD value is > 10 mm on the CL side during baseline period, the subject is a screen failure. However, if a subject is missing the contralateral arm due to an amputation or has sustained an injury on the contralateral arm that makes it impossible to measure MRCC, this subject may be considered for enrollment. The subject is pregnant and/or breastfeeding.
7. The subject has a significant medical comorbidity precluding immediate repair.
8. The nerve injury has vascular damage that cannot be repaired to provide adequate perfusion of the injured site.
9. The subject is not able to strictly adhere to the rules of the current clinical protocol, e.g., significant mental health issues, homelessness, incarceration, intellectually or developmentally challenged without proper legal representation.
10. The subject is currently enrolled in another investigational study or has participated in an investigational study within 30 days prior to screening.

4.8. Enrollment Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently and randomly assigned to the NTX-001 or SOC due to the following:

- If the subject's contralateral upper extremity s2PD value cannot be assessed during the baseline period or the value *is greater than >10mm (in the same region/nerve as the injury)*, the subject will be a screen fail.
- If during the operative period it is determined inclusion criteria #4 is not met, the subject will be a screen failure.

A minimal amount of screen failure data will be recorded to ensure transparent reporting of screen failure subjects, to meet publishing requirements and to respond to queries from regulatory authorities. The information to be recorded on screen failure subjects will include but not be limited to demography, eligibility criteria, and any adverse events.

4.9. Surgeon Training Program for Use of NTX-001

Surgeons that intend to use the NTX-001 product will be required to participate in a formal training program developed and administered by Neuraptive.

4.10. Study Intervention

Intervention Name	NTX-001
Type	Drug/Device Combination
Dose Formulation	Solution
Unit Dose Strength(s)	Based on the 2.5 mL volume of 50% PEG 3350 Da w/w in water supplied for Solution #2, the maximum single-dose exposure to PEG-3350 from the NTX-001 kit is 1.325 g, or approximately 0.02 g/kg for a 150-lb individual.
Dose Application	Solution #1 – at least 5 mL Solution #2 – no more than 2.5 mL Solution #3 – at least 10 mL
Dose Formulation – Priming Solution	NTX-001 Solution 1 – Priming Solution - Sterile Calcium-free Hypotonic Saline (14 mL contained in a 20 mL vial); free flow from a syringe via blunt needle directly onto nerve stumps. It is applied immediately following trimming of the nerve ends as needed, in preparation for repair.
Dose Formulation – Fusogen Solution	NTX-001 Solution 2 – PEG Fusogen Solution, 50 % w/w (2.5 mL in 3 mL vial); nominal concentration 543 mg/mL; free flow application from a syringe via blunt needle into isolation chamber medical device;
Dose Formulation – Irrigation Solution	NTX-001 Solution 3 – Irrigation Solution – Sterile Lactated Ringers for Injection, USP (14 mL contained in a 20 mL vial); free flow from a syringe via blunt needle directly onto surgical field after device removal.
Isolation Chamber Device	Four (4) light green, translucent isolation chamber medical devices {chamber or device(s)} of various sizes: 1 mm, 1.6 mm, 3 mm, and 5 mm contained securely in a tray. Based on surgeon assessment of nerve size, the appropriately sized isolation chamber is placed under the coapted area(s) or sutured nerve(s), this device performs no therapeutic action and only functions to temporarily contain Solution #2 in the sequence of application.
Route of Administration	Topical

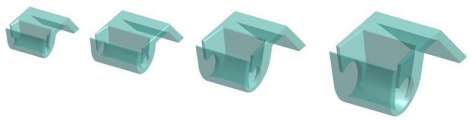
Use	NTX-001 is a single use surgical product intended for use as adjunct treatment in the repair of severed peripheral nerves in patients (16 and 80 years of age) requiring standard suture neurorrhaphy.
Packaging and Labeling	NTX-001 is packaged and labeled according to applicable local and regulatory requirements. All NTX-001 packaging will be uniquely numbered and associated with a randomization schema.
Storage	NTX-001 will be stored ambient in a securely locked area, accessible to authorized persons only, until needed for the peripheral nerve repair. NTX-001 shelf life stability will be assessed in an ongoing stability program with required and relevant documented updates provided to the clinical sites.

4.11. NTX-001 Product

NTX-001 is the embodiment of a novel technology designed to optimize reconnection of the axons after fascicle coaptation through neurorrhaphy in an attempt to abate Wallerian denegation resulting in the downstream affects that will improve the speed and quality of recovery in conjunction with standard suture nerve repair. The use and application of the NTX-001 will also be described in a separate Instructions for Use (IFU) document.

- Priming Solution #1 - Sterile Calcium-free Hypotonic Saline (5mL)
- Fusogen Solution #2 - Sterile 50% Polyethylene Glycol-3350 Da w/w in water (2.5mL)
- Irrigation Solution #3 – Sterile Lactated Ringers for Injection, USP (10mL)

NTX-001 the Investigational product (IP) is configured as a surgical use product in two different containers.



- One standard and labeled white carton contains the sterile Solutions #1, #2 and #3. The vials are secured in a foam tray.
- The other container is a pouch which contains four (4) light green, translucent isolation chamber medical devices {chamber or device(s)} of various sizes: 1mm, 1.6mm, 3mm, and 5mm.

<u>Packaging needs to be managed in the surgical suite related to sterility standards to adjust for the following non-sterile surfaces:</u>

- o External surface of vial carton is non-sterile;
- o External surfaces of vials are non-sterile;
- o External surface of the pouch containing the devices is non-sterile

Stability:
Stability of the NTX-001 will be monitored using the GMP batch placed on an ICH compliant stability program. Stability of the NTX-001 will be monitored using the GMP batch placed on an ICH compliant stability program.

Solution #1: Calcium free hypotonic saline is similar to the established product known as Plasma-Lyte A for Injection, pH 7.4 but at a lower electrolyte concentration; The inorganic salts in the solution do not degrade. Based on the extensive knowledge of the commercial product Plasma-Lyte A Injection pH 7.4 (Baxter Healthcare Inc.) a shelf-life of > 2 years is predicted.

Solution #2: PEG-3350, Da (50% w/w) in water is expected to have a shelf-life > 2 years. PEG-3350 is a compendial polymer that is used in a variety of pharmaceutical products as excipient and active ingredient. PEG-3350 is known to be heat resistant > 100° C and does not degrade under ambient conditions.

Solution #3: The irrigation solution is an isotonic solution that is based on Lactated Ringer's for Injection, USP.

Isolation Chamber Device (Device):
The device consists of NuSil MED-4930: 98% wt. and NuSil MED-50-4900-6: 2% wt. medical grade silicone. The device performs no therapeutic action and only functions to maintain the coapted nerve passively and temporarily in Solution #2 during the sequence of application. The device is not left implanted in the body.

4.12. Measures to Minimize Bias: Randomization and Blinding

The study will be executed in such a way as to minimize bias in the conduct of the postoperative evaluation of study subjects by the following methods:

- Subjects will be randomized into one of two groups using a blinded method provided by an independent statistician.
- Any records generated during the surgery will be maintained separate from the study files and will not be accessible by other study personnel. Subjects will not be informed as to which study group they have been assigned until after the study is completed.
- Subjects will be blindfolded, or actual testing obscured to the subject during assessment for items 3 and 4 as noted below.
- Postoperative evaluations such as functional motor and sensory assessments will be performed by the same qualified evaluator (if possible), blinded to treatment assignment.
- An unblinded site monitor (CRA) will review the surgical records and be responsible for NTX-001 accountability and application (IP Administration) compliance.

- Functional motor and sensory assessments will be done according to instructions for that assessment, in an attempt to prevent questionnaire fatigue, and if possible, standardize the assessment sequence as follows and conduct on contralateral (CL) side as noted:
  1. NPRS-Pain
  2. Vital Signs
  3. MRCC Sensory and/or Motor based on location of injury
     (a) CL is done during the baseline period and at Weeks 8, 12, 48 only.
  4. MHQ Patient Related Outcome
  5. Semmes Weinstein Monofilament Test based on location of injury
     (a) CL is done during the baseline period and at Weeks 8, 12, 48 only.
  6. Grip/Pinch Strength based on location of injury
     (a) CL is done during the baseline period and at Weeks 8, 12, 24, 48 only.
  7. Cold Intolerance Symptom Severity (CISS)
  8. Patient Global Impression of Change (PGIC)
  9. PT/OT/Splint Compliance
  10. EP - CMAP and NCV will be the last test conducted if all others are done on the same day or it can be done on another day within the allowable window before or after the scheduled visit.

4.13. Blinding

At Visit 1b, subjects will be assigned a unique number representing assignment into one of two groups. Subjects will be assigned in a 1:1 ratio. The randomization number encodes the subject's assignment to one of the 2 arms of the study, according to the randomization schedule generated prior to the study by the designated independent statistician. Each subject will be identified with a unique randomization number, throughout the study.
Subjects, Neuraptive personnel, and evaluators of efficacy will remain blinded to assigned intervention throughout the course of the study until database is in final lock. Surgeons and surgical staff will be unblinded to the assignment.

- Any records generated during the surgery will be maintained separate from the study files and will not be accessible by other study personnel.

- An unblinded site monitor (CRA) will review the surgical records and be responsible for NTX-001 accountability and application (IP Administration) compliance.

In order to maintain this blind, an unblinded site monitor will be responsible for the reviewing NTX-001 product accountability and application compliance of NTX-001 and will endeavor to ensure that there are no differences in subject management.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's intervention assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact Neuraptive prior to revealing the subject's assignment. If a subject's intervention assignment is revealed, Neuraptive must be notified within 24 hours after breaking the blind.

