Longitudinal Observation of Myoelectric Upper Limb Orthosis Use Among Veterans With Upper Limb Impairment

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Institutional Review Board

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Louis Stokes Cleveland Department of Veterans Affairs Medical Center Research Plan

Please contact the IRB office if you have any questions at (216) 791-3800 ext. 4658.

☐ **Request for Expedited IRB Review Form attached**

Human Subject Research: Human subject research means research involving interaction or intervention with living human beings or access to identifiable private information of living human beings.

Research Plan: The information requested in the Research Plan is designed to provide the IRB with the necessary information such that it can make the federally required determinations codified at 38 CFR Part 16, 21 CFR Parts 50, 54, & 56, and 45 CFR Part 46

The **Research Plan** is to be written so that the non-scientist/non-medical members of the IRB can understand the research proposed. Define all abbreviations and terms that are not part of common language.

Version Date: This should be updated subsequently with every modification to any part of the Research Plan. Any modification to this document, no matter how minor, must be reviewed and approved by the IRB prior to implementation. The Research Plan will be stamped with the date of IRB approval

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Section 1 – General Information

1. Version Date: 03/11/2019

2. Title of Project: Longitudinal Observation of Myoelectric Upper Limb Orthosis Use among Veterans with Upper Limb Impairment

3. Principal Investigator (PI) *(name & degrees)*: Svetlana Pundik, M.D.

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Section 2 – Research Sites and Sponsor

5. Please list all Research Sites in addition to Louis Stokes Cleveland DVA Medical Center (LSCDVAMC); NA

International studies when the PI is the Lead Investigator list the countries:

a. When study procedures including analysis of identifiable samples or data involving LSCDVAMC enrolled subjects will be conducted at any site other than the LSCDVAMC please provide the following:

Name and contact information for the site:

Describe the plan for communicating protocol amendments, reports of serious adverse events, reports of unanticipated problems involving risks to subjects or others, interim reports, and DSMB reports to external sites.

*** When the LSCDVAMC is considered the coordinating center and the PI the lead investigator on cooperative research or a multi-center trial contact AO/Research Holly.Henry@va.gov.**

6. Sponsor or other Support *(list industry sponsor, government support, etc.)*:

Department of Defense

Section 3 – Research Design and Procedures

7. Definitions- Provide a list of all abbreviations and specialized terms to be used in this document and their definitions:

Abbreviations / Specialized Terms *(Use the Enter key in this column to insert additional abbreviations and their definitions)*	**Definition**
LSCDVAMC	Louis Stokes Cleveland DVA Medical Center
DOD	Department of Defense
TBI	Traumatic Brain Injury
ADL	Activities of Daily Living
TMS	Transcranial Magnetic Stimulation
fMRI	functional Magnetic Resonance Imaging
FES	Functional Electrical Stimulation
ROM	Range of motion
BBT	Box and Blocks Test
CAHAI	Chedoke Arm and Hand Activity Inventory
OPUS-UEFS	Orthotic and Prosthetic Users' Survery upper extremity functional status

Abbreviations / Specialized Terms *(Use the Enter key in this column to insert additional abbreviations and their definitions)*	**Definition**
OPUS-Sat	Orthotic and Prosthetic Users' survey of satisfaction
CHART	Craig Handicap Assessment and Reporting Technique
MMT	Manual muscle testing
EMG	Electromyography
iSP	Ipsilateral Silent Period
MEP-rc	Motor evoked potential recruitment curve
SO	Stimulator Output

8. **Provide a BRIEF SUMMARY of the background for this research.** DO NOT CUT and PASTE paragraphs that do NOT summarize the background.

   - *Include a critical evaluation of existing knowledge, and specifically identify the information gaps that your protocol is intended to fill.*
   - *Refer to appropriate citations in the scientific literature and include your references at the end of this section.*
   - *Include the rationale for conducting the research at the VA.*

   TBI affects 1.7 million people in the general population [1] and is one of the most common neurologic disorders causing disability [2]. The estimated direct and indirect cost for TBI is $76.5 billion in the US and motor deficits are present in 30% of TBI survivors [3]. TBI is also a major challenge in the military and Veteran populations. Since 2000 to June 2015, there have been 36,000 moderate and severe TBI incidents among U.S. military and civilian casualties in the active missions Operation Freedom's Sentinel (OFS, Afghanistan) and Operation Inherent Resolve (OIR, Iraq and Syria) and, as well as operations that have ended, Operation New Dawn (OND, Iraq), Operation Iraqi Freedom (OIF, Iraq), and Operation Enduring Freedom (OEF, Afghanistan) [4]. These numbers represent medical diagnoses of TBI that occurred anywhere US forces are located, including the continental US.

   Research on motor recovery in patients with TBI is scarce compared with other neurologic diseases involving the brain, such as stroke [2]. Specifically, arm and hand paresis occurs in approximately 17% of TBI patients [5] and may limit an individual's ability to undertake activities of daily living (ADL). The recovery time of upper extremity weakness is different according to the mechanism of injury (patients with diffuse brain injury recover more slowly than those with focal injury), severity of initial weakness, and time spent unconscious [2]. Compared to stroke, motor recovery in patients with TBI is characterized by a low incidence, decreased severity, and good prognosis [2]. However, inspite of the difference in trajectory of recovery in early stages after stroke and TBI, there are similarities in the course of disease in chronic stages. In both conditions, motor defcitis are caused by injury to the corticospinal tracts or motor control centers in the brain. Furthermore, there is significant overlap in therapeutic approches for motor restoration [43]. Therefore, therapies tested in stroke population can be successfully applied in treatment for patients with TBI.

   Multi-disciplinary rehabilitation has been shown to improve the experience of living with a long term neurological condition. Although we now understand that brain plasticity plays a

significant role and offers a window of opportunity to promote recovery, we still do not know how to maximize recovery [6]. Activity-based interventions hope to maximize neural plasticity [3], however, optimal doses and schedules of training have not been adequately established. Repetition is one parameter important for experience-dependent neural plasticity. Studies assessing US rehabilitation found that stroke and TBI survivors receive an average of 32–50 repetitions of upper extremity active and passive movement per therapy session, less than the 400-600 repetitions used in animal studies [3]. Although TBI survivors benefit from traditional therapy, it is clear that more is needed to attain full recovery, especially with severely affected individuals. Hence, various technologies to supplement therapy are being investigated, including robotic therapy.

Advances in technology have led to development of a variety of robotic devices for rehabilitation of the impaired upper limb. Robotic therapy can manipulate different practice variables, including intensity, repetition and specificity [3]. Robotic technologies have been shown to efficiently provide intense task oriented therapy within a structured program [7] with comparable results to conventional therapy in improving motor impairment, activity and participation [8-12]. However, only wearable devices allow therapy with the impaired limb to be undertaken anywhere from bedside to home, potentially providing both a therapeutic effect as well as everyday functional assistance. From a therapeutic perspective, it has been proposed that facilitating the ability to practice tasks repetitively forms new neural connections in the brain and reinforces existing connections, resulting in improved ability to move the arm [13]. Functionally, this allows a person with an upper limb impairment to perform ADLs such as feeding, reaching, and lifting with the assistance of an orthosis. When asked which feature of upper limb robotics they liked the most, therapists stated that they liked that most robotic devices allow individuals with upper limb neurological impairment to do more repetitive practice on their own [14]. Further, the therapists felt that by doing more volitional movement on their own (or aided by the device in some cases), individuals with neurological impairment get more intrinsic input; this could potentially lead to greater improvements in motor performance over time [14]. Best practices for integrating robotic devices within an upper limb intervention program can only be derived through widespread collection of data [14].

Krebs and Volpe [6] argued that the basis of all assistive and therapeutic devices should be to determine intent to move followed by that movement actually happening, referred to as "intent-driven rehabilitation". This can be accomplished through myoelectric control wherein the trace electrical activity volitionally generated by contracting muscle in an impaired limb is amplified, processed, and used to control the flow of electricity from a battery to a motor, which operates an orthosis. The patient-directed "intentional" action of the device promotes patient engagement as the orthosis will only reward the patient with movement when they use the correct muscles to complete a task. Previous myoelectric driven, lab-based robotic interventions [15] have been shown to improve Fugl-Meyer motor control scores of the upper extremity [16] and reduce spasticity as assessed by the Modified Ashworth Scale (MAS) [17]. While a few one-off wearable myoelectric upper limb orthoses have been described [18-20], the only commercially available, wearable, myoelectric upper limb orthosis is the MyoPro from our collaborators at Myomo Inc., Cambridge MA (brochure in appendix).

Wearable myoelectric orthotic technology was developed in 2006 at Massachusetts Institute of Technology (MIT) and subsequently commercialized by Myomo Inc. as the e100 System in 2007 [6, 13, 14, 21-23] and updated as the mPower 1000 System in 2012 [24-28]. These initial designs enabled individuals to initiate and control only elbow motion and were used to facilitate therapy [23, 25]: individuals with decreased motor control, coordination and/or

strength use the biofeedback provided by the device to practice activation and inhibition of the biceps and triceps muscles [26]. In 2012, Myomo introduced the MyoPro custom fit powered elbow orthosis designed for home use to facilitate functional tasks and patient independence.

While Myomo reports that they currently have 16 MyoPro users with TBI, initial research publications have focused on persons with stroke [22, 23, 25-29]. The ability of severely hemiplegic stroke survivors to activate a powered elbow orthosis using myoelectric control has been reported [23], along with increased elbow range of motion with device use [29]. The feasibility of combined clinic and home use in persons post-stroke [26] has also been demonstrated. Kim et al. [26] reported that after a combined period of training and at home use of the elbow-only MyoPro device, a statistically significant 3 point change in Fugl-Meyer motor control score was found in the upper extremity of 9 persons post-stroke. This positive change occurred despite study limitations: including limited therapy (chronic post-stroke subjects received training on how to don/doff and use the device but no additional therapy) and low usage rates (had home use of less than one hour per day). Combining device training with motor therapy and encouraging greater at home use may result in further improvements. It is an unfortunate reality of clinical practice where resources are limited that persons with static central nervous system (CNS) injuries such as stroke and TBI do not continue to get therapy despite research suggesting that improvements in motor control can be made even when the conditions are chronic. Ongoing use of myoelectric devices may help to address this gap in patient care.

Goals of device use identified anecdotally by current MyoPro users are similar to those identified by people with impairments using rehabilitation robotics [30]. They include improving overall arm movement for the purpose of performing functional tasks such as feeding and drinking, lifting and carrying objects, operating light switches, cooking, dressing, and using a cell phone. However, the MyoPro has until now been limited to training/assisting a single degree of freedom at the elbow [21, 26] and enhanced device functionality is needed to help accomplish some of the goals patient's desire. Hence, Myomo recently combined the powered elbow with powered grasp in the new MyoPro Motion-G orthosis. Given the goals that patients report, it is anticipated that with the addition of the hand component, which allows a three point chuck grasp, there will be an increase in patient functionality and independence when used to augment therapy. However, the benefits of adding powered grasp in conjunction with elbow function are unknown.

