A PROSPECTIVE, NON-RANDOMIZED, UNBLINDED STUDY EVALUATING THE TREATMENT WITH THE CRYO-TOUCH III DEVICE FOR UPPER LIMB SPASTICITY

Protocol Number: MYO-0709

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Protocol Synopsis

Title	A Prospective, Non-Randomized, Unblinded Study Evaluating the Treatment with the Cryo-Touch III Device for Upper Limb Spasticity
Study Device	Cryo-Touch III (a.k.a. PCP 1.0)
Study Objective	The Cryo-Touch III study is a post-market, off-label, prospective, multicenter study of the Cryo-Touch III Device for treatment of Upper Limb Spasticity. The objective of the Study is to evaluate the temporary relief of pain and symptoms in the upper arm in subjects with Upper Limb Spasticity secondary to Stroke, Cerebral Palsy, Multiple Sclerosis, traumatic brain injury or similar disorder.
Treatment Groups	Single
Duration of Study	Enrollment and follow-up is expected to take approximately 4 months. A subject will participate for approximately 10 weeks.
Study Population	Male or female subjects, ages 18 and older, diagnosed with pain due to severe spasticity of the upper limb(s).
Total Number of Subjects	Up to 20. A minimum of 10 and a maximum of 20 subjects.
Number of Sites	1-2
Inclusion Criteria	Eligible subjects must meet the following criteria: 1. Male or female, 18 years of age and older. 2. Trial participants must have a confirmed diagnosis that results in spasticity involving muscle innervated by the musculocutaneous nerve (MCN). 3. Any medications must be maintained on a stable schedule for at least two weeks prior to treatment. No washout period is allowed. 4. Must have an average score on the Modified Ashworth Scale for Spasticity of ≥ 2 over the last 30 days in the elbow. 5. Subject, in the Investigator's opinion, will not be exposed to unacceptable risk by participation.
Exclusion Criteria	A subject is ineligible if one or more of the following criteria applies: 1. Previous surgical intervention that altered the target neural anatomy of the upper limb. 2. Any injection (neurolytic, sclerosing, anesthetic, etc.) to the upper limb within the last 4 months. 3. Current enrollment in an investigational drug or device study that specifically targets spasticity management. 4. Allergy or intolerance to local anesthesia.

	5. Any local skin condition at the treatment site that in the investigator's opinion would adversely affect treatment or outcomes. 6. Any chronic medication use (prescription, over-the-counter, etc.) that in the investigator's opinion would affect study participation or subject safety. 7. Diagnosis of cryoglobulinemia, paroxysmal cold hemoglobinuria, cold urticaria, Raynaud's disease, open and/or infected wounds. 8. Diagnosis of progressive neurologic diseases such as ALS. 9. For any reason, in the opinion of the investigator, the subject may not be a suitable candidate for study participation (i.e., history of noncompliance, drug dependency, any related upper limb injury, etc.).
Study Visit Schedule	1. Visit 1/Screening (-30 Days to Day 0) 2. Visit 2/Treatment (Day 0) 3. Visit 3/ Maintenance (Day 7) 4. Visit 4/ Maintenance (Day 30) 5. Visit 5/Study Exit (Day 56) – Telephone Follow-Up
Primary Outcome	A decrease in pain and symptoms caused by hypertonia of the upper arm as measured by an improvement of 1 point or greater on the Modified Ashworth Scale at Day 7.
Secondary Outcomes	1. Improvement in spasticity as measured by the Tardieu Scale. 2. Improvement in spasm frequency and intensity as measured by the Penn Spasm Score. 3. Improvement in upper extremity motor recovery as measured by the Fugl-Meyer Scale (post stroke subjects only). 4. Subject assessed change in Mean Spasticity Numerical Rating Scale (NRS) Score. 5. Improvement in pain as assessed by visual analog scale (VAS). 6. Duration of treatment effect.

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Declaration of Investigator

I confirm that I understand the protocol and agree to conduct the study as detailed herein. I will not make changes in the protocol without approval from the Sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.

I agree to inform any subjects, or any persons in the study, that the device has been approved for market by the US FDA, currently is contraindicated in the study population and has not previously been studied in this population, and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and Institutional Review Board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the Sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 812.150(a)(1). I have read and understand the information in the product description, including any potential risks and side effects of the product.

I agree to maintain adequate and accurate records in accordance with 21 CFR 812.140 and to make those records available for inspection in accordance with 21 CFR 812.140.

I will ensure the IRB complies with the requirements of 21 CFR Part 56 and will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB and Sponsor all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without Sponsor and IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 812.110 and 812.150. I also agree to adhere to the internationally recognized Declaration of Helsinki, International Conference on Harmonisation (ICH) guidelines, and Good Clinical Practices (GCP).

Signature: _____ Date: _____

Printed Name: _____

1. Introduction

1.1. Background

Spasticity, common in neurological disorders, is part of the upper motor neuron syndrome displaying increased tone, clonus, spasms, spastic dystonia and co-contractions. The impact of spasticity on the patient varies from a subtle neurological sign to severe spasticity causing pain and contractures. Upper limb spasticity (ULS) is the rapid contraction or shortening of the muscles in the arm causing abnormal muscle movements in the elbow, wrist and fingers. It has been reported that over 1 million Americans with traumatic injury to the brain or spinal cord, stroke, multiple sclerosis and cerebral palsy experience ULS. Tightly clenched fists, twisted wrist and elbow joints, and fixed arms in flexed positions result in extreme discomfort, pain and spasm. A nonsurgical, minimally invasive, effective approach to pain associated with ULS is desirable.

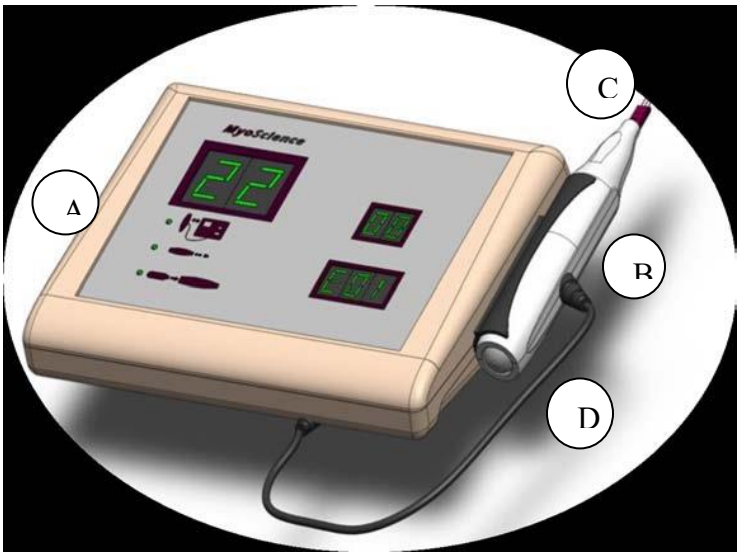
Myoscience, Inc. (Redwood City, CA) has developed a pain management device – the Cryo-Touch III – for a novel, minimally invasive procedure using focused cold therapy to target sensory nerve tissue and offer long-lasting pain relief through cryoanalgesia. The device operates on the well-established cryobiology principle that localized exposure to controlled, moderately low temperature conditions can alter tissue function. The therapy treats nerves via a probe in the form of an assembly of small diameter needles, creating a highly localized, low temperature treatment zone around the probe. This focused cold therapy creates a conduction block that prevents nerve signaling. Prior studies of the Cryo-Touch, Cryo-Touch II, Cryo-Touch III (a.k.a. PCP 1.0) devices have provided preliminary evidence of effectiveness on motor nerves and have been shown to be safe with no serious device-related adverse events.

1.2. Device Description

The Cryo-Touch III Device (a.k.a. PCP 1.0) (Figure 1) is a minimally invasive needle-based device. The device consists of a re-usable portable Control Unit, Handpiece, single use Cryoprobes (Figure 2) and Cryogen Cartridges. The Control Unit and Handpiece are powered by the Control Unit utilizing connection to a standard power outlet. The system is microprocessor controlled. Its functionality is driven by an operator controlled on/off switch. The unit displays indicator lights to guide the operator.

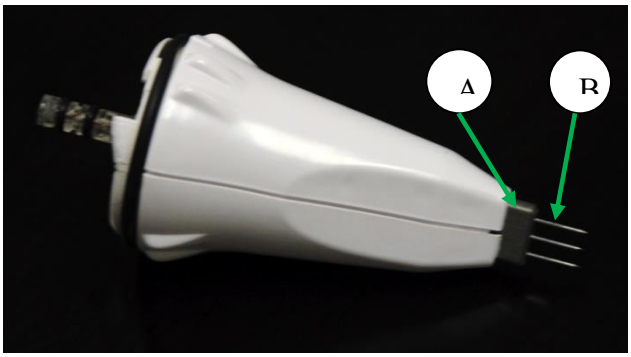
The system produces the desired effects through initiation of a cooling cycle. Each cooling cycle is initiated by subcutaneous insertion of the Cryoprobe into the selected site and activation of the cryogen flow. A freezing zone forms around the tip of the Cryoprobe and the adjacent tissue. The Cryogen Cartridges are provided in individually sealed pouches. Each cartridge contains a nitrous oxide cylinder encased with a safety cap and filter.