4.14. Study Intervention Compliance

Compliance is based on the subject attending the required study visits and will be evaluated based on the information recorded in the electronic Case Report Form (eCRF) during the treatment visits. If there are any deviations from the planned procedures, these will be recorded in eCRF.

4.15. Concomitant Therapy

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the eCRF are concomitant prescription medications related to nerve repair surgical pain or for the treatment of any adverse event. Subjects will be allowed to remain on their routine medications throughout the active study period unless prohibited in exclusion criteria in other words, routine concomitant meds that do not fit these criteria are not included on the eCRF. Prohibited therapies include nerve wraps, Bier Blocks, protectors, conduits, phentolamine or other solutions that could potentially affect the efficacy or safety outcomes.

Intraoperative Therapies Allowed:

- 05% methylene blue USP for improved visualization of the surgical field.
- Local administration of epinephrine is allowed as long as enough time is allowed for the affects to dissipate from affected area before any protocol required electrophysiology testing is performed.
- Fibrin glue is allowed for use in the standard of care group only.

4.16. Rescue Medicine

Rescue medicine is not relevant nor available in this study.

4.17. Retreatment Criteria

If the surgeon believes that the coaptation has not been successful, one more attempt may be done. If this decision is made and the subject has been randomized to treatment; a new NTX-001 product will be obtained, and the procedure will be repeated. This can occur only once.

4.18. Subject Discontinuation/Withdrawal

The subject may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The subject will be permanently discontinued both from the study intervention and from the study at that time. If the subject withdraws consent for disclosure of future information, Neuraptive may retain and continue to use any data collected before such a withdrawal of consent. If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

4.19. Lost to Follow-up

A subject will be considered lost to follow-up if they fail to return for scheduled visits and/or are unable to be contacted by the study site staff. The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit within the allowable windows or within 5 working days and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, they will be considered a withdrawal from the study with a primary reason of lost to follow-up.

4.20. Study Assessments and Procedures

Study procedures and their timing are summarized in the Schedule of Activities (SoA). Protocol waivers or exemptions are not allowed including surgical repair outside the 48 hour window from injury to repair. Immediate safety concerns should be discussed with Neuraptive immediately upon occurrence or awareness to determine if the subject should continue or discontinue participating in the study. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct. All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to

confirm eligibility or record reasons for screening failure or early termination, as applicable. Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

4.20.1. Electrophysiology Assessment(s)

Electrophysiologic assessments will be used to detect immediate reconnection of severed peripheral nerves (axons) using PEG Fusion.

- Intra-operative nerve stimulation will be performed in the NTX-001 group 1) after microsuture 2) after Solution #3 irrigation prior to surgical close.
- Intra-operative nerve stimulation will be performed in the SOC group 1) after microsuture 2) after standard rinse prior to surgical close.

A follow-up EP will be done percutaneously at Weeks 12 and 48. Contralateral testing is conducted in nerve conduction velocity only not EMG. Week 12 is considered a critical visit and is to be conducted onsite. Facility and individual infection control policies will be followed during the visit.

- Percent of responders from Electrophysiologic Assessment parameters;
    - Compound Muscle Action Potential
        - (No Contralateral Assessments)
    - Nerve Conduction Velocity
        - (Contralateral assessment is done)

Restoration of nerve conduction indicates the restoration of axon continuity, which is a prerequisite for the prevention for Wallerian degeneration, neuromuscular junction degeneration, muscle atrophy and functional recovery. All electrophysiologic equipment used for these assessments will follow manufacturer required calibration requirements and intra-facility medical equipment management standards.

4.20.2. Numeric Pain Rating Scale (NPRS)

This pain assessment will be performed during the baseline period. The follow-up assessments at Weeks 4, 8, 12, 24, 36 and 48 weeks. This test measures single dimension of global pain intensity at rest or with activity. It takes less than one (1) minute to complete. The patient is asked to make three pain ratings, corresponding to current, best and worst pain experienced over the past 24 hours. The average of the 3 ratings was used to represent the subject's level of pain

over the previous 24 hours. Testing procedure guidelines will be provided with training and documentation.

4.20.3. Vital Signs

Vital signs will be assessed at each visit up to week 48 and will include blood pressure, heart rate, respiratory rate, and temperature. If a clinically significant abnormality is found prior to or immediately after surgical repair, during the study, and/or at any of the follow-up visits, or if the investigator feels that there has been a clinically significant change from screen, it should be recorded as an adverse event and the study subject will be followed until the vital sign has normalized or stabilized.

4.20.4. Physical Examination

A physical examination will be performed during the baseline period, at weeks 12 and 48 visits. The examination will include an assessment of the following body systems: psychiatric/psychological status, head/neck, chest, lungs, heart, abdomen, skin, musculoskeletal, and neurological systems. If a clinically significant abnormality is found during any physical exam during the study, and/or at any of the follow-up visits, or if the investigator feels that there has been a clinically significant change from screening/baseline, it should be recorded as an adverse event and the study subject will be followed until the findings have normalized or stabilized.

4.20.5. MRCC – Sensory includes static and moving 2PD

The MRCC Sensory assessment includes 2 point discrimination measurements and is assessed based on location of injury. Both static and moving assessments are done on the ulnar and radial sides on the affected digits only (palmar crease to fingertip). The MRCC-sensory assessment will be performed during the baseline period. The follow-up assessments at Weeks 4, 8, 12, 24, 36 and 48. The subject will serve as their own control by comparing right to left sides. The assessment will be performed by a blinded evaluator. Static and moving 2PD will be done; these assessments are included in the sensory scale.

Static 2PD measures the innervation density (number of nerves present in an area) by testing the ability to discern the difference between 1 and 2 static pressure points. Moving 2-point discrimination returns earlier than static 2-point discrimination. Moving 2PD is used to determine progress in return of sensation.

A 2-point disk-criminator will be used to determine the shortest distance, in millimeters, that the subject can feel the two, not one, points. Each octagon measures a different range of 8 labeled, fixed 2-point intervals ranging from 1 mm to 25 mm. The discriminator will be provided to the sites. Testing procedure guidelines will be provided with training and documentation.

Grade	Recovery of sensibility	s2PD (mm)	m2PD (mm)
S0	No recovery of sensibility in the autonomous zone of the nerve		
S1	Recovery of deep cutaneous pain sensibility within the autonomous area of the nerve		
S1^{+}	Recovery of superficial pain sensibility		
S2	Recovery of superficial pain and some touch sensibility		
S2^{+}	As in S2,but with over-response		
S3	Recovery of pain and touch sensibility with disappearance of over-response	**> 15**	**> 7**
S3+	As in S3; but localization of the stimulus is good and there is imperfect recovery of 2PD	**7-15**	**4-7**
S4	Complete recovery	**2-6**	**2-3**

British Medical Research Council classification; MacKinnon and Dellon's modification of two-point discrimination. © Crown Copyright ("Used with the permission of the Medical Research Council")

4.20.6. MRCC-Motor Scale

The MRCC Motor Scale is assessed based on location of injury. This assessment it is conducted on motor and mixed motor nerve injuries only. The MRCC-motor assessment will be performed during the baseline period. The follow-up assessments at Weeks 4, 8, 12, 24, 36 and 48. Assessments will be made by a blinded evaluator. Strength can best be assessed by isolating an individual muscle group and comparing power with that of the patient. It can be conducted to assess larger muscles or muscle groups as well as intrinsic muscles of the hand.

Grade	Motor Recovery (of muscles innervated by this nerve)
M0	No contraction of any muscle
M1	Flicker/trace contraction
M2	Active movement with gravity eliminated
M3	Active movement against gravity
M4-	Slight movement against resistance
M4	Moderate movement against resistance
M4+	Strong movement against resistance
M5	Complete recovery

British Medical Research Council classification Highet and Sanders' modification. © Crown Copyright ("Used with the permission of the Medical Research Council"

- 0/5 is no muscle activation whatsoever.
- 1/5 is muscle activation without limb movement.
- 2/5 implies that the limb can be moved only when gravity is taken out of the equation
- 3/5 means that the patient can overcome gravity but not resistance.

- 4/5 (or 4+ or 4-) implies weakness with enough strength to overcome varying degrees of physical resistance.
- 5/5 is full strength.

4.20.7. Semmes-Weinstein Monofilament Test (SWMT)

The SWMT is assessed based on location of nerve injury. For sensory only (digital injuries), the ulnar and radial sides on the affected digits are tested (palmar crease to fingertip). For motor or mixed motor injuries, the testing is done based on the regions of the hand affected by the ulnar, radial, or medial nerve injury.



This assessment will be performed during the baseline period.
The follow-up assessments at Weeks 4, 8, 12, 24, 36 and 48.
Assessments will be conducted by a blinded evaluator. The subject will serve as their own control by comparing right to left sides.
SWMT provides information on protective sensation, the rigorous system can detect relatively minor differences in sensory function, and changes will occur early in nerve injury. The assessment tool consists of a set of monofilaments that vary in thickness and diameter, the gradient forces of these monofilaments range from 0.086 gm to 448gm. Normal value in the hand is in the range of the green filament (1.65 to 2.83 mN).

The Touch- Test™ Sensory Evaluators will be used to provide this non-invasive evaluation of cutaneous sensation levels that are objective and repeatable. The Sensory Evaluator is individually calibrated to deliver its targeted force within a 5% standard deviation. Testing procedure guidelines will be provided with training and documentation.