Similar to the use of Functional Electrical Stimulation (FES), use of myoelectric orthoses may be considered to have both a therapeutic and orthotic effect [31]. Therapeutic effect refers to improvements in impairment. Impairment is defined by the International Classification of Functioning, Disability and Health (ICF) framework as "problems in body function and structure" [32]. In our case these include reduced active or passive upper limb range of motion and motor performance that carryover outside of orthosis use. Orthotic effect refers to the functional improvements that are possible while wearing the orthosis that increase activity and participation. Activity and participation are defined by the ICF as "execution of a task or action" and "involvement in life situations", respectively [32]. The basis for a therapeutic benefit of intent-triggered myoelectric devices likely rests in the reinforcement of volitional muscle control [6] and the ability to gradually progress training wherein the electromyography (EMG) signal activation threshold to trigger mechanical motion can be gradually increased. Thus, myoelectric orthoses provide the opportunity to engage and build on small residual volitional muscle activation in individuals with upper limb motor impairment due to TBI.

Wearable myoelectric orthotic technology was developed in 2006 at Massachusetts Institute of Technology (MIT) and subsequently commercialized by Myomo Inc. as the e100 System in 2007[6, 21-23] and updated as the mPower 1000 System in 2012[24-27]. These initial designs enabled individuals to initiate and control only elbow motion and were used to facilitate therapy[23]: individuals with decreased motor control, coordination and/or strength use the biofeedback provided by the device to practice activation and inhibition of the biceps and triceps muscles[25]. In 2012, Myomo introduced the MyoPro custom fit powered elbow orthosis designed for home use to facilitate functional tasks and patient independence. In 2015, the Myomo added a hand/wrist component to the orthotic device enabling grasping function.

Furthermore, brain plasticity as it occurs in the TBI population has not been well studied[33], and many questions remain regarding how activity dependent use of the paretic limb leads to structural and functional reorganization of the brain after TBI[33]. Though a few studies can be found that demonstrate neuroplasticity in response to intervention for chronic TBI[34,35], no studies measuring actual cortical change in response to upper limb intervention were identified. Emerging, non-invasive methods for measurement of neuroplasticity have the capability of detecting changes in response to treatment. These measures include Magnetic Resonance Imaging (MRI) based methods and Transcranial Magnetic Stimulation (TMS) techniques. MRI-based techniques include resting state functional MRI and Diffusion Tensor Imaging and evaluate functional and structural changes in the whole brain. Using TMS, we can assess neurophysiological changes in the motor system and interactions between different brain regions. We will also obtain electromyogram – based measure of corticospinal function called H-reflex.

In summary, upper limb motor deficits in TBI are a problem that can lead to decreased independence in ADLs. In particular, there is a lack of effective ongoing therapies and supportive devices for upper limb impairment. However, a potentially powerful tool has just emerged in the form of the MyoPro Motion-G orthosis but the benefits are as yet unexplored.

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9. Provide a BRIEF SUMMARY of the purpose and scientific rationale for this research. DO NOT CUT and PASTE paragraphs that do NOT summarize the purpose and scientific rationale.

- *State clearly, in terms a non-scientist/non-medical person can comprehend, what you expect to learn from the study and the specific hypothesis (es) to be tested.*
- *The objectives should be stated in such a way that the reader can determine the appropriateness of the study design.*

This project addresses the FY15 Orthotics and Prosthetics Outcomes Research Program (OPORP) Orthotics Outcomes Research Award (OORA) challenge of using patient-centric outcomes to improve understanding of orthotic technology, allowing providers to advance implementation and optimize care for Service members, Veterans and the general population with upper limb impairment. The objective of this observational study is to document longitudinal outcomes in Veterans using the myoelectric upper limb orthosis with powered elbow and grasp using both performance-based and patient-reported outcome measures. Longitudinal observation will allow us to document therapeutic, functional and neuroplastic/neurophysiological effects of augmenting therapy with orthosis use. Hence, the Specific Aims are to (1) evaluate the therapeutic effects of myoelectric upper limb orthosis use, (2) evaluate the functional effects of myoelectric upper limb orthosis use.

10. Describe the means of analyzing the data and evaluating the results.

- *State the anticipated methods to be used for analysis and interpretation of the data.*
- *The methods must compliment the design of the study and the nature of the data which is being collected.*

As a primary analysis of therapeutic benefit, we will use a paired t-test to compare the difference between baseline and final evaluation at the end of the home use period. A similar comparison using the Box and Block Test results will be used as the primary analysis of functional benefit. For these primary analyses, critical alpha will be adjusted using the Bonferroni correction to account for Type 1 error.

Secondary analyses will assess changes over time in each outcome measure as well as correlations between satisfaction and measures of motor impairment and function (both perceived and actual). We anticipate that the therapeutic measures will increase initially before plateauing while functional measures are expected to increase slowly at first with

continued gains across the home use period. We expect that satisfaction will be positively correlated with perceived improvements in function.

We will use single subject analysis to evaluate changes over time for each outcome measure. In order to capture individual effects, baseline to end of home use outcomes data will be plotted, with outcome measure score on the vertical axis and time/transition through conditions (therapy/training to home use) on the horizontal axis. Visual inspection in the form of change in trend (i.e., a systematic variation in the slope of the data points from one phase to the next) will be used.. Dr. Fatone has some experience with single subject analyses as detailed in a paper accepted for publication that evaluated ankle foot orthoses effect on community ambulation outcomes in children with cerebral palsy.

Spearman's correlation will be used to assess the relationship between OPUS satisfaction with device and Fugl-Meyer Assessment of Motor Recovery upper limb subsection score, as well as OPUS satisfaction with device and OPUS functional status.

As a primary analysis of MRI-based measures, we will use a paired comparison between baseline and post training evaluation (prior to home use period). For the TMS-based measures, we will compare data between baseline, at week 9, after the end of the therapy and after the end of the home-use phase. We will evaluate changes over time for each outcome measure.

11. Provide a BRIEF DESCRIPTION of how the estimated number of study subjects needed for this research was determined

- *If this is a quantitative study provide the method of determining sample size estimates.*
- *If multiple studies are planned provide a power analysis or justification for each one.*

To determine our sample size, we utilized data obtained from a previous pilot study [26]. In that study of 9 patients with stroke, a change in the Fugl-Meyer Assessment of Motor Recovery upper limb subsection score of 3.2 ± 2.91 was reported to be statistically significant [26]. This data was used to calculate effect size (d = 1.107) because we do not have pilot data for TBI. Using the G*Power computer program [53] this effect size was used to estimate sample size. For a 1-tailed matched pairs t-test (comparing baseline to final evaluation at end of home use period) we would need a total sample size of 11 to detect an effect size of 1.107 with a critical alpha of 0.05 and power of 0.95. In order to account for possible attrition in subject numbers we will recruit 20 persons with TBI or stroke. Furthermore, we estimated that we would need to screen 70 subjects to recruit 20.

12. The research involves the following procedures conducted by and for what purpose:

PROCEDURE	PERFORMED BY:		PROCEDURE IS:	
	Research Staff	LSCDVAMC Clinical or Support Staff	Standard of Care*	For Research Purposes Only**
Audiotaping / Videotaping *Attach VA Form 10-3203* **REQUIRED ONLY FOR IN-PATIENT AND OUT-**	☒	☐	☐	☒

PROCEDURE	PERFORMED BY:		PROCEDURE IS:	
	Research Staff	LSCDVAMC Clinical or Support Staff	Standard of Care*	For Research Purposes Only**
PATIENT SUBJECTS				
Biopsy	☐	☐	☐	☐
Blood collection	☐	☐	☐	☐
Chart review – prospective	☒	☐	☐	☒
Chart review – retrospective	☐	☐	☐	☐
Review of existing data (ex: registry, Database , etc.)	☐	☐	☐	☐
X-ray or Ionizing radiation exposure	☐	☐	☐	☐
Clinical Tests	☐	☐	☐	☐
Device implantation	☐	☐	☐	☐
Drug administration	☐	☐	☐	☐
EEG, EKG , ECG…etc	☐	☐	☐	☐
Gene therapy, Genetic analysis	☐	☐	☐	☐
Pregnancy/Breastfeeding Screening	☒	☐	☐	☒
Interview, Questionnaire, Diary, Survey *(please attach)*	☐	☐	☐	☐
Stool collection, Urine collection, or any Non-surgical Specimen collection	☐	☐	☐	☐
Surgical procedure or Specimen removal during surgery	☐	☐	☐	☐
Tissue banking *(complete Section 12)*	☐	☐	☐	☐
Use of pre-existing tissues/specimens	☐	☐	☐	☐
Other *(list)*: fitting and treatment with MyoPro; upper limb motor learning therapy; H reflex (EMG), MRI, TMS	☒	☒	☐	☒

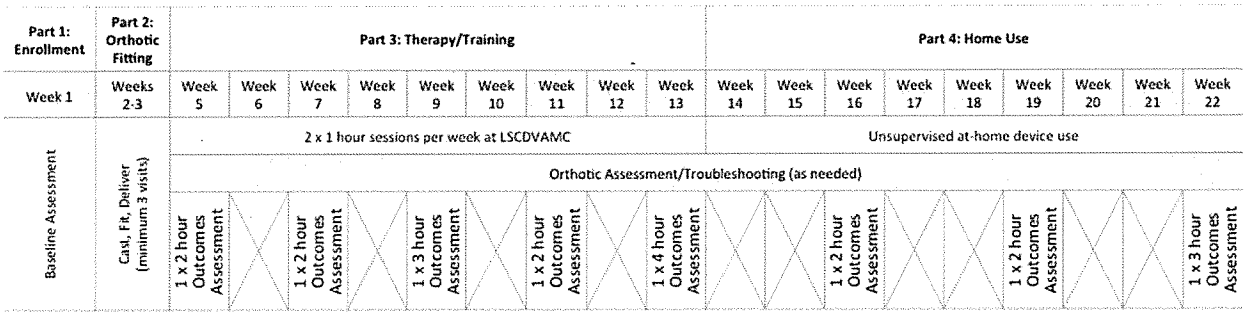
- **Standard of care procedures are procedures performed in the course of normal medical care.*
- ***Research Procedures are performed for the purposes of this research alone.*

13. Please describe the research design and all study related procedures.

- *Describe **<u>ALL PROCEDURES ASSOCIATED WITH THIS RESEARCH</u>**. This includes standard of care and research procedures.*

- *For complex studies please include diagrams and tables. Be sure to describe when each procedure will be performed. Be sure to provide information for* ***each cohort, including normal controls****).*

The study requires 31 visits over 22 weeks and is divided into four parts: enrollment, orthotic fitting, therapy/training, and home use. See below table and description for details:



Study Part 1 - Enrollment: The LSCDVAMC Institutional Review Board (IRB) requires consent both for screening and enrollment. Hence, after they provide screening consent, potential subjects will be screened to ensure that they meet the above criteria and are eligible to participate in the study. If eligibility criteria are met and the subjects provide enrollment consent, they will be enrolled in the study. The subjects will be evaluated and characterized at baseline and assessed at 2- or 3-week intervals for 18 weeks after orthosis delivery. Testing and outcome data collection will be done according to the schedule in Table 2 and in the section OUTCOME MEASURES

Study Part 2 – Orthotic Fitting: Myomo will provide three MyoPro Motion-G devices to be used through-out the study and the fit of each device will be customized for each subject. These devices will be used on a rotating basis during the study period which means that at the end of the participation in the study, a subject will return the MyoPro-G device to PI. A Certified Orthotist from either the Cleveland VA or from Myomo will custom fit all orthoses individually to each subject for optimum performance. This process will require up to three visits to cast, trial fit and deliver the orthosis.