The Cryoprobes are supplied in sterile packaging and are single-patient use. The Cyroprobe tips are closed, therefore no cryogen enters the insertion site. A skin warmer provides warming at the base of the Cryoprobe tips to keep the skin surface above freezing temperatures.



A. Control Unit
B. Handpiece
C. Cryoprobe
D. Cryogen Cartridge

Figure 1. Picture of Cryo-Touch III Device.



A. Skin Warmer
B. Cryoprobe Tips

Figure 2. Picture of the Cryoprobe.

1.3. Regulatory Status

The myoscience Cryo-Touch III Device has been cleared by the US FDA as a class II medical device, K120415. Approved indications include general tissue

destruction during surgical procedures and cryo-treatment of peripheral nerves to block pain.

2. Study Protocol

2.1. Design

This is an 8 week, post-market, prospective, non-randomized, unblinded multi-center study of the Cryo-Touch III Device for treatment of Upper Limb Spasticity.

The study device is being studied per its current labeling in a currently contraindicated population.

2.2. Study Duration

Study enrollment and follow-up is expected to take approximately 4 months.

2.3. Sample Size

Up to 20 subjects will be enrolled in the study. A minimum of 10 subjects and a maximum of 20 subjects will be included.

Male and female subjects will be included without discrimination by gender, and subjects of all races and ethnicities will be equally eligible to participate in the study.

2.4. Subject Inclusionary Criteria

1. Male or female, 18 years of age and older.
2. Confirmed diagnosis that results in spasticity involving muscle innervated by the musculocutaneous nerve (MCN).
3. Stable use of medications (if applicable) for ≥ two weeks prior to treatment. No washout period is allowed.
4. Average score on the Modified Ashworth Scale for Spasticity of ≥ 2 over the last 30 days in the elbow.
5. Subject, in Investigator's opinion, will not be exposed to unacceptable risk by participation.

2.5. Subject Exclusionary Criteria

1. Previous surgical invention that altered the target neural anatomy of the upper limb.
2. Any injection (neurolytic, sclerosing, anesthetic, etc.) to the upper limb within the last 4 months.
3. Current enrollment in an investigational drug or a device study that specifically targets spasticity management.

4. Allergy or intolerance to local anesthesia.
5. Any local skin condition at the treatment site that in the investigator's opinion would adversely affect treatment or outcomes.
6. Any chronic medication use (prescription, over-the-counter, etc.) that in the investigator's opinion would affect study participation or subject safety.
7. Diagnoses of cryoglobulinemia, paroxysmal cold hemoglobinuria, cold urticaria, Raynaud's Disease, open and/or infected wounds.
8. Diagnoses of progressive neurologic diseases such as ALS.
9. For any reason, in the opinion of the investigator, the subject may not be a suitable candidate for study participation (i.e., history of noncompliance, drug dependency, any related upper limb injury, etc.).

2.6. Schedule of Events

See Appendix B.

2.6.1. Visit 1/Screening (Day -30 to Day 0)

Potential subjects will undergo screening against the study's eligibility criteria. Subjects will be informed of all study activities and requirements. After the subject has met all criteria and had ample opportunity to ask and have questions answered, an informed consent form will be signed and a copy provided to the subject.

The investigator, or designee, will document the subject's medical history, demographic information, concomitant medications/concurrent procedures, and any other required data points.

The subject will be scheduled for the next visit. The Visit 1/ Screening and Visit 2/ Treatment may occur on the same day. Every effort will be made to reduce the time between Screening and Treatment Visits if possible.

2.6.2. Visit 2/Treatment (Day 0)

2.6.2.1. Pre-Treatment/Evaluation Preparation

No special preparation by the subject is required prior to the treatment. The investigator will reaffirm eligibility criteria and the subject's willingness to continue participation in the trial. Any changes in concomitant medications/concurrent procedures will be recorded. Any adverse events that may have occurred prior to treatment will be documented as a change in medical history.

The target nerves will be located using adjacent anatomic landmarks. Non-invasive ultrasound imaging of the treatment area may be captured. Nerve stimulation may be used to assess location of nerves via a percutaneous nerve stimulator or a transcutaneous nerve stimulator.

The Cryo-Touch III Device will be used per the Instructions for Use on awake subjects who are prepared with dermal anesthesia only. The skin in the treatment area will be cleansed with alcohol. Local anesthetic will be injected into target sites with the goal of complete cutaneous anesthesia at the target treatment areas prior to the treatment.

The target of treatment are the musculocutaneous nerves (peripheral nerves). The nerves will be treated in a linear fashion to block the nerve at a location deemed appropriate by the investigator (see Figure 3).

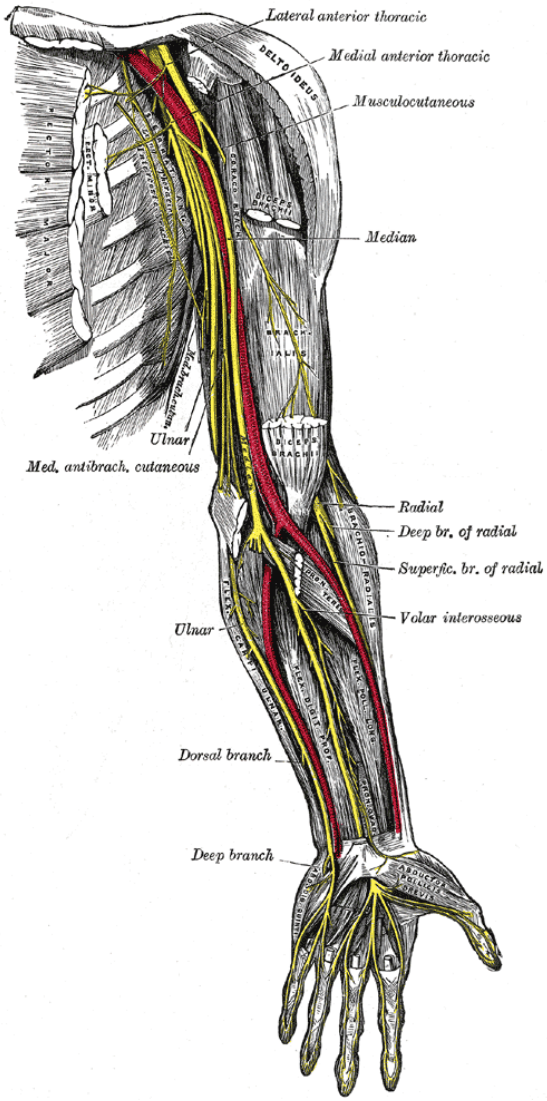


Figure 3: Nerve map of intended treatment.

2.6.2.2. Treatment

The Cryo-Touch III Device will have been prepared by the trained investigator (or Sponsor designee) according to the Instructions for Use (IFU) as provided by myoscience (see supplementary material). Representatives of myoscience may be present at the treatment. Photography and videography may be captured during the treatment.

Varying treatment algorithms will be pre-determined by the sponsor and placed into cohorts as appropriate for analysis. This is intended to determine the most effective method of treatment and to optimize the algorithm. Algorithms may include the following parameters: length of treatment, number of treatment cycles, probe tip design, and probe length.

If at any time the device does not perform as expected, the investigator (or designee) will follow procedures as outlined in the IFU.

2.6.2.3. Post-Treatment

Upon completion of treatment, the treatment area will be cleansed and the skin will be left undressed. Pressure to the treatment area with gauze for 5-10 minutes may be applied to minimize bleeding. The subject will be instructed in post-treatment care.

The subject will be instructed to report any adverse events or treatment side effects (e.g., excessive redness, swelling, bruising, soreness, altered sensation, etc.) to the investigator between and at follow-up visits. Non-invasive ultrasound may be used to assess the volume and location of the soft tissue treated below the dermis. Photography and/or videography may be obtained.

The subject will be scheduled and instructed regarding their follow-up visits and discharged from the clinic.

2.6.3. Visit 3/ Maintenance (Day 7) & Visit 4/Maintenance (Day 30)

Subject will be evaluated and data collected per the schedule of events. (Appendix B). Any changes in concomitant medications/concurrent procedures will be assessed. Any anticipated observations, adverse events, and/or SAE/UADE of the previous treatment site(s) will be documented and accessed. Non-invasive ultrasound imaging of the treatment area may be captured. Photography may be taken of the treatment area.