4.20.8. Pinch and Grip Strength

The Grip/Pinch Strength test is conducted based on location of injury. Strength testing is done on motor or mixed motor injuries only. These assessments are done after splint removal (as applicable) and with investigator approval. This assessment will be performed during the baseline period. The follow-up assessments at Weeks 4, 8, 12, 24, 36 and 48. Beginning to test grip or pinch strength has to be approved by the principal investigator and must be documented.



Assessment of grip/pinch strength using digital dynamometry equipment are some of the most common methods for assessing for functional motor outcome. The tests are used initially and in periodic retests to demonstrate improvement in the strength available to grasp or pinch. Three pinch types are measured, lateral pinch (key pinch, three-point pinch, two-point pinch, repeat each test 3 times and calculate an average. Equipment is calibrated at least annually. (Klein 2014)



4.20.9. Michigan Hand Questionnaire (MHQ)

The first assessment will be administered during the baseline period and should reflect the subject's functional ability 7 days prior to their injury. The follow-up assessments at Weeks 4, 8, 12, 24 and 48. The MHQ has a total of thirty-seven (37) questions. It takes approximately fifteen (15) minutes to complete and is self-administered. The MHQ can assess a subject's general hand function or if administered several times (i.e., pre-, and post-operatively), it can be used to assess changes in hand function. Furthermore, questions regarding function specifically refer to the impact of the involved hand and/or wrist on the activity which presumably take all joints of the upper extremity into account. The MHQ quantifies different impairments between the subjects uninjured and involved upper extremities. It was designed as a general survey of hand function and includes twenty-five items for the right and the left hand, as well as questions for both hands. The MHQ contains six distinct scales (1) overall hand function, (2) activities of daily living (ADLs), (3) pain, (4) work performance, (5) aesthetics, and (6) subject satisfaction with hand function. There is also a demographic section asking questions about subject's gender, ethnic background, etc. This questionnaire is scored from 0 to 100, with 100 being the optimal score.

4.20.10. Cold Intolerance Symptom Severity (CISS)

The CISS questionnaire will be performed during the baseline period. It takes approximately five (5) minutes to complete and is self-administered. The follow-up assessments at Weeks 4, 8, 12, 24, and 48. Cold sensitivity is a complex symptom, which may present as pain, numbness, stiffness, weakness, swelling and change in skin color. CISS is used to evaluate sensitivity of cold intolerance during daily life. Cold sensitivity, described as "an exaggerated or abnormal reaction to cold exposure of the injured part, causing discomfort or the avoidance of cold", is a common complaint following a variety of hand injuries and diseases (Carlsson 2010, Tark 1989). The onset of cold-induced symptoms or discomfort is generally reported to occur within the first few months following the injury (Collins 1996, Craigen 1999). Testing procedure guidelines will be provided with training and documentation.

4.20.11. Patient Global Impression of Change (PGIC)

This assessment will be performed during the baseline period. It takes approximately one (1) minute to complete and is self-administered. The follow-up assessments at Weeks 4, 8, 12, 24,

and 48. This scale evaluates all aspects of patients' health and assesses if there has been an improvement or decline in clinical status. Testing procedure guidelines will be provided with training and documentation.

4.20.12. Physical and Occupational Therapy Subject Compliance

Following upper extremity nerve reconstruction, rehabilitation is necessary to achieve optimal function and outcome. Compliance with post repair therapy will be assessed as applicable. The data captured will be, did the subject attend or follow the prescribed PT/OT appointments as yes or no, as well as time from start to discontinuance of therapy.

4.20.13. Splinting Assessments

Splinting is required in a flexed or extended position as necessary to maintain minimal or acceptable tension. The splint assessment will consist of total splint time and if the subject complied with the splint post-operative instructions until removal based on clinical judgement.

4.21. Safety Assessments

Planned time points for all safety assessments are provided in SoA.

4.21.1. Pregnancy (Appendix 2)

Subjects will use effective contraception for two weeks after the nerve repair is completed. Subjects will be required to report pregnancy during the active study period from signing of consent until week 48 visit. Women of child-bearing potential and men that have fathered a child during this time will contact the Clinical staff and documentation of the event will be completed. Neuraptive will need to be contacted within 24 hours following notification of pregnancy. Pregnancy Test: β-human chorionic gonadotropin (β-HCG) using a serum sample, will be done at screening/baseline for women of childbearing potential (WOCBP). A dipstick urine pregnancy test will be done at weeks 12, 24, 36, and 48.

4.21.2. Laboratory

The following laboratory tests will be done during the study during the baseline period and week

Hematology	Chemistry 7
Red blood cell count (RBC)	Sodium (Na)
White blood cell count (WBC)	Potassium (K)
Platelet count	Chloride
Hemoglobin (HbG)	Bicarbonate
Hematocrit (HCT)	Blood urea nitrogen (BUN)
Differential (Absolute & %)	Creatinine
Eosinophils	Glucose
Basophils	

Neutrophils Lymphocytes Monocytes	

Any value outside the normal range will be flagged for the attention of the investigator or designee at the site. The investigator or designee will indicate whether the value is of clinical significance. If the result of any test (or repeat test, if done) from the samples taken during the screening is indicated as clinically significant, the study subject will NOT be allowed into the study without permission of the Neuraptive Medical Monitor.

Additional testing during the study may be done if medically indicated. If a clinically significant abnormality is found in the samples taken after dosing, during the study, and/or at the follow-up visit, it should be recorded as an adverse event and the study subject will be followed until the test(s) has (have) normalized or stabilized.

4.21.3. Schedule of Assessments

A detailed schedule of assessments is provided in SoA. Baseline Period (V0, V1a, V1b, V1c, Week 1). The baseline period will take place prior to the subject being scheduled for PNI surgical repair after informed consent has been fully executed. The subject will be assessed for study participation based on the inclusion and exclusion criteria. During the baseline period, study procedures will be explained in detail by study staff, informed consent will be obtained, fully executed with copy provided to the subject or Legally Authorized Representative (LAR), in subject's aged 16 and 17, parental permission and child assent will be required. The following activities will be performed:

Baseline values are required assessments obtained at any time from fully executed consent to before or at Week 1 Visit (V2).

- Fully execute informed consent
- Begin adverse event/concomitant medication monitoring
- Inclusion/exclusion Assessment
- Demographics: race, ethnicity, sex, date of birth
- Date and Time of Injury
- NPRS - Pain
- Vital Signs
- Physical Examination
- Type of Injury
- Concurrent Injuries
- Medical History
- Labs - Serum Pregnancy (if applicable)

- MRCC Sensory and/or Motor Scale based on location of injury (CL - plus contralateral assessment)
- SWMT (CL)
- Grip/Pinch Strength (CL)
- Michigan Hand Questionnaire (MHQ)
- Cold Intolerance Symptom Severity (CISS)
- Patient Global Impression of Change (PGIC)

If, in the opinion of the investigator, the subject has any clinically significant abnormality, he/she will be excluded from the study.

4.21.3.1. Surgery (V1a, V1b, V1c) done within 48 hours of injury)

The following **Visit 1a pre-procedure** assessments will be performed:

- Reassess for inclusion and exclusion criteria.
    - Confirm Sunderland's IV or V degree (Class III) injury. This assessment will not occur until the surgeon has assessed the nerve injury intra-operatively. If the nerve is not completely severed, the subject will be considered a screen failure.
- Vital Signs

The following **Visit V1b intraoperative procedure** assessments will be performed:

- Electrophysiologic Assessment Based on surgeon assessment, if the neurorrhaphy is not optimal a second procedure attempt is allowed.

The following **Visit V1c post-procedure** assessments will be performed:

- Vital Signs

4.21.3.2. Week 1 (Part of Baseline Period +4/-2Days)

- Adverse event/concomitant medication monitoring
- Vital Signs

4.21.3.3. Week 4 (V3, +/- 5 Days)

Subjects will return to the clinic for safety and efficacy follow-up assessments as defined below:

- Adverse event and concomitant medication assessments
- NPRS
- Vital Signs
- MRCC Sensory and/or Motor based on location of injury
- MHQ
- SWMT

- Grip/Pinch Strength
- PT/OT Compliance
- Splint Compliance Assessment (as applicable)

4.21.3.4. Week 8 (V4, +/- 5 Days)

Subjects will return to the clinic for safety and efficacy follow-up assessments as defined below:

- Adverse event and concomitant medication assessments
- NPRS
- Vital Signs
- MRCC Sensory and/or Motor based on location of injury (CL)
- MHQ
- SWMT (CL)
- Grip/Pinch Strength (CL)
- CISS
- PGIC
- PT/OT Compliance
- Splint Compliance Assessment (as applicable)

4.21.3.5. Week 12, (V5, +/- 5 Days)

Subjects will return to the clinic for safety and efficacy follow-up assessments as defined below:

- Adverse event and concomitant medication assessments
- Electrophysiologic Assessment
- NPRS
- Vital Signs
- Physical Exam
- MRCC Sensory and/or Motor based on location of injury (CL)
- MHQ
- SWMT (CL)
- Grip/Pinch Strength (CL)
- CISS
- PGIC
- Labs
- Urine Pregnancy
- PT/OT Compliance
- Splint Compliance Assessment (as applicable)

4.21.3.6. Week 24, (V6, +/- 7 Days)

Subjects will return to the clinic for safety and efficacy follow-up assessments as defined below:

- Adverse event and concomitant medication assessments
- NPRS
- Vital Signs
- MRCC Sensory and/or Motor based on location of injury
- MHQ
- Semmes Weinstein Monofilament Test
- Grip/Pinch Strength **(CL)**
- Urine Pregnancy
- CISS
- PGIC
- PT/OT Compliance
- Splint Compliance Assessment (as applicable)

4.21.3.7. Week 36, (V7, +/- 7 Days)

Subjects will return to the clinic for safety and efficacy follow-up assessments as defined below:

- Adverse event and concomitant medication assessments
- NPRS
- Vital Signs
- MRCC Sensory and/or Motor based on location of injury
- Semmes Weinstein Monofilament Test
- Grip/Pinch Strength
- Urine Pregnancy
- PT/OT Compliance
- Splint Compliance Assessment (as applicable)

4.21.3.8. Week 48, (V8, +/- 7Days) or Unscheduled/Early Term

Subjects will return to the clinic for safety and efficacy follow-up assessments as defined below:

- Adverse event and concomitant medication assessments
- Electrophysiologic Assessment (+/- 4 Week Window)
- NPRS
- Vital Signs
- Physical Exam
- Labs
- Urine Pregnancy
- MRCC Sensory and/or Motor based on location of injury (CL)

- MHQ
- SWMT (CL)
- Grip/Pinch Strength (CL)
- CISS
- PGIC
- Urine Pregnancy
- PT/OT Compliance
- Splint Compliance Assessment (as applicable)
- End of Study

4.22. Adverse Events and Serious Adverse Events

The definitions of safety events and serious safety events can be found in Appendix 3.
AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the subject to discontinue the NTx20201 study.

4.22.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the informed consent form (ICF)] until the final follow-up visit 8 (48 weeks) at the time points specified in the Schedule of Activities (SoA). Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (eCRF) not the AE section.

All SAEs will be recorded and reported to Neuraptive or designee within 24 hours of becoming aware of the event., as indicated in Appendix 3. The investigator will submit any updated SAE data to Neuraptive within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE 30 days after conclusion of study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify Neuraptive.

4.22.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

4.22.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 5.19). Further information on follow-up procedures is provided in Appendix 7.2.

4.22.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to Neuraptive of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study intervention under clinical investigation are met. Neuraptive has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Neuraptive will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

All studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Neuraptive policy and forwarded to investigators, as necessary. An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from Neuraptive will review and then file it along with the Investigator Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

4.22.5. Death Event

A subject death is a serious outcome in a clinical study and need to be unambiguously reported as soon as the investigator becomes aware of the death.

4.22.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The following disease related events (DREs) are common in subjects with peripheral nerve injuries requiring surgical intervention and can be serious:

- Bleeding;

- Incomplete sensory or motor recovery;
- Neurogenic pain (acute or long-term);
- Neuroma development;
- Surgical wound infections.

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of a SAE. These events will be recorded on the eCRF page in the subject's eCRF within 24 hours after becoming aware of the event. These DREs will be monitored by the Safety Team on a routine basis.

4.22.7. Adverse Events of Special Interest

Any noteworthy event for the that Neuraptive may wish to monitor carefully. It could be serious or non-serious and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals.

4.22.8. Device Deficiencies

The isolation chamber device is being provided for use in this study and is supplied with the product. To fulfill regulatory reporting obligations worldwide; the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices. The definition of a device deficiency can be found in Appendix 4.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Appendix 3 of the protocol.

4.22.8.1. Time Period for Detecting Device Deficiencies

Device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used. If the investigator learns of any device deficiency at any time after a subject has been discharged from the study, and such incident is considered reasonably related to a device provided for the study, the investigator will promptly notify Neuraptive. The method of documenting device deficiency is provided in Appendix 4.

4.22.8.2. Follow-up of Device Deficiencies

Follow-up applies to all subjects, including those who discontinue or withdraw from the study. The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency. New or

updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

4.22.8.3. Prompt Reporting of Device Deficiencies to Sponsor

Device deficiencies will be reported to Neuraptive within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency. The Device Deficiency Report Form will be sent to Neuraptive by email. If email is unavailable, then a fax should be utilized. Neuraptive will be the contact for the receipt of device deficiency reports.

4.22.8.4. Regulatory Reporting Requirements for Device Deficiencies

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for Neuraptive to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. The investigator, or responsible person according to local requirements (e.g., the head of the institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

4.23. Treatment of Overdose

There is no treatment for an overdose in this study.

5. Statistical Considerations

5.1. Statistical Hypotheses

The following hypothesis for the primary efficacy endpoint of change from baseline of MHQ total score between NTX-001 and SOC at week 12 will be tested:

$H_0: \Delta \geq 5.0$ vs. $H_1: \Delta < 5.0$

Where Δ is the difference in the change from baseline of MHQ total score between NTX-001 and SOC at week 12. A one-sided significance level of 0.05 is considered.

5.2. Sample Size Determination

A sample size of 20 patients per group can provide 90% power to detect a difference of 5.0 with a standard deviation of 5.3 in the primary efficacy endpoint of change from baseline of MHQ total score between NTX-001 and SOC at week 12, assuming that the change from baseline MHQ total score is 7.0 and 2 for each of the NTX-001 and SOC, respectively.

Approximately 48 subjects will be enrolled to meet the goal of 40 evaluable subjects to complete the study with about 15% drop out rate. A subject is evaluable if the subject meets the modified intent to treat (mITT) population criteria.

Potential subjects who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

5.3. Populations for Analyses

The following populations are defined:

Population	Description
ITT	Subjects who successfully pass screening criteria and randomized for study treatments;
Safety	Subjects from ITT population who received or exposed to at least one application of the topical study product;
Modified Intent-to-Treat (mITT)	Subjects from ITT population who received at least one application of the study product and who provide at least up to week 4 of evaluable data for primary endpoint;
Per Protocol (PP)	Subjects from ITT population who received or exposed to at least one application of the topical study product, with no significant protocol deviations, and who provide at least up to week 4 of evaluable data for primary endpoint.

5.4. Statistical Analyses

The statistical analysis plan will be finalized prior to interim analysis and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key exploratory secondary endpoints.

5.4.1. General Considerations

Statistical testing for this study will be performed at an $\alpha = 0.05$ level (one sided). Continuous variables will be summarized in tables and will include the number of subjects, mean, standard deviation, median, minimum, and maximum. Categorical variables will be presented in tables as frequencies and percentages.

Additional details regarding the efficacy and safety variable definitions, analyses strategy, control of the overall type 1 error, statistical justification, and techniques for handling missing values will be detailed in an SAP that will be prepared before the database is locked and any analyses are undertaken.

All the primary and secondary efficacy end points will be used for the comparisons of the NTX-001 group with the SOC group. The treatment comparisons of safety endpoints will be summarized using descriptive statistics. Baseline efficacy endpoints are the results obtained at any time from fully executed consent to before or at Week 1 Visit.

5.4.2. Primary endpoint(s)

- Safety analysis will be based on the comparison of adverse events and other safety data (i.e., vital signs, clinical labs, physical exam) across 48 weeks following surgical repair.
- Change from baseline of MHQ Total Score at week 12.

5.4.3. Exploratory Secondary Endpoint(s)

Exploratory Secondary Endpoints:
The following will be evaluated intraoperatively and percutaneously at Week 12 using the following measures:

- Percent of responders from this parameters;
    - Compound Muscle Action Potential
        - No Contralateral Assessments
    - Nerve Conduction Velocity
        - Contralateral Assessments are done

Weeks 12 and 48 are considered critical visits and are conducted onsite. Facility and individual infection control policies will be followed during the visit.

The following will be evaluated at weeks 4, 8, 24 and 48 using the following measure.

- Change from baseline of MHQ Total Score

The following will be evaluated at Weeks 4, 8, 12, 24, 36 and 48 using the following measures:

- Change from baseline of MRCC Motor Scale
- Change from baseline of MRCC Sensory Scale
- Change from baseline of SWMT Assessment
- Change from baseline of Grip/Pinch Strength
- Change from baseline of NPRS Score

The following will be evaluated at Weeks 4, 8, 12, 24 and 48 using the following measures:

- Change from baseline of CISS Score
- Change from baseline of PGIC Score

5.4.4. Demographic and Baseline Characteristics

The number of subjects included in each study population will be summarized by treatment group and overall. Demographic and other baseline characteristics, including sex, age, age group, race, height, weight, and baseline values (e.g., primary, and exploratory secondary endpoints) will be summarized by treatment group, for the Safety, and ITT populations, using descriptive statistics.

5.4.5. Primary Efficacy Analysis

The primary efficacy endpoint is the change from baseline of MHQ total score at week 12. The Primary efficacy analysis will be performed using Mixed Model Repeated Measures (MMRM) analyses. The model will include treatment and visit as fixed effects and baseline MHQ total score as covariate.

5.4.6. Exploratory Secondary Efficacy Analyses

The Cochran-Mantel-Haenszel test will be used for the secondary endpoint of comparison of percentage of patients responding to an Electrophysiologic Assessment at Week 12 between NTX-001 and SOC. If a patient withdraws from the study or for any other missing assessments the Last Observation Carried Forward (LOCF) methodology will be used.

All the analyses for remaining secondary efficacy endpoints (as described in Section 6) will be performed using Mixed Model Repeated Measures (MMRM) analyses similar to the primary end point analysis. Summaries for the absolute and change from baseline values for all these secondary endpoints will be provided by treatment group and time point.