During the fitting process, first a plaster mold of the subject's arm will be taken. This mold is used for custom orthosis construction and fabrication typically takes 2 weeks. Once the orthosis has been constructed, the subject will be brought back for a fitting. During this fitting, the device will be calibrated to the subject's individual muscle signal profile and minor adjustments to the orthosis can be made to optimize comfort.

Subjects will receive both powered elbow and grasp at the same time. Throughout the duration of the study, the study orthotist will be available once a week to check the fit of the device and troubleshoot any device issues as needed.

The MyoPro is a relatively new, commercially-available custom fabricated upper limb orthosis that is individually fabricated for the patient over a positive model of the patient requiring education, training, and experience to custom-fabricate. It has been cleared by the Food and Drug Administration (FDA) for home use without direct supervision of a therapist [26]. The

MyoPro Motion G features include a lightweight elbow orthosis with a surface electromyography (sEMG) sensor, a lightweight hand orthosis with a sEMG sensor, a "motion W" manually set multi-articulating wrist and a rechargeable battery. MyoPro's sEMG controlled software continuously monitors and senses, but does not stimulate, the affected muscles. The system then filters and processes data, which is sent to a motor to enable the desired motion. The process is similar to the way power steering helps a driver maneuver a car. Based on the subject's abilities, the system parameters are adjusted by the therapist or orthotist. The power assist only applies an amount of force proportional to what users exert naturally; this encourages them to apply and maintain all the strength and control they have to achieve a range of motion.

Study Part 3 –Therapy/Training: In addition to standard-of-care motor learning based therapy [33], we will follow the PERL ("Push Eat Reach Lift") Program recommended by Myomo, which consists of a 9 week, 18 session training plan. However, consistent with recommendations that best practices for the use of robotic devices be flexible, allowing therapists to tailor the therapy protocol and use of devices to an individual's level of motor impairment and rehabilitation goals [14], clinical judgment and subject progress will be used to either increase or decrease the number of therapy sessions and to determine the type of activities that are performed during training and therapy. Similar to Kim et al. [26], the sessions will be 1 hour typically 2 times a week but combine both therapy and training. Each week, there will be one session as needed that will combine therapy/training and orthotic assessment to ensure continued optimal fit and function of the device. Every second week, there will be one session that will combine therapy/training and outcomes evaluation.
The basic steps of the training program include:
1. Start in BICEP mode and HAND CLOSE mode. While seated, teach users to flex and extend the elbow while ignoring the hand, then switch and have them open and close the hand and ignore the elbow. Progress to sequential movements, e.g. close hand, bend elbow, open hand, relax elbow. Progress to simultaneous movements, e.g. flex elbow with closed hand; flex elbow with open hand; extend elbow with open hand; extend elbow with closed hand. This can all be repeated with the subject standing. This should be done two times a day for 10-15 minute sessions. Once these are mastered the subject can move to step 2.
2. Have the subject engage in task specific practice in BICEP and HAND OPEN modes. Tasks may include stacking cups or other items, grasping and moving items (e.g. cotton balls, items from purse or bag), hand to mouth tasks (e.g. bring napkin up to mouth, drink from cup or bottle), and finger extenders may be used to grasp paper, playing cards, take paper money out of a wallet. These activities should be attempted two times a day for five minutes each and progress to one time a day for 10 minutes each category. Once these are mastered the subject can move to step 3.
3. Have the subject engage in functional training. Identify the subject's goals: ADLs, instrumental ADLs, work or school related tasks, safety during ambulation and use of walking aide. Facilitate the subject's progression towards these goals: consider environmental set-up, utensils (including use of finger extenders) if needed.
4. Subject can progress to TRICEP and HAND OPEN modes when they demonstrate consistent Tricep and Forearm Extensor EMG signals, ability to relax forearm EMG and operate grasp in ALL wrist positions (flexed, neutral and extended), and proficiency with BICEP and HAND CLOSE modes, including simultaneous control. This should occur at approximately 1 month.

5. Subject can progress to DUAL mode when they demonstrate proficiency with BICEP/TRICEP and CLOSE/OPEN modes and they do not demonstrate significant co-contractions. This should occur at approximately 2 months. Subject may progress through the modes faster at the elbow, however it may be easier to use BICEP mode with HAND CLOSE mode, TRICEP mode with HAND OPEN mode and DUAL modes together.

Based on subject presentation, the above steps can also begin in TRICEP mode and progress from there. The above program requires at-home daily exercises by the subject, which will be prescribed by the therapist. Subjects will be deemed independent with device use once they or a caregiver are able to correctly demonstrate all the technical items listed on the device competency checklist (Table 1).

Table 1 MyoPro Motion-G Competency Checklist

Is the subject/caregiver able to demonstrate the following abilities appropriately regarding using the device:

- Apply and remove the pads
- Place straps on the device
- Secure orthosis on the arm
- Attain proper sensor placement on the bicep
- Attain proper sensor placement on the tricep
- Attain proper sensor placement on the forearm flexors
- Attain proper sensor placement on the forearm extensors
- Demonstrate proficiency manipulating the pronation/supination ring and the wrist hinge to position the distal extremity
- Turn the control unit on
- Choose BICEP/TRICEP/OPEN/CLOSE/DUAL modes
- Calibrate the device
- Change the low, medium and high settings
- Change between modes
- Remove orthosis from arm
- Use proper storage techniques
- Understands all safety precautions associated with operating the device

Is the subject/caregiver able to demonstrate the following abilities appropriately regarding the home treatment program:

- Safely and correctly performs all the given tasks
- Adjust the device to the correct settings for each task
- Independently performed the home treatment program at least one time
- Understands all safety precautions associated with device usage during activities

Study Part 4 – Home Use: Having demonstrated the above competencies, subjects will start a 9-week program practicing upper limb activities at home. Subjects will have reassessments in the clinic as needed to trouble-shoot any technical issues, monitor adverse events, and/or upgrade their home program. Every third week, there will be one session at the clinic for outcomes evaluation. The subject will record daily at home use of the device in a paper calendar log.

OUTCOME MEASURES for each AIM:

Aim 1: Evaluate therapeutic and neuroplastic effects of myoelectric upper limb orthosis

When assessing robot- or orthosis-assisted functional tasks, no one measure is perfectly applicable [34], hence we will use a combination of outcome measures. To evaluate the therapeutic effect of the myoelectric upper limb orthosis with powered elbow and grasp, outcome measures will include range of motion, MAS, the Wrist Position Sense Test, monofilament test of sensation, and the Fugl-Meyer Assessment of Motor Recovery upper limb subsection. These measures will be performed without the orthosis to assess whether therapy/training combined with device usage result in carry-over effects at the body structure level over time. See Table 2 for overview of schedule of assessments.

Passive range of motion is the amount of motion of a joint measured in degrees by a clinician with a goniometer during a passive movement. Passive range of motion of the elbow and fingers will be assessed.

The MAS will be used to assess muscle tone and spasticity [17]. Using a 5 point scale, the clinician evaluates resistance to passive movement about a joint with varying degrees of velocity. The MAS has been widely used to quantify muscle tone following brain injury. Interrater reliability of MAS for arm assessments has been reported as kappa=0.92 or percent of agreement = 97.4% [35].

The Wrist Position Sense Test is a somatosensory test that measures a person's ability to recreate a wrist position without vision; muscle, joint and tendon receptors that guide the movement using a purpose built proprioception apparatus [36]. For example, for measuring proprioception at the wrist joint, the hand is placed in a splint with the thumb up and the forearm is secured in a neutral position in a splint on the table in front of the proprioception apparatus which is housed in the lab of our Cleveland VA site-PI (the Brain Plasticity and NeuroRecovery Research Lab of the Cleveland FES Center). The examiner tests discrimination accuracy at 20 different predetermined wrist positions. With vision occluded by a curtain, subjects are asked to estimate wrist position using a response pointer. The score is calculated as an average of absolute error between actual and response positions in degrees. This test has test-retest reliability of about 0.9 in stroke patients [36]. The same test can also be used to assess elbow and wrist proprioception.

Semmes-Weinstein Monofilaments provide a non-invasive evaluation of cutaneous sensation levels throughout the body. Testing will be done in a quiet area of Dr. Pundik's lab to help the subject fully attend to the testing procedure. The subject's upper limb will be rested on a stable, padded surface and their vision occluded by using a shield or by having the subject look away. The testing procedure will be explained to the subject and the subject instructed to respond when the stimulus is felt by saying "yes". Testing will proceed from distal to proximal and from small to large monofilaments. We will test different areas of the arm innervated by different nerves. For example, we will test the palmar surface of the index finger and thumb to evaluate the median nerve; the little finger and hypothenar eminence to evaluate the ulnar nerve; and the dorsum of the hand to evaluate the radial nerve. The filament will be pressed at a 90° angle against the skin until it bows, held in place for 1.5 seconds, and then removed. This is repeated up to three times. A consistent localization of the smallest filament is recorded as a score at a given site. For screening, if the subject responds to the stimulus in all sites, normal cutaneous sensation will be recorded and the examination considered complete. If the subject does not respond to the stimulus, the next largest monofilament will be used and the process repeated. For scoring as an outcome measure, we will add up the score based on the smallest monofilament size localized. In other words, monofilament score is a sum of the smallest filament sizes

localized at each testing site. For example, when testing 5 sites the smallest or the best screen is equal to 1.65 x 5.
The Fugl-Meyer Assessment of Motor Recovery upper limb subsection is one of the most widely used quantitative measures of motor impairment [37]. The upper limb subsection includes 33 items measuring movement, coordination, and reflex action about the shoulder, elbow, forearm, and wrist with a three-point scale from zero (unable to perform) to two (able to perform) used to score each item for a total score of 66. It has good intrarater (ICC = 0.99) and interrater (ICC = 0.96) reliability for use with stroke patients [38] and TBI patients (ICC = 0.97) [39].

Neuroplasticity measures.

H Reflex. Stimulation of a peripheral nerve (median nerve in our study) will evoke a compound muscle potential (M wave in the flexor carpi radialis muscle) and an H wave (H-reflex;[63]). We will evaluate and compare the H/M ratio at specific points along the course of the study. A higher H/M amplitude ratio is associated with enhanced spinal excitability and a mitigation of spasticity is correlated with a reduction of H/M ratio [64].

MRI and TMS neuroplasticity measures (described below) will be collected for study participant who meet TMS and MRI inclusion/exclusion safety criteria (Item#30). If subjects do not meet the TMS and MRI inclusion/exclusion safety criteria, these measures will not be collected.