2.6.4. Visit 5/Study Exit (Day 56) – Telephone Follow-Up

Subject will be contacted via telephone and data collected since the last visit per the schedule of events. Any changes in concomitant medications/concurrent procedures will be assessed. Any anticipated

observations, adverse events, and/or SAE/UADE of the previous treatment site(s) will be documented.

If the treatment effect remains at Day 56, the subject will be followed every four (4) weeks via telephone until there is no longer any effect noted, up to a total of 112 days post-treatment. Any clinically significant adverse event will be followed until resolution. The subject will exit the study once there are no longer treatment effects and no ongoing clinically significant events.

Study exit data will be collected and the subject reminded to contact the investigator if any new, previously unreported event occurs related to the treatment.

A subject is considered to have exited the study after completing all scheduled visits. In the event that a subject does not attend a scheduled visit, every effort will be made to reschedule. In the event of a subject lost to follow-up, study exit form will be completed and efforts documented.

If a subject decides to withdraw participation early, the subject will be requested to complete a final study visit and exit the study. The investigator or sponsor may at any time during the study remove a subject if there is any potential safety issue or non-compliance. In all cases, every attempt will be made to complete a final study visit.

3. Outcome Measures and Assessments

Outcome measures will be assessed around multiple endpoints. These measures will be: pain, duration of improvement, anticipated observations, and safety. Additional assessments may also be taken but are not considered part of the analysis (i.e. subject post-treatment questionnaire). The specific assessment tools, collection method and time points are listed herein.

3.1.1. Primary Outcome Measure

A decrease in hypertonia as measured by an improvement of 1 point or greater in the Modified Ashworth Scale at Day 7.

Hypertonia will be assessed at each study time period using the Modified Ashworth Scale. Assessment will be conducted by the same Investigator at each time point to reduce inter-assessment variation.

3.1.2. Secondary Outcome Measures

1. Improvement in spasticity as measured by the Tardieu Scale: *Subjects will undergo the Tardieu test to assess spasticity (verses stiffness) at each study visit.*

2. Improvement in spasm frequency and intensity as measured by the Penn Spasm Score: *Subjects experiencing spasm of the upper extremity will be assessed using the Penn Spasm Frequency Scale at each study visit.*

3. Improvement in upper extremity motor recovery as measured by the Fugl-Meyer Scale (post stroke subjects only): *Subjects who have spasticity due to stroke will be assessed using the Fugl-Meyer – Motor Recovery after Stroke Scale at each study visit.*

4. Subject assessed change in Mean Spasticity Numerical Rating Scale (NRS) Score: *Subjects will be asked "On a scale of '0 to 10' please indicate the average level of your spasticity over the last 24 hours" with the anchors: 0 = 'no spasticity' and 10 = 'worst possible spasticity'. 'No spasticity' is explained as the time prior to the onset of their spasticity.*

5. Improvement in pain as assessed by visual analogue scale (VAS): *Subjects will be shown a number scale and six facial expressions suggesting various pain intensities. The subject will be asked to choose the face that best describes how they feel. The far left face indicates 'No hurt' and the far right face indicates 'Hurts worst'. The VAS will be conducted at every study visit.*

3.1.3. Ancillary Measures (Potential measures not part of analysis)

Subject Post-Treatment Questionnaire (See Appendix)

3.1.4. Anticipated Observations (AO) [Data Collection Tool]

During each visit, the area treated will be assessed by the investigator (observation and subject query) for the following anticipated observations (AO's) at the treatment site. These AO's will be collected independent of adverse events and are specific to the treatment site area.

- ecchymosis (bruising)
- edema (swelling)
- erythema (redness or inflammation)
- pain and/or tenderness
- localized dysesthesia (altered sensation)
- thermal injury to the skin, skin lesions, hyper or hypo pigmentation secondary to skin injury
- dimpling of skin

3.1.5. Safety Measures [Data Collection]

Adverse events and SAEs/UADEs will be assessed at all visits. Incidence of serious adverse events (SAEs) and unanticipated adverse device effects (UADEs) will be recorded.

3.2. Adverse Event Reporting

All adverse events, regardless of seriousness, severity, or relationship to device, will be recorded and evaluated by the Investigator. The evaluation will include a determination of the seriousness and severity of the event, whether the event or the severity of the event was anticipated or unanticipated, and the relationship of the event to the study device.

A serious adverse event (SAE) is defined according to ISO14155:2003 (section 3.19) as any adverse event that:

- Led to a death
- Led to a serious deterioration in the health of the subject that
  - resulted in a life-threatening illness or injury
  - resulted in a permanent impairment of a body structure or a body function
  - required in-patient hospitalization or prolongation of existing hospitalization
  - resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function
- Led to fetal distress, fetal death or a congenital abnormality or birth defect.

An unanticipated adverse device (UADE) effect is defined in 21 CFR 812.3 as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Events NOT considered to be serious adverse events are:

1) Hospitalizations for the treatment, which was elective or pre-planned, of a pre-existing condition that did not worsen; and,

2) Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of “serious” given above and not resulting in hospital admission.

Serious Adverse Events and Unanticipated Adverse Device Effects will be reported by the Investigator to myoscience within 24 hours and to the Institutional

Review Board (IRB) within the timeframe required by the IRB, but not more than 7 days following the point at which the site becomes aware of the event.

3.3. Statistical Analysis Plan

Not applicable.

4. Risk/Benefit Analysis

4.1. Benefits

Subjects may experience an improvement in pain and spasticity symptoms post-treatment or may experience no improvement at all.

4.2. Risks

The Cryo-Touch III Device has been approved for market by the United States Food and Drug Administration (FDA) and the risks associated with its use are documented and provided in the Instructions for Use.

The risks associated with this study include the use of the device in a population not previously studied.

5. Study Management and Quality Control

5.1. Data Collection

Incoming data will be reviewed by the Sponsor or designee to identify inconsistent or missing data and to ensure compliance with the study protocol.

Investigators will be responsible for the accurate and timely completion of all source documents, case report forms, and any other required study data (i.e., worksheets, questionnaires, etc.) during the trial.

5.2. Investigator Responsibilities

Investigators are responsible for ensuring the investigation is conducted according to all signed agreements, the study protocol, and applicable regulatory agency regulations. This section outlines- these responsibilities, although this does not represent a complete description of all responsibilities.

5.2.1. Compliance with Good Clinical Research Practice

This study will be conducted in compliance with the principles of the Declaration of Helsinki, with the current Good Clinical Practice (GCP) guidelines and with other applicable regulations. The investigator and all

study staff will conduct the study in compliance with this protocol. The protocol, informed consent documents, recruitment advertisements (if applicable) and any amendments to these items will have IRB approval prior to study initiation. Every subject will give voluntary informed consent prior to the initiation of any study-related procedures. The rights, safety and welfare of the study subjects are the most important considerations and prevail over the interests of science and society. All personnel involved in the conduct of this study must be qualified by education, training and experience to perform their assigned responsibilities.

5.2.2. Institutional Review Board (IRB)

Before study initiation at each site, the investigator must have written and dated approval from the IRB for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects at his/her site. The investigator will submit documentation of the IRB approval to the Sponsor or designee.

The IRB approved consent form must include all elements required by FDA, state, and local regulations, and may include appropriate additional elements.

The investigator/designee will explain the study to each potential subject, and the subject must indicate voluntary consent by signing and dating the approved informed consent form. If the subject is not able to provide written consent, the subject's legal representative will consent on their behalf as directed by the sites IRB. The investigator/designee must provide the subject with a copy of the consent form, in a language the subject understands.

The investigator/designee will maintain documentation showing that informed consent was obtained prior to the initiation of any study-specific procedures.

Withdrawal of IRB approval of the investigator's part in the investigation shall be reported to the Sponsor within 5 working days.

5.2.3. Device Accountability

The investigator is responsible for providing a secure storage location for the devices, supervising device use, as well as return of the device as instructed by the Sponsor or designee. In addition, investigators will maintain records of receipt, use or disposition of all devices. The Sponsor or designee will maintain records of all shipments and disposition of the devices and will routinely inspect for device accountability at the clinical sites participating in this trial.

All used units and probes shall be stored and upon request returned to the Sponsor or designee for analysis unless otherwise directed. If a Sponsor representative or designee is present at the time of use, he/she may directly take possession of used device(s). All devices will be returned to the Sponsor after the study is complete.

5.2.4. Confidentiality

The investigator is responsible for ensuring the confidentiality of subjects throughout the trial. A unique identification code will be assigned to each subject participating in this trial. Any data that may be published in abstracts, scientific journals, or presented at medical meetings will reference the unique subject code and will not reveal the subject's identity.