5.4.7. Safety Analyses

5.4.7.1. Adverse Events

Reported AEs will be summarized by the number of subjects reporting the events, as well as by System Organ Class, Preferred Term, severity, seriousness, and relationship to study product. For the summary of AEs by severity, each subject will be counted only once within a System Organ Class or a Preferred Term by using the AEs with the highest intensity within each category for each analysis. For the summary of AEs by relationship to study product, each subject will be counted only once within a System Organ Class or a Preferred Term by using the AEs with the greatest reported relationship within each category. For the summary of AEs by relationship to study product and severity, each subject will be counted only once within a System Organ Class or a Preferred Term by using (1) the greatest reported relationship followed by (2) the highest reported intensity.

All information pertaining to AEs noted during the study will be listed by subject, detailing verbatim, System Organ Class, Preferred Term, start date, stop date, intensity, outcome, and relationship to study product. The AE onset will also be shown relative (in number of days) to the day of study product administration. SAEs will be tabulated by treatment group, relationship to the test article, and a reference to the occurrence of the SAEs to the relative day of treatment start.

5.4.7.2. Clinical Laboratory

Descriptive statistics for clinical laboratory values and changes from Baseline at each assessment time point will be presented by treatment group for each clinical laboratory parameter. Shift tables to summarized change from Baseline to post Baseline visits will also be presented (e.g., normal to high and normal to low). Separate listings of all data for all the laboratory parameters will be provided.

5.4.7.3. Prior and concomitant Medications

Use of medications as described in Section 5.15, prior to and during the treatment period for the safety population will be coded with the World Health Organization (WHO) Drug Dictionary and listed by subject. Summary of medication classes will also be tabulated using counts and percentages in each treatment group.

5.4.7.4. Physical Examinations

Listings of all physical examination assessments will be provided.

5.4.7.5. Nerve and Concurrent Injuries

The listings of the class, type and date/time of nerve injury and any other concurrent injuries will be provided.

5.4.7.6. **Vital Signs**

Descriptive statistics will be presented for data related to vital signs (systolic blood pressure diastolic blood pressure, pulse rate and body temperature). Change from baseline values will be presented for each post-baseline assessment.

Shift tables from baseline to each post-baseline visits and to each timepoint describing shifts to abnormality will be provided as well. Only subjects with a baseline result and a result at the specified visit for the parameter will be considered.

A listing of all vital sign assessments will be provided. In addition, a listing will be provided for each parameter where a subject had at least one abnormal result.

5.5. Interim Analyses

An interim analysis will be performed to re-assess the adequacy of the study sample size based on the primary efficacy endpoint of interest, the change from baseline MHQ total score at week 12 after the first approximately 20 (about 10 subjects in NTX-001 group and about 10 subjects in SOC group) evaluable subjects have completed 12 weeks of treatment with a demonstrable balance between sites and injury location. If the balance between the sites and the injury location is significantly different, interim analysis will be performed with additional subjects to get an approximate balance. A subject is evaluable if the subject meets the modified intent to treat (mITT) population criteria.

Sample size adjustment is based on the primary endpoint, the change from baseline of MHQ total Score. However, the sample size will not be reduced regardless of the results of the interim analysis. At the end of the study, the data will be analyzed using the Cui-Hung-Wang[1] method to reflect the fact of the sample size adjustment. Details of the interim analysis will be provided in a Statistical Analysis Plan (SAP). (Cui 1999)

A Data Monitoring Board (DMB) will be instituted for use in this study. They will operate under an approved charter describing their roles and responsibilities. Their main responsibility will be to review and adjudicate safety findings as well as reviewing preliminary efficacy endpoints. The interim statistical analysis will be performed by an external independent statistician. Based the on the interim analysis the sample size and stratification methods may be revised.

6. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

6.1.1. Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms, adult, parental and assent will be Institutional Review Board (IRB) - approved and the subject will be asked to read and review the document. As part of this procedure, the investigator (or designee) must explain orally and in writing the nature, duration, and purpose of the study, and the action of the investigational product in such a manner that the study subject is aware of the potential risks, inconveniences, or adverse events that may occur.

The subject will sign the informed consent document prior to any specific procedures being done for the study. The investigator will not undertake any investigation specifically required for the clinical study until written consent has been obtained. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice.

A copy of the informed consent document will be given to the subjects for their records. The informed consent document must be signed and dated; one copy will be handed to the subject, and the investigator will retain the original as part of the clinical study records. The terms of the consent and when it was obtained must also be documented. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The PI or designee will provide Neuraptive with a copy of the IRB-approved informed consent form prior to the start of the study. If a protocol amendment is required, then the informed consent document may need to be revised to reflect the changes to the protocol. If the informed consent document is revised, it must be reviewed and approved by the responsible IRB and signed by all subjects subsequently enrolled in the clinical study as well as those currently enrolled in the clinical study.

6.1.2. Legalized Authorized Representative (LAR)

The LAR means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research (45 CFR 46.102(c)). The regulations state that "no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative" (45 CFR 46.116).

The issue as to who can be a LAR is determined by the laws of the jurisdiction in which the research is conducted (e.g., local or state law). Some states have statutes, regulations, or common law that specifically address consent by someone other than the subject for participation in research. Most states have no law specifically addressing the issue of consent in the research context. In these states, law that addresses who is authorized to give consent on behalf of another person to specific medical procedures or generally to medical treatment may be relevant if the research involves those medical procedures or medical treatment. The LAR may be a parent, grandparent, caregiver who has the legal authority to grant consent on behalf of another who has been invited to participate in research. Subjects 16 and 17 years of age will require parental permission and child assent consent documentation.

When the laws of the jurisdiction in which the research is being conducted provide a reasonable basis for authorizing an individual to consent on behalf of a prospective subject to their participation in the research procedure(s), OHRP would consider such an individual to be a LAR as defined by HHS regulations at 45 CFR 46.102(c). IRBs may wish to consult with legal counsel when deciding who can serve as a LAR for subjects of proposed research.

As a general matter, if an adult lacks capacity to consent, for example, as a result of trauma, mental retardation, some forms of mental illness, or dementia - whether temporary, progressive, or permanent - only a legally authorized representative for that adult can give consent for participation in the research, unless the requirement to obtain informed consent is waived by the IRB in accordance with the requirements at 45 CFR 46.116(c)(d), or in accordance with the provisions for emergency waiver, which are permitted under the authority of the HHS Secretary at 45 CFR 46.101(i). Should the subject regain or develop the capacity to consent, then his or her consent must be obtained for any further research, as the consent of the legally authorized representative is no longer valid.

6.1.3. Protocol Approval and Amendment(s)

Before the start of the clinical study, the clinical study protocol and other relevant documents will be approved by the IRB, in accordance with local legal requirements. Neuraptive must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the clinical study.

This protocol is to be followed exactly. No modifications to the protocol may be made without the approval of both the investigator and Neuraptive. To alter the protocol, amendments must be written, which must be released by Neuraptive and receive IRB approval prior to implementation (as appropriate). Administrative changes may be made without the need for a formal amendment but will also be mentioned in the integrated clinical study report. All amendments

will be submitted to the FDA and distributed to all study protocol recipients, with appropriate instructions.

6.1.4. Electronic (eCRF) Completion

Electronic case report forms (eCRFs) will be utilized as the data capture system in this clinical study. Local laboratories will be used in this study. The data will be entered in the eCRF. The Investigator will ensure the accuracy, completeness, and timeliness of the data reported to Neuraptive. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained for all data changes. Within form and cross form consistency checks will be used to identify errors or inconsistencies. This information will be provided to the respective study sites by means of queries. Queries may also be manually generated upon request by the Site Monitor or after manual review of eCRFs.

6.1.5. Study Discontinuation and Closure

The study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending, or terminating party to study subjects, investigators, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study subjects, the Institutional Review Board (IRB), and Neuraptive and will provide the reason(s) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy Neuraptive, IRB and/or Food and Drug Administration (FDA). If the investigator, Neuraptive, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to subjects if the clinical study continues, then the clinical study may be terminated after appropriate consultation among the involved parties. The clinical study may

be terminated at Neuraptive's discretion also in the absence of such a finding. Conditions that may warrant termination of the clinical study include, but are not limited to:

- discovery of an unexpected, relevant, or unacceptable risk to the subjects enrolled in the clinical study;
- failure to enroll subjects at the required rate; or a decision by Neuraptive to suspend or to discontinue development of the investigational product.

Should the study be terminated, and/or the site closed for whatever reason, all documentation pertaining to the study and the Investigational Product must be returned to Neuraptive or destroyed with authorization. Any actions required for assessing or maintaining study subject safety will continue as required, despite termination of the study by Neuraptive.

6.1.6. Institutional Review Board or Independent Ethics Committee

Requirements for institutional review as set forth in Title 21 of the Code of Federal Regulations (21 CFR), Part 56, or other relevant local regulations for institutional review will be followed. The Protocol, Informed Consent, Investigator's Brochure, and other required documents must be approved by the IRB before enrollment of subjects in the study. Neuraptive or designee must confirm that the IRB follows the general standards for the composition, operation, and responsibility of an IRB as set forth in ICH Guidelines for GCP, and 21 CFR, Part 56. Any member of the IRB who is directly affiliated with this study as an investigator or as site personnel must abstain from the IRB vote on the approval of the protocol. The investigator, in collaboration with Neuraptive or designee, will be responsible for reporting to the IRB all changes in research activity, including protocol amendments, updates of Investigator's Brochures, investigational new drug (IND) safety reports, all unanticipated problems involving risks to human subjects, and study termination. The investigator will also be responsible for submitting progress reports to the IRB at regular intervals appropriate to the degree of subject risk involved, but no less than once per year. Copies of all IRB notifications and approvals (if required) will be provided to Neuraptive.