MRI. In order to identify the changes in neuronal networks following device use, we will obtain an MRI before and after treatment. MRI will be obtained in the MRI suite of the Cleveland VA by a trained technologist using manufacture pre-programmed protocols. Changes in MRI-based measures will be analyzed by our laboratory to determine if any structural or functional changes have occurred as a result of device use. MRI will be performed during a separate visit from the rest of the outcome measures data collection.

Single-pulse TMS-induced measures.
Motor Evoked Potential recruitment curve (MEP-rc). We will use a Magstim 2002 transcranial magnetic stimulator (Magstim Company Ltd., Wales, UK). While patients are seated, a TMS coil will be placed tangential to the skull in the anterior posterior direction. The location of targets for stimulation will be guided using frameless stereotactic navigation (Brainsight2, Rogue Research, Inc., Montreal, QC). Surface electromyographic (EMG) electrodes will be placed over the bellies and tendons of the contralateral first dorsal interosseous muscle, extensor carpi radialis and flexor carpi radialis. EMG will record Motor Evoked Potentials (MEPs) in response to TMS of primary motor area, M1. The optimal site for each muscle in the contralateral M1 will be identified as the 'hotspot'[59]. The hotspot will be defined as the site that evokes 50μV MEPs, using the lowest TMS intensity (resting motor threshold, rMT), in the contralateral muscle reliably in 6 out of 10 trials. Active motor threshold (aMT) will be determined as a lowest stimulator output to produce 200μV MEP in 6 out of 10 trials while the subject activates a targeted muscle at 20% of maximum voluntary contraction, monitored with visual feedback of the EMG recording.
After determining the 'hot spot' location, we will obtain MEP-rc. MEP-rc will be generated first dorsal interosseous muscle, extensor carpi radialis and flexor carpi radialis of the paretic and non-paretic upper limb. Resting and active MEPs will be recorded with EMG skin adhesive

electrodes placed over muscles' bellies. Single-pulse TMS will be applied at the hotspot. The evoked MEPs will be recorded at stimulator intensities between 50% and 150% of. The mean MEP peak-to-peak amplitude is plotted against SO creating the recruitment curve MEP-rc. The area under the MEP-rc curve is the cortical excitability outcome measure[60]. The range of stimuli recorded will be determined for each subject separately, and held constant at each recording session to compensate for the more variable nature of the stroke-affected MEP response[61]. The EMG electrodes positions will also be replicated between sessions. The area under MEP-rc captures the cortical excitability changes while controlling for TMS and EMG recording variables.

Ipsilateral silent period (iSP). In order to evaluate transcallosal inhibition, we will analyze the iSP in the flexor dorsal interosseous muscle. An iSP in the affected limb is elicited by stimulating the M1 hotspot of the unaffected muscle while the paretic muscle is active. The reduction in muscle activity due to the ipsilateral stimulation is analyzed. Suprathreshold TMS is applied at 150% of the unaffected muscle's rMT (or at 100% SO, in the event of high rMT) while the subject activates their affected muscle at 20% of their maximum voluntary contraction level, monitored with visual feedback of the EMG recording. The EMG data from 10 stimuli are recorded, averaged and rectified. The iSP onset and offset are determined by analyzing the averaged, rectified data relative to a threshold determined by the pre-stimulus mean EMG value. iSP onset is defined as when the EMG falls below the threshold, and iSP offset is when the EMG returns to within 25% of the threshold for at least 50 ms[62]. We will compute both duration and the amount of EMG suppression during iSP.

Aim 2: Evaluate functional effects of myoelectric upper limb orthosis

To evaluate the functional effect of the myoelectric upper limb orthosis with powered elbow and grasp, outcome measures will include performance-based measures such as the Box and Block Test (BBT) and the Chedoke Arm and Hand Activity Inventory (CAHAI). The performance-based measures will be performed both with and without the orthosis to assess whether device usage improves function at the level of activity over time. During the period of home use, patient reported measures such as the Orthotic and Prosthetic Users' Survey (OPUS) upper extremity functional status (OPUS-UEFS) and satisfaction with device (OPUS-Sat) as well as the Revised Craig Handicap Assessment and Reporting Technique (CHART) to assess life-role participation and level of community integration will be added. The patient-reported measures will be completed to assess whether device usage at home improves perception of function and participation over time. See Table 2 for overview of schedule of assessments.

The Box and Block Test (BBT) is a standardized assessment of unilateral gross manual dexterity. Individuals are seated at a table, facing a rectangular box that is divided into two square compartments of equal dimension by means of a partition. One hundred and fifty colored, wooden 2.5cm blocks are placed in one of the compartments. The individual is instructed to move as many blocks as possible, one at a time, from one compartment to the other for a period of one minute. Standardized dimensions for the test materials and procedures for test administration and scoring have been described [40]. To administer the test, the examiner is seated opposite the individual in order to observe test performance. The BBT is scored by counting the number of blocks carried over the partition during the one-minute trial period. Subject's hand must cross over the partition in order for a point to be given, and blocks that drop

or bounce out of the second compartment onto the floor are still rewarded with a point. Multiple blocks carried over at the same time count as a single point. Higher scores on this test indicate better gross manual dexterity. Psychometric properties have tested well in numerous populations including TBI [39].

Performance of ADLs will be assessed using the Chedoke Arm and Hand Activity Inventory (CAHAI), which is suitable for populations with upper limb paresis [41]. This test consists of 13 functional tasks (open jar of coffee, call 911, draw a line with a ruler, put toothpaste on toothbrush, cut medium consistency putty, pour a glass of water, wring out washcloth, clean pair of eyeglasses, zip up a zipper, do up five buttons, dry back with towel, place container on table, carry bag upstairs). It is not designed to measure the subject's ability to complete the task using only their unaffected hand, but rather to encourage bilateral function.

Patient's perception of function and satisfaction with the myoelectric arm orthosis will be assessed using the OPUS. The OPUS is a set of self-report instruments that assess functional status, quality of life, and satisfaction with device and service in persons who use orthoses and prostheses [42]. The original OPUS-UEFS was composed of 14 bilateral and 9 unilateral activities. Examples include drinking from a paper cup, buttoning a shirt, and tying shoelaces. The five-point rating scale ranges from "cannot perform" to "very easy." Jarl et al. [43] evaluated six additional items in a sample of 134 upper limb orthosis and prosthesis users. The new items included taking bank notes from a wallet, twisting a lid off a small bottle, and sharpening a pencil. One original item misfit and one new item demonstrated a high residual correlation. The resulting 27-item scale showed excellent reliability for orthosis users.

For the OPUS satisfaction with device 12-item set [42], the easiest items to endorse are "the weight of my prosthesis (or orthosis) is manageable" and "my prosthesis (or orthosis) is durable." Items of average difficulty were "it is easy to put on my prosthesis (or orthosis)" and "my clothes are free of wear and tear from my prosthesis (or orthosis)." The most difficult items to endorse are "my skin is free of abrasions and irritations" and "my prosthesis (or orthosis) is pain free to wear." A recent literature review suggested that the OPUS is the only measure available to assess satisfaction with devices in orthosis users [44]. The OPUS uses Likert scale responses for each item of each module. However, these responses can be converted into a single score for each module for analysis[45-48].

The Revised Craig Handicap Assessment and Reporting Technique (CHART) is a questionnaire designed to identify the extent of life-role participation and level of community integration [49]. It is a 32-question instrument with life role domains pertaining to cognition, physical and financial independence, mobility, occupation, and social integration. The CHART is a stable and reliable measure for a variety of diseases and impairments and has been tested in SCI, TBI, multiple sclerosis and stroke [50,51,52].

Clinical assessments will be performed by PI, therapist and study staff.

Table 2 Schedule of Assessments

	Part 1: Enrollment		**Part 3: Therapy/Training**					**Part 4: Home Use**		
Assessment	**Screen**	**Week 1 (Baseline)**	**Wk 5**	**Wk 7**	**Wk 9**	**Wk 11**	**Wk 13**	**Wk 16**	**Wk 19**	**Wk 22**
X assessed without orthosis; O assessed with orthosis										
Passive ROM	X	X	X	X	X	X	X	X	X	X
Active shoulder ROM	X		X	X	X	X	X	X	X	X

MMT	X		X				X	X	X	X
EMG signal	X		X				X	X	X	X
MAS	X	X	X	X	X	X	X	X	X	X
Read English	X									
Shoulder subluxation, pain, dislocation	X	Ongoing monitoring for safety. Development of shoulder pain or additional subluxation would result in subject withdrawal from the study if modifications such as adding a shoulder harness was insufficient to overcome shoulder stability issues.								
Skin rash/open wounds	X									
Monofilament	X	X	X		X		X	X		X
Performance-Based Measures										
Wrist Position Sense Test		X	X		X		X	X		X
Fugl-Meyer		X	XO	XO	XO		XO	XO	XO	XO
BBT		X	XO		XO		XO	XO	XO	XO
CAHAI		X	XO		XO		XO	XO	XO	XO
Patient-Reported Measures										
OPUS-UEFS		X					X			X
OPUS-Sat		X					X			X
CHART		X					X			X
MRI		X					X			
TMS (MEP-rc/iSP		X			X		X			X
H-reflex		X			X		X			X

14. Will the research involve the following?

☐ **N/A** **Chart/Data Review**

Placebo Group ☒ **No** ☐ **Yes** *(describe)*:

Other Control Group ☒ **No** ☐ **Yes** *(describe)*:

Randomization ☒ **No** ☐ **Yes** *(describe)*:

Deception ☒ **No** ☐ **Yes** *(describe)*:

15. Does the research involve the use and/or disclosure of Individually Identifiable Health Information in any form or medium?

☐ **No** ☒ **Yes** **If yes, complete the required HIPAA Waiver/Authorization forms.**

16. Does the study include the administration of a study agent that does not require FDA approval and does not require an IND (e.g. vitamins, food supplements, isotope tracers, alternative medicines, etc.)?