5.2.5. Record Retention

The investigator must maintain all study records (including device disposition, informed consents, case report forms/worksheets, source documents, correspondence, regulatory documents, contracts etc.) for the maximum period required by the Sponsor or the institution where the study is conducted, whichever is longer.

The investigator must contact the Sponsor prior to destroying any records associated with this study.

If the investigator withdraws from the study, the records shall be transferred to a mutually agreed upon designee.

5.3. Sponsor Responsibilities

myoscience or designee's responsibilities in the study include:

- Developing the protocol & CRFs
- Selecting qualified investigators (21CFR812.43(a))
- Maintaining Site/Investigator's Agreement and CVs/licenses
- Assisting sites in completing IRB approvals and reporting
- Ensuring device availability
- Reviewing data for study rationale and subject safety
- Providing site training on all study aspects and procedures
- Monitoring study data
- Informing site(s) & IRB(s) of any new, significant safety information
- Maintaining SOPs
- Analyzing results and assisting with presentation(s) and/or publication(s)
- Retaining custodianship of the multi-center clinical data generated

5.3.1. Study Monitoring

Representatives of the Sponsor or designee must be allowed to visit all study sites, to review study records and to directly compare them with source documents (including, but not limited to patient and hospital records), to discuss the study conduct with the investigator and study staff and to verify that the investigator, study staff, and facilities remain acceptable for the conduct of the study.

Representatives of government regulatory authorities may also evaluate the study records, source documents, investigator, study staff, and facilities.

The investigator should immediately notify the Sponsor or designee of any audits of this study by any regulatory agency, and must promptly provide copies of any audit reports.

5.3.2. Protocol Revisions

The Sponsor or designee must prepare all protocol revisions. All protocol amendments must receive IRB approval prior to implementation. All administrative letters must be submitted to the IRB for their information. All correspondence with the IRB regarding this study must be maintained in the site regulatory file and made available to the Sponsor or designee.

The most recent IRB approved version of the informed consent form (ICF) must be administered to all subjects upon enrollment. In some cases, due to new information or protocol amendments, an ICF may be updated. Subjects must be re-consented using the latest approved version only if directed to do so by the IRB and/or Sponsor.

6. Data Ownership

myoscience, Inc., the study Sponsor, retains ownership of all data generated in this study, and controls the use of the data for purposes of regulatory submissions to the United States and/or other governments. Investigator(s) and institution(s) (which shall include their employees, agents, and representatives) may not issue or disseminate any press release or statement, nor initiate any communication of information regarding this study (written or oral) to the communications media or third parties without the prior written consent of myoscience.

Appendix A: Abbreviations

AE	Adverse Event
AO	Anticipated Observations
CFR	Code of Federal Regulations
CRF	Case Report Form
US FDA	United States Food and Drug Administration
EOS	End of Study
FMA	Fugl-Meyer Assessment
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IFU	Instructions for Use
IRB	Institutional Review Board/Independent Review Board
ISO	International Organization for Standardization
MAS	Modified Ashworth Scale
NRS	Mean Spasticity Numerical Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
ROM	Range of Motion
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Device Effect
ULS	Upper Limb Spasticity
VAS	Visual Analog Scale

Appendix B: Schedule of Events

Study Activity	V1 Screening	V2 Treatment	V3	V4	V5 Phone Follow-up/EOS
	Day -30 to Day 0	*Day 0*	*Day 7**	*Day 30***	*Day 56***
Obtain Informed Consent	X				
Review Eligibility Criteria	X	X			
Physical Examination	X				
Medical History	X	X			
Concomitant Medications/Procedures	X	X	X	X	X
Modified Ashworth Scale	X	X	X	X	
Tardieu Scale	X	X	X	X	
Penn Spasm Frequency Score	X	X	X	X	
Fugl-Meyer Assessment (Post Stroke Only)	X	X	X	X	
Visual Analog Scale (VAS) For Pain	X	X[1]	X	X	
Mean Spasticity Numerical Rating Scale (Nrs)	X	X	X	X	
Treatment		X			
AO Assessment		X	X	X	X
Subject Post-Treatment Questionnaire		X	X	X	
Adverse Events/Procedures Review		X	X	X	X
Duration Of Treatment Effect/No Effect			X	X	X

**** A variance of +/- 3 days is allowed.***
***** A variance of +/- 7 days is allowed.***
[1]VAS assessment for pain at Visit 2 should be taken pre-treatment and post-treatment

Appendix C: Validated Assessment Tools

Modified Ashworth Scale

Modified Ashworth Scale Instructions

General Information (derived Bohannon and Smith, 1987):

- Place the patient in a supine position
- If testing a muscle that primarily flexes a joint, place the joint in a maximally flexed position and move to a position of maximal extension over one second (count "one thousand one")
- If testing a muscle that primarily extends a joint, place the joint in a maximally extended position and move to a position of maximal flexion over one second (count "one thousand one")
- Score based on the classification below

Scoring (taken from Bohannon and Smith, 1987):

0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM
2	More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

Patient Instructions:
The patient should be instructed to relax.

Test instructions provided courtesy of Richard Bohannon PT, PhD and Melissa Smith, PT
Page 1

Modified Ashworth Scale Testing Form

Name:_____ Date:_____

Muscle Tested	Score
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

Reference for test instructions:

Bohannon, R. and Smith, M. (1987). "Interrater reliability of a modified Ashworth scale of muscle spasticity." Physical Therapy 67(2): 206.

Tardieu Scale

TARDIEU SCALE

This scale quantifies muscle spasticity by assessing the response of the muscle to stretch applied at specified velocities.

Grading is always performed at the same time of day, in a constant position of the body for a given limb. For each muscle group, reaction to stretch is rated at a specified stretch velocity with 2 parameters x and y.

Velocity to stretch (V)

V1 As slow as possible
V2 Speed of the limb segment falling
V3 As fast as possible (> natural drop)

V1 is used to measure the passive range of Motion. (PROM). Only V2 and V3 are used to rate spasticity

Quality of muscle reaction (X)

0 No resistance throughout passive movement
1 Slight resistance throughout, with no clear catch at a precise angle
2 Clear catch at a precise angle, followed by release
3 Fatigable clonus (<10secs) occurring at a precise angle
4 Unfatigable clonus (>10secs) occurring at a precise angle
5. Joint Immobile

Angle of muscle reaction (Y)

Measure relative to the position of minimal stretch of the muscle (corresponding at angle)

Spasticity Angle

R1 Angle of catch seen at Velocity V2 or V3

R2 Full range of motion achieved when muscle is at rest and tested at V1 velocity

Boyd, Graham 1999

- A large difference between R1 & R2 values in the outer to middle range of normal m. length indicates a large dynamic component
- A small difference in the R1 & R2 measurement in the middle to inner range indicates predominantly fixed contracture

Date	Joint/ Muscle	L/R	V	X	R1	R2	Active ROM	Power MRC	Ashworth Rating	°

Ref: Boyd R, Graham K. Objective Measurement of clinical findings in the use of Botox type A for the management of children with Cerebral Palsy. European Journal of Neurology 6(Supp 4) S23-35
Tardieu G, Rondont O, Mensch J, Dalloz J, Monfraix C, Tabary J. Responses electromyograhpiques a l'etirement musculaire chez l'homme normal. Revue Neurologie + 97(1), 60-61
Gracies J, Marosszzeky J, Renton R, Sandaman J, Gandevia S, Burke D. Short term effects of dynamic splints on the upper limb in hemiplegic patients. Archives of Physical Medicine and Rehabilitation, 81 1547-1555.

Testing Positions

Upper Limb

To be tested in a sitting position, elbow flexed by 90° at the recommended joint positions and velocities.

Shoulder	Horizontal Adductors	V3	
	Vertical Adductors	V3	
	Internal Rotators	V3	
Elbow	Flexors	V2	Shoulder adducted
	Extensors	V3	Shoulder abducted
	Pronators	V3	Shoulder adducted
	Supinators	V3	Shoulder adducted
Wrist	Flexors	V3	
	Extensors	V3	
	Fingers		Angle PII of digit III- MCP
	Palmar Interossei + FDS	V3	Wrist resting position

Lower Limb

To be tested in supine position, at recommended joint positions and velocities

Hip	Extensors	V3	Knee extended
	Adductors	V3	Knee extended
	External Rotators	V3	Knee flexed by 90
	Internal Rotators	V3	Knee flexed by 90
Knee	Extensors	V2	Hip flexed by 30
	Flexors	V3	Hip flexed
Ankle	Plantarflexors	V3	Knee flexed by 30

Penn Spasm Score

TABLE 21.2
Spasm Frequency Scales

PENN SPASM FREQUENCY SCORE (PSFS)

0 No spasms
1 Mild spasms induced by stimulation
2 Infrequent spasms occurring less than once per hour
3 Spasms occurring more than once per hour
4 Spasms occurring more than ten times per hour

MODIFIED PSFS: 2 PART

Part 1: spasm frequency score (as above)
Part 2: spasm severity scale
1 Mild
2 Moderate
3 Severe

SPASM FREQUENCY SCORE

0 No spasms
1 1 or fewer spasms per day
2 Between 1 and 5 spasms per day
3 5 to >10 spasms per day
4 10 or more spasms per day, or continuous contraction

Fugl-Meyer Assessment of Physical Performance – Upper Extremity & Sensation (Stroke only)

General Procedure and Rules

PROCEDURE

Description: This assessment is a measure of upper extremity (UE) and lower extremity (LE) motor and sensory impairment.