6.1.7. Confidentiality and Privacy

Subject confidentiality and privacy are strictly held in trust by the participating investigators, their staff, and Neuraptive(s) and their interventions. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of Neuraptive. All research activities will be conducted in as private a setting as possible. The Site Monitor, other authorized representatives of Neuraptive, representatives of the Institutional Review Board (IRB),

regulatory agencies or company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records. The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or Neuraptive requirements. Study data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Data Management Vendor. This will not include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Data Management Vendor staff will be secured, and password protected. At the end of the study, all study databases will be de-identified and archived with the Data Management Vendor. All clinical study findings and documents will be regarded as confidential. Study documents (protocols, IBs, and other material) will be stored appropriately to ensure their confidentiality. The investigator and members of their research team (including the IRB) must not disclose such information without prior written approval from Neuraptive, except to the extent necessary to obtain informed consent from subjects who wish to participate in the study or to comply with regulatory requirements. The anonymity of participating subjects must be maintained. Subjects will be specified on study documents by their subject number and initials, not by name. Documents that identify the subject (e.g., the signed informed consent document) must be maintained in confidence by the investigator. To further protect the privacy of study participants, a Certificate of Confidentiality (if applicable) may be issued. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to subjects.

6.1.8. Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored with the Data Management Vendor until study completion. After the study is completed, the de-identified, archived data will be transmitted to and stored with the Data Management Vendor. Permission to transmit data to the Data Management Vendor will be included in the informed consent. With the subject's approval and as approved by local Institutional Review Boards (IRBs), de-identified samples will be stored at the clinical site with the same goal as the sharing of data with the Data Management Vendor. During the conduct of the study, an individual subject can choose to withdraw consent

to have specimens stored for future research. However, withdrawal of consent regarding sample storage may not be possible after the study is completed. When the study is completed, access to study data and/or samples will be provided through the Data Management Vendor or Neuraptive.

6.1.9. Financial Disclosure

Investigators and sub-investigators will provide Neuraptive with sufficient, accurate financial information as requested to allow Neuraptive to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one (1) year after completion of the study. If participants can be rescreened, add the text to state whether the participant needs to sign a new ICF for rescreening. If participants will be asked to consent to optional exploratory research using the remainder of mandatory samples, include text that addresses the use of remaining mandatory samples for optional exploratory research.

6.1.10. Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and specimen collection, documentation, and completion. Quality Control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution. Following written Standard Operating Procedures (SOPs), the Site Monitors will verify that the clinical study is conducted, and data are generated, and specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Documentation Practices [GDP]). The investigational site will provide direct access to all study related sites, source data/documents, and reports for monitoring and auditing by Neuraptive, and inspection by local and regulatory authorities.

6.1.11. In-Home Research Visits (rRV) for Follow-Up Assessments with Telemedicine Oversight

Even prior to infection emergencies such as COVID-19, subject participation in clinical studies can cause difficulties for subjects due to the frequency of visits, travel to the study sites, long visit wait times, disruption in their schedules and activities. This can result in the potential for poor enrollment and increased dropout rates in multi-visit studies.

The study will be conducted using a hybrid model of on-site and remote visits to meet FDA expectations for safety oversight when conducting clinical studies. It has been determined that alternative methods for conducting the study will only be allowed if restrictions are in affect at the time of a visit or per subject request due to their concerns about the restrictions.

Assessments will be performed by qualified research nurses with the training, knowledge, and ability to conduct the subject "hands on" assessments Some of the assessments conducted in the home are:

- Blood draws (safety labs);
- Clinical assessments (vital signs, functional and sensory nerve testing, concomitant medications, adverse events);
- Study coordination with investigator sites;
- Physical examinations;
- Administration of required questionnaires.

6.1.12. Clinical Monitoring

Neuraptive will conduct a site qualification evaluation or pre-study visit unless this visit has been waived based on documented and defined criteria, to verify the qualifications of the investigator and inspect the facilities. A study initiation visit will also be conducted to inform the investigator of responsibilities and procedures for ensuring adequate and correct documentation. The investigator must prepare and maintain adequate and accurate records of all observations and other data pertinent to the clinical study for each study subject. Frequent communication between the clinical site and the Neuraptive is essential to ensure that the safety of the subjects is monitored adequately. The investigator will make all appropriate safety assessments on an ongoing basis. The Medical Monitor may review safety information as it becomes available throughout the study. All aspects of the study will be carefully monitored with respect to GCP and standard operating procedures (SOPs) as frequently as necessary to ensure compliance with the protocol, accurate data collection, and conformance with applicable government regulations. The Site Monitor will be an authorized individual designated by the Neuraptive. The Site Monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the PI. The investigator or designee will cooperate with Neuraptive's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the source documents and eCRF at each scheduled monitoring visit. Electronic consistency checks and manual reviews will be used to identify any errors or inconsistencies in the data. This information will be provided to the respective study sites by means of manual queries. The investigator or designee will prepare and maintain adequate and accurate study source documents (medical records, adverse event and concomitant medication reporting, raw data collection forms, etc.) designed to record all observations and other pertinent data for each subject. The investigator will allow Neuraptive representatives, contract designees, authorized regulatory authority inspectors, and the IRB to have direct access to all documents pertaining to the study. Neuraptive assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

6.1.13. Source Documents

Source data includes all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical investigation used for reconstructing and evaluating the investigation. Source data should be attributable, legible, contemporaneous, original, and accurate (ALCOA) and must meet the regulatory requirements for recordkeeping. Capturing source data electronically and transmitting it to the eCRF should:

- Eliminate unnecessary duplication of data
- Reduce the possibility for transcription errors
- Encourage entering source data during a subject's visit, where appropriate
- Eliminate transcription of source data prior to entry into an eCRF
- Facilitate remote monitoring of data
- Promote real-time access for data review
- Facilitate the collection of accurate and complete data

Data Originator:

A list of all authorized data originators (i.e., persons, systems, devices, and instruments) will be developed and maintained by Neuraptive or their designee and made available at each clinical site. In the case of electronic, patient-reported outcome measures, the subject (e.g., unique subject identifier) will be listed as the originator.

Direct Data Entry:

Many data elements (e.g., blood pressure, weight, temperature, resolution of a symptom or sign) in a clinical study can be obtained at a study visit and will be entered directly into the eCRF by an authorized data originator. This direct entry of data eliminates errors by not using a paper transcription step before entry into the eCRF. For the following data elements, the eCRF will be the source.

List Data Elements:

No data in this study will be direct data entry.

Automatic Transmission of Data from Devices or Instruments Directly to the eCRF:

If a device or instrument is the data originator and data are automatically transmitted directly to the eCRF, the eCRF is the source. If a process is used by which the device or instrument transmits data automatically to, for example, an electronic health record system or to a service provider's database, then the EHR or the service provider's database is the source.

List Data Elements:

No data in this study will be automatically transferred from devices or instruments to the eCRF.

Transcription of Data from Paper or Electronic Sources to the eCRF:
For these data elements, the electronic or paper documents from which the data elements are transcribed are the source. These data must be maintained by the clinical investigator(s) and available to Neuraptive and the FDA if requested (e.g., an original or certified copy of a laboratory report, instrument printout, progress notes of the physician, the study subject's hospital chart(s), nurses' notes). If a paper transcription step is used, then the paper documentation should be retained and made available for Neuraptive and FDA inspection.

List Data Elements:

- Vital Signs
- Intraoperative Nerve Stimulation
- Electrophysiologic Assessment (CMAP/NCV)
- Physical Exam
- MRCCs/m
- SWMT
- Grip/Pinch Strength
- Numeric Pain Response Scale
- Michigan Hand Questionnaire
- Cold Intolerance Symptom Severity
- Patient Global Impression of Change
- PT/OT Compliance
- Splint Assessment
- Local Lab Reports

Direct Transmission of Data from the Electronic Health Record (EHR) to the eCRF:
Data elements originating in an EHR can be transmitted directly into the eCRF automatically. In this circumstance, the EHR is the source. The EHR is the source for the following in this study:

List Data Elements:
No data in this study will be transferred from the Electronic Health Record to the eCRF.

6.1.14. Study Records Retention

According to International Conference on Harmonization (ICH) guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational drug. However, these documents should be retained for a longer period if required by the applicable legal requirements.

6.1.15. Protocol Deviations

A protocol deviation is any noncompliance with the study protocol, ICH GCP regulations, study reference manual (SRM) or other supportive and directive document requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. Because of deviations, corrective actions are to be developed by the site and implemented promptly. It is the responsibility of the site investigator to use continuous vigilance to identify and report protocol deviations within 1 working day of identification of the deviation, or within 5 working days of the scheduled protocol-required activity.

All deviations must be addressed in study source documents, reported to Neuraptive within 24 hours of discovery. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The principal investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the relevant Neuraptive's guidance documents.

6.1.16. Publication Policy

By signing the study protocol, the investigator agrees with the use of results of the study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, regulatory, and competent authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. An investigator shall not publish any data (poster, abstract, paper, etc.) without having received consent from Neuraptive in advance. The investigator must seek consent within not less than 45 days prior to any public disclosure.

6.2. Appendix 2: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP) - A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with one of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy.
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the subject's medical records, medical examination, or medical history interview.