☒ **No** ☐ **Yes** *-provide a detailed description of the procedures used to assure patient safety:*

17. Will radioactive material be administered or will subjects be exposed to ionizing radiation?

- *Ex. Radiographic equipment, fluoroscopic equipment, and CT scanners, etc.*

☒ **No** ☐ **Yes**

18. In your judgment, could the objectives of the research be met in a way that presents less risk to subjects?

☒ **No** ☐ **Yes** *please explain*:

Section 4 – Subject Selection, Recruitment, and Vulnerable Populations

19. Anticipated duration of entire study reported in years: 6 years **or** till July 2022

20. Estimated number of subjects to be studied at the LSCDVAMC or charts/records to be reviewed.

- *Provide answers for **each cohort** including normal controls; (patients, family members, treating physicians,)*:

70 TBI or stroke subjects to enroll 20

21. Estimated number of subjects to be studied or charts/records to be reviewed at all sites

- *Provide answers for **each cohort** including normal controls; (patients, family members, treating physicians,)*

N/A SINGLE SITE ☒

22. Duration of individual subject participation

*Provide answers for **each cohort** including normal controls; (patients, family members, treating physicians,).* 31 study related visits (over approximately 22 weeks)

Chart/record review ☐ **N/A**

23. Age range of subjects

- *provide answers for **each cohort**, including normal controls*:

☒ **Adults 18 years or greater**

☐ **Specific age range** (list age range):

☐ **Children –waiver from VACO:** ☐ **attached** ☐ **pending- *provide submission date:***

***Contact AO/Research holly.henry@va.gov for guidance..*

24. Which of the following will be recruited or reviewed for this study *(check all that apply)*?

☐ **Veteran Inpatients**
☒ **Veteran Outpatients**
☒ **Men**
☒ **Women**

☐ **Veteran Families**

☐ ***Normal volunteers**

☒ ***Non-Veterans; Provide justification** If we are unable to recruit sufficient Veterans within our LSCDVAMC population that meet the study selection criteria and allow us to keep pace with the target enrollment rate, we will recruit subjects from the non-VA community. Our Cleveland VA site-PI, has experience recruiting non-VA research subjects in the Cleveland area. Specifically, should we have challenges recruiting Veterans, we will recruit from civilians with TBI with the help of Physical Medicine and Rehabilitation physicians at MetroHealth Medical Center, a local trauma center (See Letter of Support). In 2014, MetroHealth Medical Center had 166 inpatient TBI admissions: 101 had TBI as their sole disabling injury, 58 also had multiple fractures, and 5 also had spinal cord injuries. These statistics are typical of any given year at Metro Hospital. About half of the above patients will be followed in the outpatient clinic, some for a short time, and others chronically. About 250 chronic patients are seen sporadically about 1-4 times per year depending on their needs. A small fraction of this population have upper extremity weakness.

*According to VHA Handbook 1605.04 Notice of Privacy Practices VHA must provide a copy of its VHA Notice of Privacy Practices to all non-Veteran patients (e.g., active duty personnel or those seeking care in humanitarian circumstances) receiving care or treatment at a VHA health care facility or non-Veteran research subjects enrolled in an approved VHA research study with clinical trials. VA Form 10-0483 Acknowledgement of the Notice of Privacy Practices should be signed by the non-Veteran research subject at the time of consent and given a copy of the Notice of Privacy Practices. Once the Acknowledgement Form is signed please send a copy to the Privacy Officer. If additional information is needed please contact your Facility Privacy Officers Joseph Picklo or Tomica Jefferson joseph.picklo@va.gov / phone 8214102 tomica.jefferson@va.gov / phone 8214101.

25. Which vulnerable population(s) will be TARGETED for recruitment in this study:

- *Indicate only those populations that are specifically targeted for the research described in this document.*
- ***It is not necessary to check any box if, for example, your study will include a full range of subjects, some of whom may be elderly or subjects who might incidentally be employees.***

☐ **N/A Chart Review** (*proceed to Item 30*)

☒ **NONE** (*proceed to Item 26*)

☐ **Medical students, house staff, or Employees of the VAMC or Case**

☐ **Pregnant Women OR Women who are Breastfeeding, Human Fetuses, or Neonates**

☐ **Children – Complete Section 14 "Children as Research Subjects"**

☐ **Prisoners (The LSCDVAMC does not conduct research involving prisoners)**

☐ **Targeting Persons over Age 65**

☐ **Persons with Acute/Severe Mental/Physical Disabilities** *(describe)*:

☐ **Persons with Cognitive, Social, Economic, or Educational Disadvantages** *(describe)*:

☐ **Others** *(describe)*:

a. Provide the Scientific and Ethical reasons for Targeting these vulnerable populations in the research:

b. What additional safeguards or provisions will be used to protect the rights and welfare of the identified targeted vulnerable subjects?

☐ **Surrogate consent**

☐ **Subject assent**

☐ **Use of a consent or Medical monitor**

☐ **Use of a waiting period**

☐ **A patient advocate will participate in the informed consent process**

☐ **Key elements of informed consent will be presented orally**

☐ **No supervisor or rater will be involved in obtaining consent**

☐ **Other - Describe Additional safeguards you plan to use**

c. Describe the procedures used to ensure that the subject's legally authorized representative is well informed regarding his/her role and obligation to protect persons with impaired decision making capacity:

26. Procedures for Recruiting Subjects -check all that apply and attach all recruitment materials:

☐ **Not Applicable**

☒ **Materials; Recruitment Letter, Posting on Bulletin Board, Brochure, Flyer, Post card, etc.**

☐ **Media; Internet Ads, Press Releases, Newspaper, Radio**

☒ **Investigator's Patient Population**

☒ **Physician Referral**

☐ **Letters to Physicians/Clinicians**

☒ **Other** *(describe)*: registry of study on clinicaltrials.gov or equivalent public study registry

27. Will VA computer systems be used to identify potential subjects?

- *e.g. VISTA, CPRS, Pharmacy Databases, other clinical databases, etc,*

☐ **No** ☒ **Yes- Describe how the computer will be used to identify patients. List all systems used and all information to be collected:** We will review medical records on CPRS during the screening process that pertains to medical history and medications.

28. Will subjects be identified and/or recruited in clinics and/or inpatient wards at the LSDCVAMC?

☐ No ☒ Yes- **explicitly describe your process for identifying and/or recruiting these patients:** *(address all cohorts):* a flier will be posted in clinical areas and information about the study will be disseminated by word of mouth to clinicians working with the study population.

29. In addition to the consent form will any other materials be given to the subject?

☐ **N/A Chart/data review**

☐ **No** ☒ **Yes- check all that apply and submit for IRB review:**

☐ **Letter**

☐ **Information Sheets**

☒ **Questionnaire, Survey, Diary**

☒ **Other** *(flyer, brochure, describe):* Recruitment flyers

30. Please list by bullet point inclusion/exclusion criteria for the study.

- *Entry criteria should be as detailed as necessary to define the subject population(s) under study and reduce confounding design. Include precise criteria for age, gender, and other relevant factors.*

- *List specific exclusion criteria which could interfere with the study design or place a subject at risk during the study.*

- *Provide answers for* ***each cohort****, including normal controls*

INCLUSION CRITERIA.

- Over 18 years of age
- Minimum 6 months since injury or stroke
- Full passive range of motion at the elbow, forearm, wrist, and hand [26]
- Active shoulder flexion of at least 30 degrees and active shoulder abduction of at least 20 degrees
- Minimum of 1/5 on manual muscle test of elbow flexion and extension (biceps and triceps) [26] and forearm flexors and extensors
- Ability to generate volitional, consistent, and detectable EMG signals from the upper arm and forearm sensor sites with wrist in neutral or flexed positions as detected by the MyoPro Motion-G software
- MAS score ≤ 3 for the biceps, triceps, supinators and pronators of the impaired arm
- Able to read and comprehend the English language
-
- Demonstrate ability to follow two-stage command
- Cognitive abilities sufficient to perform testing and training protocols
- Able to tolerate functional tasks for 60 minutes without excessive fatigue [26]
- Medically and psychologically stable [26]
- At home support from a family member or care giver if needed [26]
-

EXCLUSION CRITERIA:

- Spasticity of both the flexors and extensors (defined as > 3 on MAS for both) and also the shoulder internal rotators [26]

- Shoulder subluxation, pain or dislocation
- Shoulder passive range of motion < 45 degrees in flexion and abduction
- Fixed upper limb contractures on the impaired arm and hand
- Unable to safely support the weight of their arm plus 4 lbs (1.82 kg) (the weight of the device) without pain
- Unable to safely bear a torque of 14 Newton Meters (Nm) or less on their elbow
- Less than 12 weeks since botulinum toxin injection in the impaired arm [26]
- New therapies/medications planned during study period
- Skin rash or open wound on impaired arm [26]
- Absent sensation (light touch or pain) on impaired arm
- Involuntary movements of the impaired arm [26]
- Pain or hypersensitivity in the impaired arm
- Inability to understand English

EXCLUSION CRITERIA for MRI OUTCOME MEASURE

- Pregnancy or pregnancy planning during the study period
- Inability to tolerate MRI or contraindications for MRI

EXCLUSION CRITERIA for TMS OUTCOME MEASURES

- Presence of implanted medical devices such as cardiac pacemakers and defibrillators, intrathecal drug delivery pumps, or spinal cord, vagus nerve or similar stimulators, or cochlear implants [65]
- Presence of metallic hardware that would be in close contact with the TMS discharging coil such as intracranial implants, aneurysm clips, plates, electrodes
- Past history of seizures
- History of substance abuse within the last 6 months
- Recently stopped taking the following drugs within the past 6 months: barbiturates, benzodiazepines, meprobamate and chloral hydrate
- Currently taking medications or substances that significantly lower the threshold for onset of seizure [65]

☐ **N/A Chart/data review**

31. By role, (PI, Coordinator, etc.) who will assess for eligibility and how will this be accomplished?

After consent for screening is obtained, the Study PI, therapist and study staff will screen the candidates. They will meet and review the screen data. PI will contact candidate's medical provider as necessary. Study PI in consultation with a physical therapist and study staff will make a decision regarding subject's eligibility.

32. Are any subjects excluded on the basis of race, ethnic group, understanding of English, socioeconomic status, education, gender, or pregnancy?

- *Note: It is appropriate to indicate that you do not anticipate encountering potential subjects who do not speak English* ***based on the population to be studied***

☐ **No** ☒ **Yes** - *(provide justification)*: Subjects who do not understand English will not be included as understanding of study procedures is critical to ensure safety of the subject. Pregnancy is an exclusionary criteria for MRI and TMS outcome data collection

☐ **N/A Chart/data review**

33. Will subjects be reimbursed or paid an incentive for participating?

☒ **No (skip to item #35)** ☐ **Yes**

☐ **N/A Chart/data review (skip to item #38)**

34. How and when will they be paid?

☐ **Cash** ☐ **Check** ☐ **Other** -please explain:

☐ **Prorated** -provide schedule: ☐ **Fixed** -provide schedule

35. Will subjects be responsible for any of the costs related to the research?

☒ **No** ☐ **Yes**- please explain:

36. Will treating physicians, clinicians, or researchers be compensated or paid an incentive for referring or enrolling subjects?

☒ **No** ☐ **Yes** -please explain:

37. Please describe steps you will take to ensure that subject selection is fair and equitable:

1. There are no restrictions regarding inclusion of women and minorities in the study. Pregnancy will exclude subject from having TMS and MRI outcome measures collected.

2. All potential study subjects will be evaluated using the defined inclusion/exclusion criteria.

Section 5 – Risks and Benefits

38. Please list by bullet and describe the reasonably foreseeable physical, psychological, social, economic, and privacy risks, side effects, or discomforts associated with the research and their expected frequency and severity.

- *If this study is a retrospective chart review, or involves only the analysis of data, risk may still be present in the form of data security concerns.*

Risk Assessment

- *Potential Foreseeable Risks-orthosis and study treatment/testing procedures*
  - Prolonged duration of the study.
  - Discomfort/pain from wearing the orthosis.

- Failure of the safety mechanisms of the orthosis.
- Sensitivity to materials of the orthosis or electrodes.
- Loss of confidentiality
- Fatigue during study interventions.
- Muscle soreness from exercising weak/deconditioned muscles
- Lying Quietly In A Confined Space and Loud Noise during MRI testing
- Mild risk of developing a headache during TMS testing
- Discomfort during EMG

- *Unforeseeable Risks*

  Although the myoelectric arm brace has been used since 2007 in both studies and clinical practice, it is possible that there may be other risks that we cannot predict.