Equipment: A chair, bedside table, reflex hammer, cotton ball, pencil, small piece of cardboard or paper, small can, tennis ball, stop watch, and blindfold.

Administration: The complete assessment usually requires 45 minutes.

GENERAL RULES

Perform the assessment in a quiet area when the patient is maximally alert.

Volitional movement assessment: This includes flexor synergy, extensor synergy, movement combining synergies, movement out of synergy, wrist, hand, and coordination/speed. For all tests of volitional motion, these guidelines are to be followed:

1. Give clear and concise instructions. Mime as well as verbal instructions permissible.
2. Have patient perform the movement with non-affected extremity first. On affected side, check for available passive range of motion (PROM) prior to asking patient to perform the movement.
3. Repeat each movement 3x on the affected side and score best performance. If full score is attained on trials 1 or 2, do not have to repeat 3 times. Only test Coordination/speed, one time.
4. Do not assist patient, however verbal encouragement is permitted.
5. Test the wrist and hand function independently of the arm. During the wrist tests (items 7a-e), support under the elbow may be provided to decrease demand at the shoulder; however, the patient should be activating the elbow flexors during the elbow at 90 degree tests and activating the elbow extensors during the elbow at 0 degree tests. In contrast, assistance can be provided to the arm at the elbow and just proximal to the wrist in order to position the arm during the hand tests (items 8a-g).

Upper Extremity		
Item	**Instructions**	**Scoring**

I. Reflex activity	• Patient is sitting.
	• Attempt to elicit the biceps and triceps reflexes.
	• Test reflexes on unaffected side first.
	• Test affected side.
		• *Scoring* (Maximum possible score = 4):
		  • (0) - No reflex activity can be elicited
		  • (2) - Reflex activity can be elicited

II. Flexor synergy	• Patient is sitting.
	• Have patient perform movement with unaffected side first.
	• On the affected side, check patient's available PROM at each joint to be tested.
	• The starting position should be that of full extensor synergy. If the patient cannot actively achieve the starting position, the limb may be passively placed extended towards opposite knee in shoulder adduction/internal rotation, elbow extension, and forearm pronation.
	• Instruct the patient to fully supinate his/her forearm, flex the elbow, and bring the hand to the ear of the affected side. The shoulder should be abducted at least 90 degrees.
	• Test 3x on the affected side and score best movement at each joint
		• *Scoring* (Maximum possible score = 12):
		  • (0) - Cannot be performed at all
		  • (1) - Performed partly
		  • (2) - Performed faultlessly
		• Items to be scored are: Elevation (scapular), shoulder retraction (scapular), shoulder abduction (at least 90 degrees) and external rotation, elbow flexion, and forearm supination.
		  •

III. Extensor synergy	• Patient is sitting.
	• Have patient perform movement with unaffected side first.
	• On the affected side, check patient's available PROM at each joint to be tested.
	• The starting position should be that the limb is passively placed at patient's side in elbow flexion and supination. The examiner must ensure that the patient does not rotate and flex the trunk forward, thereby allowing gravity to assist with the movement. The pectoralis major and triceps brachii tendons may be palpated to assess active movement.
	• Instruct the patient to adduct & internally rotate the shoulder, extend his arm towards the unaffected knee with the forearm pronated.
	• Test 3x on the affected side and score best movement at each joint.
		• *Scoring* (Maximum possible score = 6):
		  • (0) - Cannot be performed at all
		  • (1) - Performed partly
		  • (2) - Performed faultlessly
		• Items to be scored are: Shoulder adduction/internal rotation, elbow extension, and forearm pronation.

IV. Movement combining synergies The patient is asked to perform	4a. Hand to lumbar spine: • Patient is sitting with arm at side, shoulder at 0°, elbow at 0°. • Have patient perform movement with unaffected side first.	• *Scoring* (Maximum possible score = 2): • (0) – No specific action is performed (or patient moves but does not reach

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three separate movements (4a, 4b, 4c).	• Check patient's available PROM on the affected side for this motion. • Patient is instructed to actively position the affected hand on the lumbar spine by asking them to "put your hand behind your back". • Test 3x on the affected side and score best movement.	ASIS) • (1) - Hand must pass anterior superior iliac spine (performed partly) • (2) - Performed faultlessly (patient clears ASIS and can extend arm behind back towards sacrum; full elbow extension is not required to score a 2)
	4b. Shoulder flexion to 90°, elbow at 0°: • Patient is sitting with hand resting on lap. • Have patient perform movement with unaffected side first. • On the affected side, check patient's available PROM for shoulder flexion to 90° and full elbow extension. • Patient is instructed to flex the shoulder to 90°, keeping the elbow extended. The elbow must be fully extended throughout the shoulder flexor movement; the forearm can be in pronation or in a mid-position between pronation and supination. • Test 3x on the affected side and score best movement.	• *Scoring* (Maximum possible score = 2): • (0) – Arm is immediately abducted, or elbow flexes at start of motion • (1) - Abduction or elbow flexion occurs in later phase of motion • (2) - Performed faultlessly (patient can flex shoulder keeping elbow extended)
	4c. Pronation/supination of forearm, elbow at 90°, shoulder at 0°: • Patient is sitting with arm at side, elbow flexed, and forearm in supination. • Have patient perform movement with unaffected side first. • On the affected side, check patient's available PROM for end range of pronation and supination. • Patient is instructed to actively flex the elbow to 90° and pronate/supinate the forearm through the full available ROM. • Test 3x on the affected side and score best movement.	• *Scoring* (Maximum possible score = 2): • (0) – Correct position of shoulder held in adduction at side of body and elbow flexion, and/or pronation or supination cannot be performed. • (1) – Active pronation or supination can be performed even within a limited range of motion, with elbow flexed at 90° and arm at side. • (2) - Complete pronation and supination with with elbow flexed at 90° and arm at side.
V. Movement out of synergy The patient is asked to perform three separate movements (5a, 5b, 5c).	5a. Shoulder abduction to 90°, elbow at 0°, and forearm pronated: • Patient is sitting with arm and hand resting at side. • Have patient perform movement with unaffected side first. • Check patient's available PROM on the affected side for this motion. • Patient is instructed to abduct the shoulder to 90°, in a pure abduction motion, with the elbow fully extended	• *Scoring* (Maximum possible score = 2): • (0) – Initial elbow flexion occurs, or any deviation from pronated forearm occurs • (1) - Motion can be performed partly, or, if during motion, elbow is

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	and the forearm pronated. • Test 3x on the affected side and score best movement.	flexed, or forearm cannot be kept in pronation; • (2) - Performed faultlessly (patient can fully abduct shoulder, keeping forearm pronated with no elbow flexion)
	5b. Shoulder flexion from 90°-180°, elbow at 0°, and forearm in mid-position: • Patient is sitting with elbow extended, hand resting on knee. • Have patient perform movement with unaffected side first. • Check patient's available PROM on the affected side for this motion. • Patient is instructed to flex the shoulder above 90°, with the elbow fully extended and the forearm in the mid-position between pronation and supination. • Test 3x on the affected side and score best movement.	• *Scoring* (Maximum possible score = 2): • (0) – Initial flexion of elbow or shoulder abduction occurs (arm is immediately abducted, or elbow flexes at start of motion) • (1) – Elbow flexion or shoulder abduction occurs during shoulder flexion (in later phases of motion) • (2) - Performed faultlessly (patient can flex shoulder above, with forearm in mid-position and no elbow flexion)
	5c. Pronation/supination of forearm, elbow at 0°, and shoulder at 30°-90° of flexion: • Patient is sitting with elbow extended, shoulder between 30°-90° of flexion. • Have patient perform movement with unaffected side first. • Check patient's available PROM on the affected side for this motion. • Patient is instructed to pronate and supinate the forearm as the shoulder remains flexed between 30-90° and the elbow is fully extended. • Test 3x on the affected side and score best movement.	• *Scoring* (Maximum possible score = 2): • (0) – Supination and pronation cannot be performed at all, or elbow and shoulder positions cannot be attained • (1) – Elbow and shoulder properly positioned and supination performed in a limited range • (2) - Performed faultlessly (complete pronation and supination with correct positions at elbow and shoulder)
VI. Normal Reflexes (sitting)	• This item is only included if the patient achieves a maximum score on all previous upper extremity items, otherwise score 0. • The examiner shall elicit biceps and triceps phasic reflexes with a reflex hammer and finger flexors with quick stretch and note if the reflexes are hyperactive or not.	• *Scoring* (Maximum possible score = 2): • (0) - At least 2 of the 3 phasic reflexes are markedly hyperactive • (1) – One reflex is markedly hyperactive or at least 2 reflexes are lively • (2) - No more than one