3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance - Collection of Pregnancy Information

- Male subjects with partners who become pregnant
    - The investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive NTX-001.

- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to Neuraptive within [24 hours] of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Neuraptive. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- Female Subjects who become pregnant
  - The investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to Neuraptive within [24 hours] of learning of a subject's pregnancy.
  - The subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject and the neonate, and the information will be forwarded to Neuraptive. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
  - Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
  - While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
  - A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
  - Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to Neuraptive.
  - While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.
  - Any female subject who becomes pregnant while participating in the study, can stay in the study, can be withdrawn from the study or may request continuation of study intervention.

6.3. Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Safety Contact Information:	
Blinded Medical Monitor:	Seth Schulman MD Seth.schulman@neuraptive.com Mobile: 215-206-9504
Unblinded Medical Monitor:	Valerie Riddle MD Valerie.Riddle@neuraptive.com Mobile: 410-845-7020
Study Lead:	Vicki Abbas BSN RN Vicki.abbas@neuraptive.com Mobile: 303-263-4646
General Safety:	NeuraptiveDrugSafety@mmsholdings.com

6.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study subject, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., diagnostic scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention application even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected action” also constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

6.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Leads to a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

6.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to Neuraptive in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by Neuraptive. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to Neuraptive.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will assess intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- **Mild:** An event that is easily tolerated by the subject, causing minimal discomfort, and not interfering with everyday activities.

- **Moderate:** An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe:** An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
    - An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention application will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) in their assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that they have reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to Neuraptive. However, it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data to Neuraptive.
- The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- Causality for Serious Adverse Events:
    - Related
    - Not Related

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Neuraptive to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed eCRF. • The investigator will submit any updated SAE data to Neuraptive within 24 hours of receipt of the information.

6.3.4. Reporting of SAEs

SAE Reporting to Neuraptive via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Neuraptive will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (provided by Neuraptive) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to Seth Schulman, Medical Monitor, or designee by telephone.
SAE Reporting to Neuraptive via Fax or Mail
• Facsimile transmission of the SAE paper eCRF is the preferred method to transmit this information to Seth Schulman, Medical Monitor, or designee by telephone. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE eCRF pages within the designated reporting time frames.

6.4. Appendix 4: Medical Device Adverse Events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs) and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155.
- Both the investigator and Neuraptive will comply with all local medical device reporting requirements.

6.4.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study subjects, users, or other persons, whether related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices. • An adverse device effect (ADE) is defined as an adverse event related to the use of an investigational medical device. This definition includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

6.4.2. Definition of SAE, SADE and USADE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is an AE that:
a. Led to death
b. Led to serious deterioration in the health of the subject, that either resulted in: 1. A life-threatening illness or injury. The term ‘life-threatening' in the definition of serious refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. 2. A permanent impairment of a body structure or a body function,

3. Inpatient or prolonged hospitalization, planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. 4. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
c. Led to fetal distress, fetal death or a congenital abnormality or birth defect
SADE definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
USADE definition
• A USADE is a serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report

6.4.3. Definition of Device Deficiency

Device Deficiency definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

6.4.4. Recording and Follow-Up of AE and/or SAE and Device Deficiencies

AE, SAE, and Device Deficiency Recording
• When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE/device deficiency information in the subject's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of the eCRF. • It is **not** acceptable for the investigator to send photocopies of the subject's medical records to Neuraptive in lieu of completion of the AE/SAE/device deficiency eCRF page. • There may be instances when copies of medical records for certain cases are requested by Neuraptive. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to Neuraptive. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE device deficiency.

- For device deficiencies, it is particularly important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident
    - A remedial action is any action other than routine maintenance or servicing of a device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

The investigator will assess intensity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories:

- **Mild**: An event that is easily tolerated by the subject, causing minimal discomfort, and not interfering with everyday activities.
- **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
    - An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Medical Monitor in his/her assessment.
- For each AE/SAE/device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE device deficiency has occurred, and the investigator has minimal information to include in the initial report to Neuraptive.
- However, it is very important that the investigator always assess causality for every event before the initial transmission of the SAE device deficiency data to Neuraptive.

- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE device deficiency follow-up report with the updated causality assessment.
- Causality for Serious Adverse Device Deficiency:
  - Related
  - Not Related

Follow-up of AE/SAE/device deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Neuraptive to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject die during participation in the study or during a recognized follow-up period, the investigator will provide Neuraptive with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed ECRF.
- The investigator will submit any updated SAE device deficiency data to Neuraptive within 24 hours of receipt of the information.

6.4.5. Reporting of SAEs

SAE Reporting to Neuraptive via Medical Monitor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Neuraptive will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool in order to report the event within 24 hours.
- The site will enter the SAE device deficiency data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to Seth Schulman MD, Medical Monitor, or designee by telephone.

6.4.6. Reporting of SADEs

SADE Reporting to Neuraptive via Medical Monitor

NOTE: There are additional reporting obligations for medical device incidents that are potentially related to SAE device deficiency that must fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE device deficiency must be reported to Neuraptive within 24 hours after the investigator determines that the event meets the definition of a SAE device deficiency.
- Neuraptive shall review all device deficiencies and determine and document in writing whether they could have led to an SAE device deficiency. These shall be reported to the regulatory authorities and IRBs/IECs as required by national regulations.

6.5. Appendix 5: Patients Global Impression of Change

Date:_____

Name:_____ **DOB:**_____

Chief Complaint (Presenting Problem): Peripheral Nerve Injury Requiring Surgical Repair

Since beginning treatment at this facility, how would you describe the change (if any) in ACTIVITY LIMITATIONS, SYMPTOMS, EMOTIONS and OVERALL QUALITY OF LIFE, related to your condition?

Choose ONE.

___No change (or condition has gotten worse) (1)
___Almost the same, hardly any change at all (2)
___A little better, but no noticeable change (3)
___Somewhat better, but the change has not made any real difference (4)
___Moderately better, and a slight but noticeable change (5)
___Better and a definite improvement that has made a real and worthwhile difference (6)
___A great deal better and a considerable improvement that has made all the difference (7)

Patient's Signature:_____

6.6. Appendix 6: Cold Intolerance Sensitivity Questionnaire

Table 1 | CISS Questionnaire.

Question	Score*
1. Which of the following symptoms of cold intolerance do you experience in your injured limb on exposure to cold?	
Pain, numbness, stiffness, weakness, aching, skin colour change (white/bluish white/blue)	Not scored
2. How often do you experience these symptoms? (Please tick)	
Continuously / all the time	10
Several times a day	8
Once a day	6
Once a week	4
Once a month or less	2
Never†	0
3. When you develop cold induced symptoms, on your return to a warm environment are the symptoms relieved (please tick):	
Not applicable†	0
Within a few minutes	2
Within 30 minutes	6
After more than 30 minutes	10
4. What do you do to ease or prevent your symptoms occurring? (please tick)	
Take no special action	0
Keep hand in pocket	2
Wear gloves in cold weather	4
Wear gloves all the time	6
Avoid cold weather / stay indoors	8
Other (please specify)	10
5. How much does cold bother your injured hand in the following situations (please score 0-10)	
Holding a glass of ice water‡	10
Holding a frozen package from the freezer‡	10
Washing in cold water‡	10
When you get out of a hot bath/shower with air room temperature‡	10
During cold wintry weather	10
6. Please state how each of the following activities have been affected as a consequence of cold induced symptoms in your injured hand and score each (please score 0-4)	
Domestic chores	4
Hobbies and interests	4
Dressing and undressing	4
Tying your shoe laces	4
Your job	4

*In question one, patients are asked to score their symptoms as follows: "Please give each symptom a score between 0 and 10, where 0=no symptoms at all and 10=the most severe symptoms you can possibly imagine." However, the scores given in this question do not count towards the final CISS test score.
†These are two questions developed by Ruijs et al. to improve the scoring
‡These are the questions of the McCabe cold sensitivity test.

6.7. Appendix 7: The Numeric Pain Rating Scale

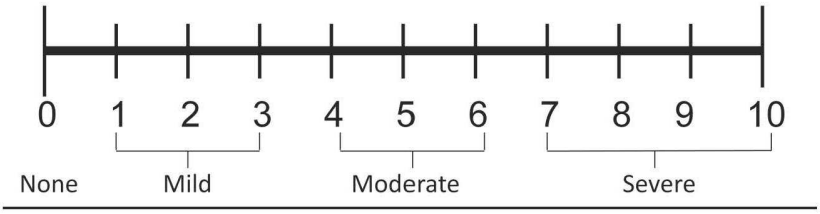
The Numeric Pain Rating Scale Instructions

General Information:

- The patient is asked to make three pain ratings, corresponding to current, best and worst pain experienced over the past 24 hours.
- The average of the 3 ratings was used to represent the patient's level of pain over the previous 24 hours.

Patient Instructions (adopted from (McCaffery, Beebe et al. 1989):

"Please indicate the intensity of current, best, and worst pain levels over the past 24 hours on a scale of 0 (no pain) to 10 (worst pain imaginable)"



Reference:

McCaffery, M., Beebe, A., et al. (1989). Pain: Clinical manual for nursing practice, Mosby St. Louis, MO.

Downloaded from www.rehabmeasures.org
Test instructions derived from McCaffery et al, 1989 Page 1

6.8. Appendix 8: Michigan Hand Questionnaire

HUM00000852

Study ID _____

MICHIGAN HAND OUTCOMES

QUESTIONNAIRE (MHQ)

Today's date: _____
Month Day Year

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Instructions: This survey asks for your views about your hands and your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer ***EVERY*** question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

I. The following questions refer to the function of your hand(s)/wrist(s) ***during the past week***. (Please circle one answer for each question). Please answer ***EVERY*** question, even if you do not experience any problems with the hand and/or wrist.