- *Risks of data security breach*

*Certificate of Confidentiality:

- Certificates of Confidentiality are issued by the National Institutes of Health (NIH) to protect identifiable research information from forced disclosure.
- They allow the investigator and others who have access to research records to refuse to disclose identifying information on research subjects in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level.
- Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation.
- By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy to subjects.
- **For more information, see http://grants1.nih.gov/grants/policy/coc/index.htm.**

39. Is this project principally concerned with the collection of sensitive information such as sexual attitudes, use of drugs or addictive products, and illegal conduct that would need to be protected against subpoena or forced disclosure in order to protect subjects?

☒ No

☐ Yes- will an application for a *Certificate of Confidentiality be submitted to the National Institute of Health upon IRB approval (or approval contingent on the issuance of such a certificate)?

☐ Yes ☐ **No provide a justification as to why a Certificate of Confidentiality will not be obtained:**

40. Describe all procedures that minimize risks, please include study and standard of care procedures:

Procedures that minimize Potential Foreseeable Risks-orthosis and study treatment/testing procedures

- The total duration of the study is about 31 visits over a period 22 weeks, which is a long commitment and increases risk of subject dropout. Subjects are informed of their time commitment during the screening phase and at enrollment consent and throughout their study participation.
- There is a possibility that some discomfort may arise while wearing the orthosis. Subjects will be required to wear the device for up to two hours during training and as long as tolerated at home. If at any time they feel uncomfortable, they are instructed to inform the researchers so that modifications can be made to the orthosis to improve comfort.
- There is a possibility that if the subject had ever experienced issues with shoulder instability or pain using the orthosis may cause these issues to flare up again Shoulder stability and pain will be monitored throughout the study to ensure that the device is not causing problems. Development of shoulder pain or additional subluxation during the course of the study would result in subject withdrawal from the study if modifications such as adding a shoulder harness were insufficient to overcome shoulder stability issues.
- The manufacturers of the orthosis have been careful to ensure that it is safe and cannot apply a dangerous amount of force to the arm or hand. Safety mechanisms have been implemented into the control software, the electronics hardware, and the mechanical hardware of the brace. For example, in the software commands that control the orthosis and the electronics of the orthosis, there are limits on the amount of force that can be commanded to the system. The mechanical system contains physical limits that prevent the orthosis from exerting force in an unsafe direction. In the worst case scenario, if all of these safety mechanisms fail, there is a small risk that the arm could be injured.
- The orthosis incorporates stainless steel, non-allergenic surface electrodes with no adhesive. It is very rare that these electrodes will cause skin irritation, but they might if the subject has allergies to certain metals (not including nickel) and/or orthosis fit is not correct. Development of skin rashes or open wounds as a result of the orthosis that could not be overcome by modifications to fit or improved donning/doffing procedures would result in subject withdrawal from the study.
- Functional performance of the arm with the orthosis will be videotaped during some of the outcome evaluations. The subjects' upper body, head, and neck will be visible in the video tapes which increases the risk of loss of confidentiality. The tapes will be stored in a locked cupboard. The only people with access to the cupboard will be the treating therapist and Dr. Pundik.
- Fatigue during study interventions. During the therapy sessions and testing sessions, subjects could become fatigued during a given motor learning session. Subjects could experience mild muscle soreness associated with using muscles that have not been utilized for a number of months or years. Exercises will be progressed to patient tolerance and monitored both within and between sessions by the therapist.
- ***Risk management and emergency response***
  Subjects will be monitored at all study visits to ensure that there are no open wounds or skin rashes on the impaired arm and that the shoulder is not dislocated, subluxed or painful.
  If at any time during the use of the device, the subject notices any of the following, they should immediately discontinue use and seek guidance from the researchers:
  - Unusual noises from the orthosis (skipping, clicking, etc.)
  - Smells from the orthosis (smoking, burning plastic, etc.)

The investigators may stop a subject's participation in the study without their consent if they think that it will be in the best interest of the subject, if the subject does not follow the study plan, if the subject experiences a study-related injury, or for any other reason.
If subjects sustain an injury as a direct result of the study, medical care will be provided by the Cleveland VA Medical Center at no cost to the subject. Financial compensation for such things as lost wages, disability, or discomfort due to an injury is not available.

Discomforts/Risks associated with neuroplastic measures (MRI, TMS, EMG)

- MRI Testing, Lying Quietly In A Confined Space and Loud Noise. The MRI testing includes lying quietly in a small space for about 40 minutes. Some patients may experience a feeling of claustrophobia or the sensation of being enclosed in a small space. The MRI testing also entails loud noises that occur during the testing.

- Single Pulse TMS caries no serious risks if used according to the guidelines of the TMS Consensus group[65]. TMS-use guidelines were published in 2009 as an outcome of a consensus conference that took place in 2008 and involved leading researchers with a track record for TMS use, manufacturing representatives, and representatives from various regulatory agencies[65]. In our protocol we will follow the guidelines for TMS and its safe use[65]. Below we describe in detail, any potential side effects of TMS, actions we will take to minimize the potential for any side effects, and protocols for the management of side effects, should any occur.
    i. Headaches or neck pain have been reported by 20%-40% subjects following long TMS protocols. This potential adverse effect is thought to be due to straight posture of the head and neck during the application of TMS. Since all prior cases of headache were resolved with a single dose of acetaminophen or aspirin, we will provide this, if needed.
        - In order to ensure good care of head and neck muscles, we will incorporate two actions into our protocol: 1) We will provide subjects the opportunity to stretch and move about to avoid muscle stiffness during the sessions; and 2) To ensure comfortable positioning, subjects will be positioned in a reclining chair with good neck support.

- EMG is usually well tolerated by patients. EMG entails applying brief electric shocks to a subject's arm. Participants may feel tingling and experience some discomfort. Testing will be administered by study staff trained in administration of the EMG who will ensure that the level of stimulation is kept as low as possible.

Unforseeable Risks

Although the myoelectric arm brace has been used since 2007 in both studies and clinical practice, it is possible that there may be other risks that we cannot predict. We will continue to monitor published literature and confer with the device manufacturer to ensure we have up to date knowledge of all device related risks.
Although the neuroplasticity measures have been used extensively in both clinical and research settings, there is always the possibility that new information will come to light. We will continue to monitor published literature to ensure we have up to date knowledge of all measurement related risks.

Data security breach risk

To minimize the risk, the following safeguards will be followed, 1) all electronic PHI will be kept on the secure password protected server, and 2) hard copies will be stored in a locked cabinet stored and locked room

41. Describe alternative procedures or course of treatment, if any, which might be advantageous to the subject. State if no alternatives exist or if this is not a treatment study.

Alternative treatment for motor impairment is occupational or physical therapy. Patients may ask their medical provider to refer them to an occupational or physical therapist for evaluation.

Minimal Risk: Minimal risk means that the risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

42. Please give your overall risk classification for the research:

☒ **Minimal Risk**

☐ **Greater than Minimal Risk**

43. Will subjects receive any direct benefit from this research?

☐ **No** ☒ **Yes** -describe the direct benefits:

Combining orthosis training with motor therapy and encouraging greater at home use may result in therapeutic and functional benefits.

44. Please explain briefly why you consider the risks associated with the study to be reasonable in relation to its benefits?

This study will result in better understanding of the role of myoelectric orthoses in treatment of upper limb motor impairment after TBI, in furthering our knowledge of brain function and re-organization and subsequently in development of superior methods to enhance functional recovery for individuals with severe disabilities secondary to TBI. Current treatments available for upper limb dysfunction are inadequate. Most importantly, while the risks of adverse effects are rather small and can be easily managed, study participants will likely provide very important information for future clinical trials.

Section 6 – Informed Consent

45. Type and number of Consent-

- *When more than one consent form is being used a descriptor MUST be in the header section describing the population and/or phase of the study*:

☒ **Written Informed Consent –number used in this study** 2 in total: 1 screen and 1 enrollment

☐ ***Oral Script/Letter/Information Sheet- number used in this study** ***Submit Request for Consent Waiver Form-waiver of documentation of informed consent**

☐ **No informed consent at all in this study- Submit a Request for Consent Waiver Form-waiver of informed consent and proceed to item 53**

46. Will all adult subjects have the capacity to give informed consent?

☒ **Yes** ☐ **No- Describe range of impairment.**

- *Research involving more than minimal risk, capacity should be determined by a psychiatrist, clinical psychologist, or other qualified professional not otherwise involved in the research.*
- *Individuals who lack the capacity to consent may participate in research only if a legally authorized representative gives consent on their behalf.*

47. Will anyone other than the subject be authorized to provide consent or permission for the subject's involvement in the research?

- *e.g., parents, court ordered guardian, spouse, etc.*

☐ **No** ☒ **Yes** -please explain: Given the nature of the Traumatic Brain Injury, it is likely that many potential participants will have a legal guardian who helps them make decisions about their care. If this is the case, during consenting we will obtain consent both from the subject and the designated legal guardian.

48. Describe <u>how</u> and <u>where</u> informed consent will be obtained:

Study PI or the study therapist, will be responsible for explaining the study, answering questions, and obtaining informed consent. Subjects will be in regular contact with the study therapist for the duration of the study providing subjects with frequent opportunities ask questions and have them answered throughout the trial.

Consent will be obtained in a quiet and private space within the site PI's lab, the Brain Plasticity and NeuroRecovery Research Lab of the Cleveland FES Center. If they wish, subjects will be allowed to take the consent form home to discuss with others before making a decision.

All candidates will undergo standardized screening using a medical history evaluation. Specific questions address neurologic illness, head trauma, seizure history, metallic implants, and current medications. All subjects will undergo a neurologic examination. Eligibility will be determined according to the inclusion/exclusion criteria listed above for both study cohorts. The evaluation will be performed in the so designated space within the Cleveland FES Center.

The informed consent process will include a scheduled meeting time with the potential candidate and family member/caregiver/significant other/legal guardian. The meeting will be held in a room (B-E235) in which everyone can sit in chairs, see and hear each other clearly, and feel no reason to hurry. This is a private room, providing protection of the subject's privacy. During the meeting the following will occur: verbal description of the study, including all content in the consent form; time for questions throughout each portion of the informed consent process and a time for questions at the end of the session; the candidate will be queried about understanding the study. That is, the candidate will be asked to describe the study in his/her own words. In order to be accepted into the study, the candidate will be required to express understanding of each point in the consent form. If the candidate then agrees to enter the study, he/she will sign the consent form, the investigator will sign the consent form, and a copy of the consent form will be provided to the subject. In the case where a subject has a legal guardian, we will obtain the signature of the legal guardian during the consenting of the patient.

Although the study will require 22 weeks of participation, subjects are considered to have a static neurological injury and hence we should not need to obtain ongoing consent or re-assess the capacity to consent over the course of the study.

49. Will there be an opportunity for potential subject to take the consent form home to discuss participation and options with family members?