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		reflex is lively, and none are hyperactive
VII. Wrist During the wrist tests, support under the elbow to may be provided to decrease demand at the shoulder; however, the patient should be activating the elbow flexors during the elbow at 90 degree tests and activating the elbow extensors during the elbow at 0 degree tests. The patient is asked to perform five separate movements (7a, 7b, 7c, 7d, 7e).	7a. Stability, elbow at 90°, and shoulder at 0°: • Patient is sitting with arm and hand resting at side. • Have patient perform movement with unaffected side first. • Check patient's available PROM on the affected side for this motion. • Patient is instructed to dorsiflex (extend) the wrist to the full range of 15° (or full available range) with the elbow at 90° flexion and the shoulder at 0°. If full range of dorsiflexion is attained, slight resistance is given. • Test 3x on the affected side and score best movement.	• *Scoring* (Maximum possible score = 2): • (0) - Patient cannot dorsiflex wrist to required 15° • (1) – Dorsiflexion is accomplished, but no resistance is taken • (2) - Position can be maintained with some (slight) resistance
	7b. Flexion/extension, elbow at 90°, and shoulder at 0°: • Patient is sitting with arm and hand resting at side. • Have patient perform movement with unaffected side first. • Patient is instructed to perform repeated smooth alternating movements from 15 degrees of flexion (wrist extension) to 15 degrees of extension. • Test 3x on the affected side and score best movement	• *Scoring* (Maximum possible score = 2): • (0) - Volitional movement does not occur • (1) – Patient cannot actively move through the wrist joint throughout the total range of motion • (2) – Faultless, smooth movement (repetitive through full available ROM)
	7c. Stability, elbow at 0°, and shoulder at 30° flexion: • Patient is sitting with elbow extended, hand resting on knee and forearm pronated. • Have patient perform movement with unaffected side first. • Check patient's available PROM on the affected side for this motion. • Patient is instructed to dorsiflex (extend) the wrist to the full range of 15° (or full available range) with the elbow fully extended and the shoulder at 30° flexion. If full range of dorsiflexion is attained, slight resistance is given. • Test 3x on the affected side and score best movement.	• *Scoring* (Maximum possible score = 2): • (0) - Patient cannot dorsiflex wrist to required 15° • (1) – Dorsiflexion is accomplished, but no resistance is taken • (2) - Position can be maintained with some (slight) resistance
	7d. Flexion/extension, elbow at 0°, and shoulder at 30° flexion: • Patient is sitting with elbow extended, hand resting on knee and forearm pronated. • Have patient perform movement with unaffected side first. • Patient is instructed to perform repeated smooth alternating movements from maximum dorsiflexion to maximum volar flexion with the fingers somewhat flexed to the full range of 15° (or full available range)	• *Scoring* (Maximum possible score = 2): • (0) - Volitional movement does not occur • (1) – Patient cannot actively move throughout the total range of motion; • (2) – Faultlessly, smooth movement (repetitive through full ROM)

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	with the elbow fully extended and the shoulder at 30° flex. • Test 3x on the affected side and score best movement.	
	7e. Circumduction: • Patient is sitting with arm at side elbow flexed to 90°, and forearm pronated. • Have patient perform movement with unaffected side first. • Check patient's available PROM on the affected side for this motion. • Patient is instructed to circumduct the wrist with smooth alternating movements throughout the full range of circumduction. • Test 3x on the affected side and score best movement.	• *Scoring* (Maximum possible score = 2): • (0) – Cannot be performed (volitional movement does not occur) • (1) – Jerky motion or incomplete circumduction • (2) – Complete motion with smoothness (performs faultlessly, smooth, repetitive movement through full ROM)
VIII. Hand During the hand tests, assistance can be provided to the arm at the elbow and just proximal to the wrist in order to position the arm for the grasp tasks. The patient is asked to perform seven separate movements (8a, 8b, 8c, 8d, 8e, 8f, 8g). The object is not placed in the hand but presented to the patient so that it requires sufficient opening to grasp test object, closure on object, ability to hold against a slight tug.	8a. Finger mass flexion:  • Patient is sitting with arm on bedside table or lap. • Have patient perform movement with unaffected side first. • Check patient's available PROM on the affected side for this motion. • Starting from the position of finger extension (this may be attained passively if necessary), instruct the patient to fully flex all fingers. • Test 3x on the affected side and score best movement	• *Scoring* (Maximum possible score = 2): • (0) – No flexion occurs • (1) – Some flexion, but not full motion • (2) – Completed active flexion (compared to unaffected hand)
	8b. Finger mass extension:  • Patient is sitting with arm on bedside table or lap. • Have patient perform movement with unaffected side first. • Check patient's available PROM on the affected side for this motion. • Starting from the position of finger flexion (this may be attained passively if necessary), instruct the patient to fully extend all fingers. • Test 3x on the affected side and score best movement.	• *Scoring* (Maximum possible score = 2): • (0) – No extension occurs • (1) – Patient can release an active mass flexion grasp • (2) – Full active extension (compared to unaffected side)
	8c. Grasp I: • Patient is sitting with arm on bedside table. • Have patient perform movement with unaffected side first. • Check patient's available PROM on the affected side for	• *Scoring* (Maximum possible score = 2): • (0) – Required position cannot be attained • (1) – Grasp is weak

	this motion. • Instruct the patient to extend the metacarpophalangeal joints of digits II-V and flex the proximal & distal interphalangeal joints. Test this grip against resistance. You can tell the patient "pretend you are holding the handle of a briefcase." • Test 3x on the affected side and score best movement.	• (2) – Grasp can be maintained against relatively great resistance
	8d. Grasp II:  • • Patient is sitting with arm on bedside table. • Have patient perform movement with unaffected side first. • Instruct the patient to abduct the thumb to grasp a piece of paper. Then ask the patient to perform pure thumb adduction with the scrap of paper interposed between the thumb and first digit (as in figure). Test this grip against resistance by asking the patient to hold as you attempt to pull the paper out with a slight tug. • Test 3x on the affected side and score best movement.	• *Scoring* (Maximum possible score = 2): • (0) – Function cannot be performed • (1) – Scrap of paper interposed between the thumb and index finger can be kept in place, but not against a slight tug • (2) – Paper is held firmly against a tug
	8e. Grasp III:  • Patient is sitting with arm on bedside table. • Have patient perform movement with unaffected side first. • Instruct the patient to grasp a pen or pencil by opposing the thumb and index finger pads around the pen. The tester may support the patient's arm but may not assist with the hand function required for the retrieval task. The pen may not be stabilized by the therapist or the patient's other hand. To minimize excessive movement, however, a pen with a 'pocket clip' that prevents rolling more than 180° may be used. • Once the pencil is retrieved, instruct the patient to oppose the thumb pad against the pad of the index finger with a pencil interposed. Test this grip against resistance by asking the patient to hold as you attempt to pull the pencil out with a slight tug upwards. • Test 3x on the affected side and score best movement.	• *Scoring* (Maximum possible score = 2): • (0) – Function cannot be performed • (1) – A pencil interposed between the thumb pad and the pad of the index finger can be kept in place, but not against a slight tug • (2) – Pencil is held firmly against a tug
	8f. Grasp IV:  • Patient is sitting with arm on bedside table.	• *Scoring* (Maximum possible score = 2): • (0) Function cannot be performed • (1) – A can interposed between the thumb and