A. The following questions refer to your ***right*** hand/wrist.

	Very Good	Good	Fair	Poor	Very Poor
1. Overall, how well did your ***right*** hand work?	1	2	3	4	5
2. How well did your ***right*** fingers move?	1	2	3	4	5
3. How well did your ***right*** wrist move?	1	2	3	4	5
4. How was the strength in your ***right*** hand?	1	2	3	4	5
5. How was the sensation (feeling) in your ***right*** hand?	1	2	3	4	5

B. The following questions refer to your ***left*** hand/wrist.

	Very Good	Good	Fair	Poor	Very Poor
1. Overall, how well did your ***left*** hand work?	1	2	3	4	5
2. How well did your ***left*** fingers move?	1	2	3	4	5
3. How well did your ***left*** wrist move?	1	2	3	4	5
4. How was the strength in your ***left*** hand?	1	2	3	4	5
5. How was the sensation (feeling) in your ***left*** hand?	1	2	3	4	5

2

II. The following questions refer to the ability of your hand(s) to do certain tasks ***during the past week***. (Please circle one answer for each question). If you do not do a certain task, please estimate the difficulty with which you would have in performing it.

A. How difficult was it for you to perform the following activities using your ***right hand***?

	Not at All Difficult	A Little Difficult	Somewhat Difficult	Moderately Difficult	Very Difficult
1. Turn a door knob	1	2	3	4	5
2. Pick up a coin	1	2	3	4	5
3. Hold a glass of water	1	2	3	4	5
4. Turn a key in a lock	1	2	3	4	5
5. Hold a frying pan	1	2	3	4	5

B. How difficult was it for you to perform the following activities using your ***left hand***?

	Not at All Difficult	A Little Difficult	Somewhat Difficult	Moderately Difficult	Very Difficult
1. Turn a door knob	1	2	3	4	5
2. Pick up a coin	1	2	3	4	5
3. Hold a glass of water	1	2	3	4	5
4. Turn a key in a lock	1	2	3	4	5
5. Hold a frying pan	1	2	3	4	5

C. How difficult was it for you to perform the following activities using ***both of your hands***?

	Not at All Difficult	A Little Difficult	Somewhat Difficult	Moderately Difficult	Very Difficult
1. Open a jar	1	2	3	4	5
2. Button a shirt/blouse	1	2	3	4	5
3. Eat with a knife/fork	1	2	3	4	5
4. Carry a grocery bag	1	2	3	4	5
5. Wash dishes	1	2	3	4	5
6. Wash your hair	1	2	3	4	5
7. Tie shoelaces/knots	1	2	3	4	5

4

3

III. The following questions refer to how you did in your ***normal work*** (including both housework and school work) during the ***past four weeks***. (Please circle one answer for each question).

	Always	Often	Sometimes	Rarely	Never
1. How often were you unable to do your work because of problems with your hand(s)/wrist(s)?	1	2	3	4	5
2. How often did you have to shorten your work day because of problems with your hand(s)/ wrist(s)?	1	2	3	4	5
3. How often did you have to take it easy at your work because of problems with your hand(s)/ wrist(s)?	1	2	3	4	5
4. How often did you accomplish less in your work because of problems with your hand(s)/ wrist(s)?	1	2	3	4	5
5. How often did you take longer to do the tasks in your work because of problems with your hand(s)/ wrist(s)?	1	2	3	4	5

The following questions refer to how much ***pain*** you had in your hand(s)/wrist(s) ***during the past week***. (Please circle one answer for each question).

A. The following questions refer to **pain** in your ***right*** hand/wirst.

1. How often did you have pain in your ***right*** hand(s)/wrist(s)?
   1. Always
   2. Often
   3. Sometimes
   4. Rarely
   5. Never

If you answered **never** to **question IV-A1** above, please skip the following questions and go to the next page.

2. Please describe the pain you had in your ***right*** hand(s)/wrist(s).
   1. Very mild
   2. Mild
   3. Moderate
   4. Severe
   5. Very severe

	Always	Often	Sometimes	Rarely	Never
3. How often did the pain in your ***right*** hand(s)/wrist(s) interfere with your sleep?	1	2	3	4	5
4. How often did the pain in your ***right*** hand(s)/wrist(s) interfere with your daily activities (such as eating or bathing)?	1	2	3	4	5
5. How often did the pain in your ***right*** hand(s)/wrist(s) make you unhappy?	1	2	3	4	5

B. The following questions refer to **pain** in your ***left*** hand/wirst.

1. How often did you have pain in your ***left*** hand(s)/wrist(s)?
   1. Always
   2. Often
   3. Sometimes
   4. Rarely
   5. Never

If you answered **never** to **question IV-B1** above, please skip the following questions and go to the next page.

2. Please describe the pain you had in your ***left*** hand(s)/wrist(s).
   1. Very mild
   2. Mild
   3. Moderate
   4. Severe
   5. Very severe

	Always	Often	Sometimes	Rarely	Never
3. How often did the pain in your ***left*** hand(s)/wrist(s) interfere with your sleep?	1	2	3	4	5
4. How often did the pain in your ***left*** hand(s)/wrist(s) interfere with your daily activities (such as eating or bathing)?	1	2	3	4	5
5. How often did the pain in your ***left*** hand(s)/wrist(s) make you unhappy?	1	2	3	4	5

V. A. The following questions refer to the appearance (look) of your ***right*** hand **during the past week**. (Please circle one answer for each question).

	Strongly Agree	Agree	Neither Agree **nor** Disagree	Disagree	Strongly Disagree
1. I am satisfied with the appearance (look) of my ***right*** hand.	1	2	3	4	5
2. The appearance (look) of my ***right*** hand sometimes made me uncomfortable in public.	1	2	3	4	5
3. The appearance (look) of my ***right*** hand made me depressed.	1	2	3	4	5
4. The appearance (look) of my ***right*** hand interfered with my normal social activities.	1	2	3	4	5

B. The following questions refer to the appearance (look) of your ***left*** hand **during the past week**. (Please circle one answer for each question).

	Strongly Agree	Agree	Neither Agree **nor** Disagree	Disagree	Strongly Disagree
1. I am satisfied with the appearance (look) of my ***left*** hand.	1	2	3	4	5
2. The appearance (look) of my ***left*** hand sometimes made me uncomfortable in public.	1	2	3	4	5
3. The appearance (look) of my ***left*** hand made me depressed.	1	2	3	4	5
4. The appearance (look) of my ***left*** hand interfered with my normal social activities.	1	2	3	4	5

VI. A. The following questions refer to your satisfaction with your ***right*** hand/wrist **during the past week**. (Please circle one answer for each question).

	Very Satisfied	Somewhat Satisfied	Neither Satisfied **nor** Dissatisfied	Somewhat Dissatisfied	Very Dissatisfied
1. Overall function of your ***right*** hand	1	2	3	4	5
2. Motion of the fingers in your ***right*** hand	1	2	3	4	5
3. Motion of your ***right*** wrist	1	2	3	4	5
4. Strength of your ***right*** hand	1	2	3	4	5
5. Pain level of your ***right*** hand	1	2	3	4	5
6. Sensation (feeling) of your ***right*** hand	1	2	3	4	5

B. The following questions refer to your satisfaction with your ***left*** hand/wrist **during the past week**. (Please circle one answer for each question).

	Very Satisfied	Somewhat Satisfied	Neither Satisfied **nor** Dissatisfied	Somewhat Dissatisfied	Very Dissatisfied
1. Overall function of your ***left*** hand	1	2	3	4	5
2. Motion of the fingers in your ***left*** hand	1	2	3	4	5
3. Motion of your ***left*** wrist	1	2	3	4	5
4. Strength of your ***left*** hand	1	2	3	4	5
5. Pain level of your ***left*** hand	1	2	3	4	5
6. Sensation (feeling) of your ***left*** hand	1	2	3	4	5

Please provide the following information about yourself. (Please circle one answer for each question).

1. Are you right-handed or left-handed?
   a. Right-handed
   b. Left-handed
   c. Both

2. What is your ethnic background?
   a. Hispanic or Latino/a
   b. Not Hispanic or Latino/a

3. What is your racial background?
   a. American Indian or Alaskan Native
   b. Asian
   c. Native Hawaiian or other Pacific Islander
   d. Black or African-American
   e. White
   f. Other (Please specify). _____

4. a. Please describe the type of job you did **before** you injured your hands(s).

   _____

   b. Please describe the type of job you are doing **now**.

   _____

5. How long after your surgery did you return to work?_____
6. How long after your surgery did you return to the same job you were doing before your injury?_____

7. What is your gender?
   a. Male
   b. Female

8. What is the highest level of education you received?
   a. Less than high school graduate
   b. High school graduate or GED
   c. Vocational/technical school
   d. Some college or Associate degree
   e. College graduate
   f. Professional or graduate school

9. What is your approximate family income including wages, disability payment, retirement income and welfare?

a. Less than $10,000
b. $10,000 - $19,999
c. $20,000 - $29,999
d. $30,000 - $39,999
e. $40,000 - $49,999
f. $50,000 - $59,999
g. $60,000 - $69,999
h. More than $70,000

Thank you very much for completing this questionnaire.

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6.9. Appendix 9: References

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