☒ **Yes** ☐ **No** - please explain:

50. List by role who will be obtaining informed consent from subjects or their legally authorized representatives:

- *ex. study coordinator, co-investigator, research nurse, research assistant, PI*

Study PI or Physical Therapist

51. Please describe how informed consent will be obtained from subjects who do not read or understand English;

- *identify any languages likely to be encountered, and attach a copy of a translated and authenticated informed consent document*
- *It is appropriate to indicate that you do not anticipate encountering potential subjects who do not speak English based on the population to be studied*

We will not be able to include subjects who do not understand English.

52. Describe who *(by Role ex. PI, Coordinator, etc.)* **and how it will be determined that subjects and/or legally authorized representative understand the research and their rights.**

- *ex. question and answer, repeat back parts of the research, describe a procedure...etc*

This will be determined during the consenting process and during the examination completed by the neurologist, reviewed by the necessary study personnel (PI, therapist). Candidates will be encouraged to ask questions and repeat back key part of the research. Subjects will be encouraged to ask questions.

Section 7 – Privacy and Confidentiality

Privacy - refers to a person's desire to control the access of others to themselves. For example, persons may not want to be seen entering a place that might stigmatize them, such as a pregnancy counseling center that is clearly identified as such by signs on the front of the building. Privacy concerns people, whereas confidentiality concerns data. The research proposal should outline strategies to protect privacy including how the investigator will access information about potential subjects.

In developing strategies for the protection of subjects' privacy, consideration should be given to:

- Methods used to identify and contact potential subjects
- Settings in which an individual will be interacting with an investigator
- Appropriateness of all personnel present for research activities
- Methods used to obtain information about subjects and the nature of the requested information
- Information that is obtained about individuals other than the "target subjects," and whether such individuals meet the regulatory definition of "human subject" (e.g., a subject provides information about a family member for a survey)
- How to access the minimum amount of information necessary to complete the study

Confidentiality - methods used to ensure that information obtained by researchers about their subjects is not improperly divulged. Confidentiality refers to the researcher's agreement with the subject about how the subject's identifiable private information will be handled, managed, and disseminated. The research proposal should outline strategies to maintain confidentiality of identifiable data, including controls on storage, handling, and sharing of data. When appropriate, certificates of confidentiality could be used to maintain the

confidentiality of identifiable data

When the IRB evaluates research proposals for strategies for maintaining confidentiality, where appropriate, consideration will be given as to whether:

- Methods to shield subjects' identity adequately protect subject privacy
- There is a long-range plan for protecting the confidentiality of research data, including a schedule for destruction of identifiers associated with the data
- The consent form and other information presented to potential research subjects adequately and clearly describe confidentiality risks.
- The informed consent process and the informed consent document, and if applicable the Authorization Form, clearly delineates who will have access to the subject's information and under what circumstances data may be shared (i.e., government agencies, sponsors).

53. Describe when and where subjects will provide their information. Include the nature of the information and who will receive and use the information. Document the provisions used to protect privacy interests of those subjects when gathering their information and data.

A history and physical will be conducted in a research laboratory (room B-E235), where the subject's provision of private information cannot be heard by others. Subjects will be asked questions about their past illnesses, current health, name of primary care physician, and personal contact information. The research team physician and therapist will receive the information, and will enter the information into a research study form that will be maintained in a chart that is locked in a cabinet in a locked room (BE-235) in the LSCDVAMC. Video/audio recording is part of the subject's testing procedure. Recording is made with camcorder in our treatment laboratory. The tapes are kept in the laboratory and stored in the locked cabinet behind a locked door. For data analysis, video/audio data is transferred onto VA computer and is stored on the VA network behind firewall (Shared drive).

54. Will researchers have access to identifiable private information about potential subjects <u>outside</u> of this research project? *Ex. PI is provider who has access to medical records for clinical care*

☒ **No** ☐ **Yes- please explain:**

55. Will Researchers collect identifiable private information on anyone other than the subject?

- *Ex. family members, friends, colleagues, classmates...etc.*

☒ **No** ☐ **Yes -please explain:**

56. At the time data are transcribed or recorded for this study they are?

☒ **Fully identifiable- list identifiers to be collected:** Audio/video data by its nature remains identifiable.

☒ **Coded with a unique identifier- describe the code:** It is a random configuration of letters and numbers

a. Who will have access to the key? the study PI, therapist and study staff

b. Where is the key maintained? Two locking barriers must be in place between the coded data and the key. behind the VA network firewall, s-drive

☐ **De-identified-by Privacy Officer or Statistician.**

☐ **Other** *(describe)*:

57. How will electronic research data be secured while the study is active?

☐ **No electronic data will be stored**

☐ **VA encrypted laptop**

☐ **Encrypted VA device/media- describe:**

☒ **VA network drive;**

☐ **M: drive; whose?**

☒ **S: drive**

☒ **Folder access password protected**

☐ **Other drive location** *(for example P: drive)*:

☐ **Folder access password protected**

58. How will hardcopy research data be secured while the study is active? Two locking barriers must be in place.

☐ **No hardcopy data will be stored**

☒ **Locked office and locked file cabinet**

☒ **Data coded by PI or study staff with a master list secured and kept separately**

☐ **Data de-identified by Privacy Officer or Statistician-** *(***VA does not consider coded data to be de-identified)**

☐ **Other -specify:**

59. Provide the physical location including room number (and address if outside of this VA) where all electronic and hardcopy data will be stored: In a locked cabinet in a locked office of the Brain Plasticity and NeuroRecovery Research Lab at the LSCDVAMC (room BE235 and BE-251).

60. Is identifiable information physically or electronically sent <u>TO</u> the LSCDVAMC from other institutions or locations?

☒ **No** ☐ **Yes** - contact Privacy Officer Joseph Picklo or Tomica Jefferson joseph.picklo@va.gov / phone 8214102 tomica.jefferson@va.gov / 8214101 or Information Security Officer Bruce Frankford bruce.frankford@va.gov / phone 821 1604 – prior to submitting to the Research Service.

****If yes complete the following:**

a. LSCDVAMC investigator will receive:

☐ **Hardcopy information or specimens**

☐ **Electronic information**

b. What are the procedures for transporting and/or transmitting identifiable information securely?

c. What will be the final disposition of the identifiable data transferred to the LSCDVAMC?

- **Record Control Schedule 10-1 indicates that all research records must be retained indefinitely**

61. Is identifiable information physically or electronically sent FROM the LSCDVAMC to other institutions or locations?

☒ **No** ☐ **Yes** contact Privacy Officer Joseph Picklo or Tomica Jefferson joseph.picklo@va.gov / phone 8214102 tomica.jefferson@va.gov / 8214101 or Information Security Officer Bruce Frankford bruce.frankford@va.gov / phone 821 1604 – prior to submitting to the Research Service

****If yes complete the following:**

a. The LSCDVAMC investigator will send:

☐ **Hardcopy information or specimens**

☐ **Electronic information**

b. What are the procedures for transporting and/or transmitting identifiable information securely?

c. What will be the final disposition of the identifiable data transferred offsite?

- **Record Control Schedule 10-1 indicates that all research records must be retained indefinitely**

62. Record Control Schedule 10-1 indicates all research records must be retained indefinitely. Please indicate where this information will be stored and the safe guards to protect it:

a. Electronic Safeguards:

☐ **No electronic data will be stored**

☐ **VA encrypted laptop**

☐ **Encrypted VA device/media- describe:**

☒ **VA network drive;**

- ☐ **M: drive; whose?**
- ☒ **S: drive**
  - ☒ **Folder access password protected**
- ☐ **Other drive location** *(for example P: drive)*:
  - ☐ **Folder access password protected**

b. Hardcopy safeguards. Two locking barriers must be in place.

☐ **No hardcopy data will be stored**

☒ **Locked Office and Locked File Cabinet**

☐ **Coded by Study Staff**

☐ **De-identified by Privacy Officer or Statistician**

☐ **Other- Describe:**

Facility name, address, and room number where hardcopy or electronic data will be stored: Hard copies will be stored in rooms BE-240 and BE-251 at the Louis Stokes Cleveland DVA Medical Center, 10701 E. Blvd, Cleveland. OH 44106. Electronic copies are stored on Cleveland VA secured server managed by IT Service.

Section 8 – Data and Safety Monitoring –Greater than Minimal Risk Study

- For all research that is greater than minimal risk a Data and Safety Monitoring Plan must be developed.
- This is a plan to assure the research includes a system of appropriate oversight and monitoring of the conduct of the study to ensure the safety of subjects and the validity and integrity of the data.

***CHECK BOX IF THIS IS A MINIMAL RISK STUDY ☒ SKIP TO #65**

63. Safety monitoring for this greater than minimal risk project will include:

☐ **Data Safety Monitoring Board**:

☐ **Data Monitoring Committee**

☐ **Other**

- *Attach the plan or provide details including whether committee is independent from the study sponsor, how often it meets, whether written reports are available, etc*

64. Describe the plan for on-site data monitoring by the sponsor, contract research organization (CRO), or other independent body:

This is not a requirement of the funding agency.

- **Research Office must be notified of all on-site monitoring visits.*

65. Conditions that may result in removal of subjects from the research *(check all that apply)*:

☐ **Medical condition unchanged**

☒ **Medical condition worsened**

☒ **Serious adverse event**

☒ **Intolerable complications**

☒ **Pregnancy**

☒ **Investigator's clinical judgment**

☐ **Subject withdrawal**

☒ **Subject uncooperative or noncompliant**

☐ **Study closure by sponsor or FDA**

☐ **Refusal to suspend breast-feeding**

☐ **Other-describe:**

☐ **Not Applicable**

66. If a subject withdraws or is removed from the study, describe the potential risks of early withdrawal and the procedures in place to minimize these risks:

There are no risks of early withdrawal from the study.

Section 9 – FDA-Regulated Drugs/Biologics

NOTE: If this research involves the use of <u>any</u> drugs or biologics, the study is subject to the Food and Drug Administration (FDA) regulations.

- **Documentation of FDA approval for the experimental use of these agents must be provided for review (industry sponsored protocol listing the IND number, letter from the FDA, letter from industry sponsor, or other document and/or communication verifying the IND for this study).**
- All drug/biologic products must be dispensed and tracked through the LSCDVAMC Research Pharmacy.
- An M.D. must be part of the Research Team for all studies that involve the use of a device or drugs.
- The LSCDVAMC Pharmacy and Therapeutics (P&T) Committee must approve: (1) Studies of investigational drugs (2) research involving an FDA-approved drug used in a non-approved manner, and (3) an FDA-approved drug, used as approved, when its use is part of a research protocol.
- **VA Form 10-9012 Investigational Drug Information Record** –must be completed for each drug being evaluated in a research study, regardless of IND status. In addition, the VA Form 10-9012 provides a listing of all authorized prescribers for the study drug(s).