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	• Have patient perform movement with unaffected side first. • Instruct the patient to grasp a small can (placed upright on a table without stabilization) by opening the fingers and opposing the volar surfaces of the thumb and digits. The arm may be supported but the tester may not assist with hand function. • Once the can is grasped, test this grip against resistance by asking the patient to hold as you attempt to pull the can out with a slight tug. Test 3x on the affected side and score best movement.	index finger can be kept in place, but not against a slight tug • (2) – Can is held firmly against a tug • NOTE: the hand must open and close on the can; it is not acceptable to have the patient grasp can by coming down from the top of the can.
	8g. Grasp V:  • Patient is sitting with arm on bedside table. • Have patient perform movement with unaffected side first. • Instruct the patient to perform a spherical grasp by grasping a tennis ball The tester may support the patient's arm but may not assist with the hand function required for the retrieval task. The ball may not be stabilized by the therapist or the patient's other hand. To minimize excessive movement, the ball can be placed on an object that reduces rolling. An inverted medium-sized bottle cap placed under the ball to prevent rolling is acceptable. Once the tennis ball is grasped, test this grip against resistance by asking the patient to hold as you attempt to pull the ball out with a slight tug. • Test 3x on the affected side and score best movement.	• *Scoring (*Maximum possible score = 2): • (0) Function cannot be performed • (1) – A tennis ball can be kept in place with a spherical grasp, but not against a slight tug • (2) – Tennis ball is held firmly against a tug
IX. Coordination and speed - Sitting: Finger to nose (5 repetitions in rapid succession)	• Patient positioned in sitting with eyes open. • Starting position is with hand on lap. • Have patient perform movement with unaffected side first. • Check patient's available PROM on the affected side for this motion. • Patient is instructed to "bring your finger from your knee to your nose, as fast as possible." • Use a stopwatch to time how long it takes the patient to do 5 repetitions. • Repeat the same movement with the affected arm. Record the time for both the unaffected and affected sides. Observe for evidence of tremor or dysmetria during the movement. • NOTE: This item attempts to discriminate between basal ganglia, thalamic, or cerebellar strokes in which tremor or dysmetria may result as a direct result of lesion to these areas. The majority of stroke cases are	• *Scoring Tremor* (Maximum possible score = 2): • (0) - Marked tremor • (1) – Slight tremor • (2) – No tremor • *Scoring Dysmetria* (Maximum possible score = 2): • (0)- Pronounced or unsystematic dysmetria • (1) – Slight or systematic dysmetria • (2) – No dysmetria • *Scoring Speed* (Maximum possible score = 2): • (0) – Activity is more than 6 seconds longer than unaffected hand • (1) – (2-5.9) seconds longer

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	in the middle cerebral artery or basilar artery where we expect to observe paralysis that affects movement speed but does not cause tremor or dysmetria. In cases of complete paralysis, observe for any indication of tremor or dysmetria that may be evident in face, voice, arms or legs. If there are no indicators of tremor or dysmetria, then score these items 2 and score speed 0. If active ROM of affected limb is significantly less than that of affected limb, patient should be scored "0" for speed.	than unaffected side • (2) – less than 2 seconds difference

Fugl Meyer Sensory Assessment		
Light Touch	**Procedure:** • For light touch assessment, area of skin to be touched, should be free of clothing and exposed. • The procedure can be tested in the sitting or supine positions. Explain to the patient with their eyes open, "I am going to touch you with this cotton ball and I would like you to tell me if you can feel that you are being touched." Lightly touch patient with cotton ball over the unaffected muscle belly. Ask them, "Can you feel that you are being touched?" This part of the procedure confirms that the patient understands the test. • Explain to the patient, "I am going to ask you to close your eyes. Then I am going to touch you with the cotton ball on your right/left (unaffected) side followed by your right/left (affected) side. When I ask you, tell me if you can feel the touch." Ask the patient to close their eyes. Lightly touch unaffected area with cotton ball and ask, "Do you feel this?" Lightly touch affected area with cotton ball and ask "Do you feel this?" If the patient says they feel the touch on both sides, then repeat the procedure by touching first the unaffected side immediately followed by the affected side and ask the following question. "Does 'this' (unaffected area touch) feel the same as 'this' (affected area touch)?" The intent is to determine if there are differences in the characteristics of the touch between the two sides. • If the tester is not confident that the patient understands this procedure or that the response is inconsistent, the tester may confirm their impression by using the following procedure. With the eyes closed, touch the patient on the affected side and ask them to point to where they were touched with the unaffected side. If the patient does not recognize that they are being touched, the score would be absent. If they recognize the touch but are not accurate on the localization, the score will be impaired. If they recognize the touch and are accurate on the localization, the score will be intact. **Upper Extremity** • Upper arm: Follow above procedure by touching patient over the unaffected and affected biceps muscle belly. • Palmar surface of the hand: Follow above procedure by touching patient over the unaffected and affected palmar surface of the hand.	• *Scoring :* • (0) – Absent - If the patient states that he does not feel the touch on the affected side, the score is absent. • (1) – Impaired - If the patient states that he feels the touch on the affected side and the touch does not feel the same between affected and unaffected sides or the response is delayed or unsure, the score is impaired. • (2) – Intact - If the patient states that he feels the touch on the affected side and the touch feels the same between affected and unaffected sides, the score is intact.

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	Lower Extremity • Thigh: Follow above procedure by touching patient over the unaffected and affected thigh of the leg. • Sole of foot: Follow above procedure by touching patient over the unaffected and affected sole of the foot.	
Proprioception The objective of this test is to determine a consistent response that is accurate and timely. If unsure, the tester can add additional repetitions to determine if a missed response is true sensory loss or an error by the patient due to test length not sensory loss.	**Procedure:** • Proprioception can be tested in the sitting or supine positions for the upper extremity and in supine for the lower extremity. Start with the unaffected limb. Explain to the patient with their eyes open, "I am going to move your arm. This is up; this is down (demonstrate test). I want you to close your eyes and tell me if I am moving you up or down." Use the hand positions described below for each joint movement. • Move the joint through a small range of motion (approximately 10 degrees for the limb joints and 5 degrees for the digit joints of the hand and foot). Move the limb at least 3 times in random directions. If the patient is wrong on any direction, then add several more repetitions to determine if the accuracy is great than 75% (score 2) or 75% or less (score 1). • Start with the most proximal limb joint on the unaffected side. Move to the same joint on the affected side. The intent is to determine if there are differences in the perception of proprioception between the two sides. For example, if the patient identifies the movement stimulus with the same accuracy and responsiveness of the unaffected side then the score would be 2. However, if the patient is accurate but responses are delayed or unsure then the score would be 1. (At this point, you could ask the patient if the movement on this side feels the same as the other side). No perception of joint movement is scored 0. **Upper Extremity** • Shoulder: Therapist supports patient's arm by the medial and lateral epicondyles of the humerus and at the distal ulnar and radius. Have patient look at arm. Move shoulder, saying "This is up. This is down." I am now going to have you close your eyes and I'm going to move your shoulder in either direction. I want you to tell me "up" or "down." Randomly move arm approximately 10 degrees, 4 times (more if needed), keeping track of correct responses. • Elbow: Therapist supports patient's arm by the medial and lateral epicondyles and the distal ulnar and radius. Have patient look at elbow. Move elbow, saying "This is up. This is down." I am now going to have you close	• *Scoring:* • (0) – Absent (no sensation) • (1) – Impaired (inconsistent response or three quarters of answers are correct, but considerable difference in sensation compared with unaffected side) • (2) – Intact (all answers are correct, little or no difference).

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your eyes and I'm going to move your elbow in either direction. I want you to tell me "up" or "down." Randomly move elbow approximately 10 degrees, 4 times (more if needed) keeping track of correct responses.

- Wrist: Therapist supports patient's wrist at the distal ulna and radius and the heads of the 2nd and 5th metacarpal. Have patient look at wrist. Move wrist, saying "This is up. This is down." I am now going to have you close your eyes and I'm going to move your wrist in either direction. I want you to tell me "up" or "down." Randomly move wrist approximately 10 degrees, 4 times (more if needed), keeping track of correct responses.
- Thumb: Therapist supports patient's thumb proximal to the interphalangeal joint and either side of the most distal aspect of the thumb. Have patient look at thumb. Move thumb at interphalangeal joint, saying "This is up. This is down." I am now going to have you close your eyes and I'm going to move your thumb in either direction. I want you to tell me "up" or "down." Randomly move thumb approximately 10 degrees, 4 times (more if needed), keeping track of correct responses.