67. Type of Product- check all that apply:

☒ **Not Applicable -No FDA-regulated drugs/biologics involved – Proceed to Section 10**

☐ **Drug**

☐ **Biologic or Other:**

68. Type of Trial *(check as applicable)*:

☐ **Phase I** ☐ **Phase II** ☐ **Phase III** ☐ **Phase IV** ☐ **NA**

Phase I Trials: Initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy subjects and/or patients.
Phase II Trials: Controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks.
Phase III Trials: Expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide adequate basis for physician labeling.
Phase IV Trials: Post-marketing studies to delineate additional information including the drug's risks, benefits, and optimal use.

69. FDA Status of Drugs/Biologics –

*** For drugs, an IND may not be necessary if ALL seven of the following conditions are met:**

1. The drug being used in the research is lawfully marketed in the United States;
2. The research is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
3. The research is not intended to support a significant change in the advertising for the product;

4. The research does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
5. The research is conducted in compliance with the requirements for IRB review and informed consent (21 CFR parts 56 and 50, respectively);
6. The research is conducted in compliance with the requirements concerning the promotion and sale of drugs (21 CFR 312.7);
7. The research does not intend to invoke 21 CFR 50.24 (Exception from informed consent requirements for emergency research).

Provide the following information for <u>each</u> drug/biologic used in this study:

Trade and Generic Name	**Manufacturer**	FDA Approved	**Product use consistent with product labeling**	**IND Required***	**IND Number**	**IND Sponsor or Holder****

70. **When the PI holds the IND, complete the following:

i. The PI has reviewed the Guidance on Requirements of the Sponsor and the Investigator as Sponsor

☐ **Yes**

ii. As the PI, you will comply with the regulatory responsibilities of a sponsor

☐ **Yes**

71. Drug Information for each drug listed in the protocol -check as applicable

☐ **Approved Drugs**

☐ **Not Approved**

- **Attach VA Form 10-9012 Investigational Drug Information Record for each drug used in the protocol**
- **Attach Package Insert or PDR monograph – copy ready, 8.5 x 11 for each drug listed in the protocol**
- **Attach Investigator's Brochure**

72. Provide a detailed description of how FDA-regulated drugs/biologics will be stored, secured, dispensed, administered, tracked, and returned.

Section 10 – FDA-Regulated Devices

This section should be completed for a medical device that is the <u>subject</u> of a clinical study designed to evaluate the effectiveness and/or safety of the device.

- An investigational device may be an FDA approved device that is being studied for an unapproved use or efficacy. This also includes an approved device that is being studied for an unapproved or approved use in a controlled, randomized, or blinded clinical trial.
- Documentation of FDA approval for the experimental use of the device must be provided for review (industry sponsored protocol listing the IDE number, letter from the FDA, letter from industry sponsor, or other document and/or communication verifying the IDE for this study).

Device Risk Determination:

Significant Risk (SR) Device is an investigational device that: (1) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject, or (2) is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; or (3) is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Non significant Risk (NSR) Device is a device other than a significant risk device.

The IRB is required to document the basis for risk determination based on the proposed use of a device in the research by considering the nature of the harm that may result from the use of the device. FDA has the ultimate decision in determining SR and NSR.

An M.D. must be part of the Research Team for all studies that involve the use of a device.

The Environment of Care Committee (EOC) must approve all research that involves electrically line-operated devices, which have leads or electrodes and will come in contact with human subjects.

73. Type of Product-check all that apply:

☐ **Not Applicable -No FDA-regulated devices involved – Proceed to Section 11)**

☐ **An FDA regulated device will be used BUT not with intent of studying safety or efficacy** *(Proceed to Section 11)*

☒ **Device**

74. List the device-include name and manufacturer: MyoPro myoelectric upper limb orthosis, Myomo Inc., Cambridge MA

75. FDA Regulatory Status of the Device:

☒ **FDA Approved Device**

- **A device approved by the FDA for distribution, marketing, sale to, and use by, the public for the study's indication.**

☐ **New Indication of an FDA Approved Device**

- **A device NOT approved by the FDA for distribution, marketing, sale to, and use by, the public for the indication used in the study.**

☐ **Investigational - Investigational Device Exemption (IDE)**

- **An FDA designation that permits a manufacturer to lawfully ship an unapproved device for use in a research study.**

Provide the following:

a. **IDE Number:**

b. **IDE Sponsor or Holder:**

If the PI holds the IDE, complete the following:

i. The PI reviewed the Guidance on Requirements of the Sponsor and the Investigator as Sponsor

☐ **Yes**

ii. As the PI, you will comply with the regulatory responsibilities of a sponsor

☐ **Yes**

c. FDA or Sponsor Device Risk Determination

☐ **Non-Significant Risk**

☐ **Significant Risk**

d. Attach documentation of FDA approval for the experimental use of the device (industry sponsored protocol listing the IDE number, letter from the FDA, letter from industry sponsor, or other document and/or communication verifying the IDE for this study).

☐ **Humanitarian Use Device (HUD)**

- **An FDA designation for a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. For more information about Humanitarian Use Devices see the HRPP SOP manual on the R&D website.**

Provide the following:

a. HUD Number:

b. HUD Sponsor or Holder:

c. Include a copy of the FDA letter granting Humanitarian Use Device (HUD) status.

☐ **510(k) Status –**

- **A device determined by the FDA to be "substantially equivalent" to an existing device that is legally marketed in the U.S. Until a 510(k) device is approved, it is still considered investigational.**

a. Provide the name of an equivalent device and sufficient documentation to justify 510(k)

76. Attach device information (i.e., brochure, device label) -Brochure attached.

77. Provide a detailed description of how FDA-regulated devices will be stored, secured, dispensed, administered, tracked, and returned.

Devices will be custom fit by the manufacturer and subjects will utilize the device for the duration of the study. Once their participation has ended, the device will be returned to the study manufacturer.

Section 11 – Genetic Testing and Discovery of Genetic Information (DNA)

78. Does the research involve genetic testing or DNA/RNA extraction?

☒ **No genetic testing** (*Proceed to Section 12)*

☐ **Yes- complete the following:**

a. Describe the purpose of the genetic testing component of the study

- *Is it to establish risks, associations, or prevalence?*

b. Describe whether the test is a standard test already in clinical use or a new or experimental laboratory study

c. Describe the accuracy of the test

- *Sensitivity, specificity, reliability, validity, and variability*

79. Does an abnormal test result indicate that the subject:

☐ **Has a specific condition**

☐ **Is at risk for a specific condition**

☐ **May be at risk for a specific condition**

☐ **Has, is, or may be at risk for some other outcome**

☐ **Other** *(describe):*

80. Does a normal test result indicate that the subject

☐ **Is not at risk for a specific condition**

☐ **Is at a lower risk for a specific condition**

☐ **Is at a population risk for a specific condition**

81. Is there a risk of discovery of other results such as non-parentage or other genetic conditions?

☐ **No** ☐ **Yes- please explain:**

82. Will test results produce information on anyone (e.g. a first-degree relative) besides the subject?

☐ **No** ☐ **Yes- please explain:**

83. To whom and in what manner will genetic information be reported?

84. Will genetic counseling be made available to subjects?

☐ **No** ☐ **Yes- indicate who will conduct the counseling and whether there are any additional charges:**

85. Will DNA samples be stored?

☐ **No** ☐ **Yes--describe where, how, and for how long the samples will be stored:**

86. Who will own the DNA samples?

87. Will there be any subsequent analysis of the DNA samples?

☐ **No** ☐ **Yes- describe the purpose of the subsequent analysis and whether there will be dissemination of any new information:**

88. Describe how samples will be handled if the subject withdraws consent for further participation:

89. Will the samples be distributed to other investigators?

☐ **No** ☐ **Yes- please explain:**

90. Describe the provisions to maintain the confidentiality of research data, especially in cases where data can be linked to individual subjects:

Section 12 – Tissue Collection/Storage/Banking*

It is VA policy to ensure that human biological specimens, as well as the linked data collected as part of research projects conducted by VA investigators in VA facilities or approved off-site locations, are maintained at *VA approved tissue banks or VA-sponsored tissue banks.

See VHA Directive 2000-043 "Banking of Human Research Subjects' Specimens" for more information and also visit http://www.research.va.gov/programs/tissue_banking/default.cfm

Human biological specimens (specimens).

- **Human biological specimens are materials, such as blood, urine, tissue, organs, hair, nail clippings, buccal swabs or any other materials that are derived from human subjects and are either collected specifically for research purposes or as residual specimens from diagnostic, therapeutic or surgical procedures.**

91. *Does the research involve storage or banking of human specimens or identifiable private information for use in future studies? *(check all that apply)*

☒ **No** *(proceed to Section 13)* ☐ **Yes-describe status of VA approved or VA sponsored facility:**

☐ **Storing or banking identifiable private information**

☐ **Storing or banking human specimens**

Please provide the following information:

a. **What identifying information will be required?**

b. **What are the foreseeable uses of the specimens (e.g., research, pharmaceutical products, production of cellular lines for various uses, etc.)?**

c. **What is the VA approved or VA sponsored location/institution where the information and/or specimens will be stored?**

d. **How long will the information and/or specimens be stored?**

e. **Is the storage facility an on-site or off-site location?**

f. **Will subjects be able to request that their specimen and/or information be withdrawn from the bank or repository?** *(explain)*

Section 13 – Children as Research Subjects

Research involving children must not be conducted by VA investigators while on official duty or at VA or VA-approved offsite facilities unless a waiver has been granted by the CRADO (See VHA Directive 2001-028 "Research Involving Children" for more information.

92. Do you plan to enroll children as research subjects?

☒ **No** *(Proceed to Section 14)*

☐ **Yes- Age range of subjects:**

93. Category of Research *(Check the box next to the category of research you believe your research falls under. The IRB will make a final category determination during review.)*:

☐ **Research involving minimal risk (the probability & magnitude of harm or discomfort anticipated are not greater than those ordinarily encountered in daily life or during routine physical or psychological tests.)** *(46.404)*

☐ **Research involving greater than minimal risk but of potentially direct benefit to the subject.** *(46.405)*

☐ **Research involving greater than minimal risk and no prospect of direct benefit to the subject but likely to yield generalizable knowledge about the subject's disorder or condition.** *(46.406)*

☐ **Research not otherwise approvable which presents an opportunity to understand, prevent or alleviate a serious problem affecting children/decisionally impaired adults.** *(46.407)*

94. Do you anticipate enrolling minors who are wards of the state?

☐ **No** ☐ **Yes**

95. Permission of parents or guardian *(check one only)*:

☐ **The permission of each child's parents or guardian will be sought unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child (required for categories 46.406 and 46.407 above in item 104).**

☐ **The permission of only one parent will be sought (acceptable for categories 46.404 or 46.405). If marked, provide justification:**

96. Assent of Children *(check one only)*:

☐ **The assent of each child who is capable of providing assent based on age, maturity, and psychological state will be sought.**

☐ **The assent of each child will not be sought because the capability of all of the children in this study population is so limited that they cannot reasonably be consulted. Explain why the capacity is so limited, e.g., age, maturity and/or psychological state:**

☐ **The assent of each child will not be sought because the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research. Explain what the direct benefit may be and why it is only available in the context of the research:**

Section 14 – Other

97. Please describe any other study procedures not referenced in the previous sections:

☒ **Not applicable**

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