Lower Extremity

- The hip and knee should be tested in the supine position. The ankle and toe can be tested in the supine or sitting position.
- Hip: Therapist supports patient's leg at the femoral condyles and the medial and lateral malleolus. Have patient look at leg. Move hip, saying "This is up. This is down." I am now going to have you close your eyes and I'm going to move your hip in either direction. I want you to tell me "up" or "down." Randomly move hip approximately 10 degrees, 4 times (more if needed), keeping track of correct responses.
- Knee: Therapist supports patient's leg at the femoral condyles and the medial and lateral malleolus. Have patient look at knee. Move knee, saying "This is up. This is down." I am now going to have you close your eyes and I'm going to move your knee in either direction. I want you to tell me "up" or "down." Randomly move knee approximately 10 degrees, 4 times (more if needed), keeping track of correct responses.
- Ankle: Therapist supports patient's leg at the medial and lateral malleoli and the heads of the 1st and 5th metatarsal. Have patient look at ankle. Move ankle, saying "This is up. This is down." I am now going to

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FUGL-MEYER ASSESSMENT OF PHYSICAL PERFORMANCE

Motor Function Upper Extremity

TEST	ITEM	SCORE		SCORING CRITERIA
		Pre	Post	
I. Reflexes	Biceps			0-No reflex activity can be elicited
	Triceps			2-Reflex activity can be elicited
II. Flexor Synergy	Elevation			0-Cannot be performed at all
	Shoulder retraction			1-Performed partly
	Abduction (at least 90^0)			2-Performed faultlessly
	External rotation			
	Elbow flexion			
	Forearm supination			
III. Extensor Synergy	Shoulder add./int. rot.			0-Cannot be performed at all
	Elbow extension			1-Performed partly
	Forearm pronation			2-Performed faultlessly
IV. Movement combining synergies	Hand to lumbar spine			0-No specific action performed 1-Hand must pass anterior superior iliac spine 2-Performed faultlessly
	Shoulder flexion to 90^0, elbow at 0^0			0-Arm is immediately abducted, or elbow flexes at start of motion 1-Abduction or elbow flexion occurs in later phase of motion 2-Performed faultlessly
	Pronation/supination of forearm with elbow at 90^0 & shoulder at 0^0			0-Correct position of shoulder and elbow cannot be attained, and/or pronation or supination cannot be performed at all 1-Active pronation or supination can be performed even within a limited range of motion, and at the same time the shoulder and elbow are correctly positioned 2-Complete pronation and supination with correct positions at elbow and shoulder
V. Movement out of synergy	Shoulder abduction to 90^0, elbow at 0^0, and forearm pronated			0-Initial elbow flexion occurs, or any deviation from pronated forearm occurs 1-Motion can be performed partly, or, if during motion, elbow is flexed, or forearm cannot be kept in pronation 2-Performed faultlessly
	Shoulder flexion 90-180^0, elbow at 0^0, and forearm in mid-position			0-*Initial* flexion of elbow or shoulder abduction occurs 1-Elbow flexion or shoulder abduction occurs during shoulder flexion 2- Performed faultlessly
	Pronation/supination of forearm, elbow at 0^0 and shoulder between 30-90^0 of flexion			0-Supination and pronation cannot be performed at all, or elbow and shoulder positions cannot be attained 1-Elbow and shoulder properly positioned and pronation and supination performed in a limited range 2-Performed faultlessly
VI. Normal reflex activity	Biceps and/or finger flexors and triceps (This item is only included if the patient achieves a maximum score on all previous items, otherwise score 0)			0-At least 2 of the 3 phasic reflexes are markedly hyperactive 1-One reflex is markedly hyperactive, or at least 2 reflexes are lively 2-No more than one reflex is lively and none are hyperactive

TEST	ITEM	SCORE		SCORING CRITERIA
VII. Wrist	Stability, elbow at 90°, shoulder at 0°			0-Patient cannot dorsiflex wrist to required 15° 1-Dorsiflexion is accomplished, but no resistance is taken 2-Position can be maintained with some (slight) resistance
	Flexion/extension, elbow at 90°, shoulder at 0°			0-Volitional movement does not occur 1-Patient cannot actively move the wrist joint throughout the total ROM 2-Faultless, smooth movement
	Stability, elbow at 0°, shoulder at 30°			0-Patient cannot dorsiflex wrist to required 15° 1-Dorsiflexion is accomplished, but no resistance is taken 2-Position can be maintained with some (slight) resistance
	Flexion/extension, elbow at 0°, shoulder at 30°			0-Volitional movement does not occur 1-Patient cannot actively move the wrist joint throughout the total ROM 2-Faultless, smooth movement
	Circumduction			0-Cannot be performed 1-Jerky motion or incomplete circumduction 2-Complete motion with smoothness
VIII. Hand	Finger mass flexion			0-No flexion occurs 1-Some flexion, but not full motion 2-Complete active flexion (compared with unaffected hand)
	Finger mass extension			0-No extension occurs 1-Patient can release an active mass flexion grasp 2-Full active extension
	Grasp I - MCP joints extended and proximal & distal IP joints are flexed; grasp is tested against resistance			0-Required position cannot be acquired 1-Grasp is weak 2-Grasp can be maintained against relatively great resistance
	Grasp II - Patient is instructed to adduct thumb, with a scrap of paper inter-posed			0-Function cannot be performed 1-Scrap of paper interposed between the thumb and index finger can be kept in place, but not against a slight tug 2-Paper is held firmly against a tug
	Grasp III - Patient opposes thumb pad against the pad of index finger, with a pencil interposed			0-Function cannot be performed 1-Pencil interposed between the thumb and index finger can be kept in place, but not against a slight tug 2-Pencil is held firmly against a tug
	Grasp IV - The patient should grasp a can by oppos-ing the volar surfaces of the 1st and 2nd digits.			0-Function cannot be performed 1-A can interposed between the thumb and index finger can be kept in place, but not against a slight tug 2-Can is held firmly against a tug
	Grasp V - The patient grasps a tennis ball with a spherical grip or is instructed to place his/her fingers in a position with abduction position of the thumb and abduction flexion of the 2nd, 3rd, 4th & 5th fingers			0-Function cannot be performed 1-A tennis ball can be kept in place with a spherical grasp but not against a slight tug 2-Tennis ball is held firmly against a tug
IX.Coordination/ Speed- Finger from knee to nose (5 repetitions in rapid succession)	Tremor			0-Marked tremor 1-Slight tremor 2-No tremor
	Dysmetria			0-Pronounced or unsystematic dysmetria 1-Slight or systematic dysmetria 2-No dysmetria
	Speed			0-Activity is more than 6 seconds longer than unaffected hand 1-(2-5.9) seconds longer than unaffected hand 2-Less than 2 seconds difference
Upper Extremity Total				**Maximum = 66**

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Sensation				
TYPE OF SENSATION	AREA	SCORE		SCORING CRITERIA
		Pre	Post	
I. Light Touch	Upper Arm			0-Anesthesia 1-Hyperesthesia / dysesthesia 2-Normal
	Palm of Hand			
	Thigh			
	Sole of Foot			
II. Proprioception	Shoulder			0-No Sensation 1-75% of answers are correct, but considerable difference in sensation relative to unaffected side 2- All answers are correct, little or no difference
	Elbow			
	Wrist			
	Thumb			
	Hip			
	Knee			
	Ankle			
	Toe			
Total Sensation Score				Maximum = 24
Total Motor and Sensory Score				Maximum = 124
Comments	Pre:			
	Post:			

Pain Visual Analog Scale

Instructions: Adults may have difficulty using a number scale and may be assisted with the use of the six facial expressions suggesting various pain intensities. Ask the subject to choose the face that best describes how they feel. The far left face indicates 'No hurt' and the far right face indicates 'hurts worst'. Document number below the face chosen.

Faces rating scale (FRS)

Mean Spasticity Numerical Rating Scale (NRS) Score

Instructions: Subjects will be asked "On a scale of '0 to 10' please indicate the average level of your spasticity over the last 24 hours" with the anchors: 0 = 'no spasticity' and 10 = 'worst possible spasticity'. 'No spasticity' is explained as the time prior to the onset of their spasticity.

Visual Scale

1	2	3	4	5	6	7	8	9	10
No spasticity				Moderate spasticity					Worst possible spasticity

Appendix D: Subject Post-Treatment Questionnaire

Instructions: To better help the sponsor understand the dynamics of the treatment the following questions have been compiled. The investigator, or designee, will request a response from the subject at the designated time and complete the source document as appropriate. If no response or not applicable check the appropriate box.

Day 0/Visit 2/Post-Treatment

1. How nervous were you during the procedure? On a scale from 1-5, 1 being extremely nervous and 5 being completely relaxed.
2. Prior to your treatment today, how effective or helpful was the information provided beforehand (information pamphlet, informed consent, etc.)? On a scale from 1-5, 1 being not at all effective/helpful to 5 being very effective/helpful.
3. Was the treatment painful? On a scale from 1-5, 1 being not at all painful to 5 being very painful.

Visit 3/Day 7 and Visit 4/Day 30

1. If you had any anticipated observations (AO) from your treatment (i.e., bruising, swelling), how much did they/it impact your daily routine? On a scale from 1-5, 1 being the AO had a very negative impact to 5 being no impact at all.
2. Would you recommend this treatment to a friend or family member? Yes or No.
3. Would you have the treatment again if available? Yes or No.
4. Is there any pain present from the treatment? On a scale from 1-5, 1 being not at all painful to 5 being very painful.