VA Pittsburgh Healthcare System

ProSPECT - Protocol Submission Portal and Electronic Communication Tracker

Date: Wednesday, April 21, 2021 10:51:23 AM

Print | Close

ID: Pro00003161 View: 0.0 Type of Submission Entry

Study Identification Information

This is the first step in your Human Research Application. You will automatically be guided to the appropriate forms needed to complete your submissions.

1.0 * **Study Name:**
Neurophysiological and Kinematic Predictors of Response in Chronic Stroke (SRT5)

2.0 * **Brief Description (using layman's terms) - 500 words or less:**
Stroke is the leading cause of neurological disability in the veteran population and upper extremity dysfunction is a major cause of functional loss. The costs of rehabilitation are significant and practically limits therapy to the first few months after stroke onset. Recent results show clearly that patients with chronic stroke benefit from rehabilitation and robot assisted therapy offers a more cost effective approach to this patient group. In this study, we are validating a predictive model that uses demographics, functional status, genomics, neurophysiology, neuroanatomy, and other potential biomarkers to predict the likelihood of a clinically significant change in impairment at the end of a robot assisted therapy intervention.

3.0 * **Is this research study a Greater than Minimal Risk Clinical Trial?** ◉ **Yes** ○ No

4.0 * **Is this study a Greater than Minimal Risk Comparative Effectiveness research?** ○
Yes ◉ **No**

5.0 * **Principal Investigator:**
George Wittenberg

5.1 * **VA hours per week the PI is devoted to project:**
10

5.2 * **Is the PI working with ionizing radiation?** ○ Yes ◉ **No**

5.3 * **Is the PI working with biological hazards?** ○ Yes ◉ **No**

5.4 * **Is the PI shipping biological hazards?** ○ Yes ◉ **No**

A completed and signed Research Financial Conflict of Interest Statement is required for all investigators (including Principal Investigators, Co-Principal Investigators, and Co-Investigators) listed on the study application. **Financial Conflict of Interest Form-Nov. 2013**

5.5 **Upload Financial Conflict of Interest Statement:**
GW FCOI(0.01)

6.0 **Research Staff:**

Researcher	Role in Project	Hours per Week devoted to project	Administer Informed Consent	Working with Ionizing Radiation	Working with Biologicial Hazards?	Shipping biological hazards?	FCOI Form
Kasey Stepansky	Research Staff	2	no	no	no	no	
Amy Boos	Research Staff Coordinator	30	yes	no	no	no	
Stacy Eckstein	Coordinator	1	no	no	no	no	
Jennifer Collinger	Co-Investigator	1	no	no	no	no	Collinger FCOI (0.01)

7.0 Type of Submission:

Description	
(●)	**This is a new study. This has not previously been submitted to the IRB.**
( )	This is a new paper conversion. This study has been previously approved by the IRB.

If this is a 'New Paper Conversion' please include the MIRB Number:

Please upload a letter certifying that you have made no modifications or amendments in converting this research study from paper to electronic:

ID: Pro00003161 View: 1.0 Study Identification Information

Study Identification Information (Continued)

1.0 * **Do you certify that all research staff administering informed consent are knowledgeable about the study?**

yes

2.0 * **To the best of your knowledge do you, or any member of your research staff, have any potential, actual or perceived conflict of interest of a professional or personal nature that may affect any aspect of the research, including, but not limited to, the review and/or conduct of this study?**

○ Yes ◉ **No**

If yes, provide a description, including name of study team member with conflict:

3.0 * **Qualifications of the Investigators:**

Dr. George Wittenberg, MD, PhD, FASNR, is a clinician-scientist at the VAPHS and University of Pittsburgh. He has an A.B. degree in Engineering and Applied Sciences from Harvard College, and both doctoral degrees from UCSD. He was trained in transcranial magnetic stimulation at NINDS by Leonardo Cohen. He has extensive experience since 1996 as an investigator in neurorehabilitation clinical trials, and has been a principal investigator on many of them. He was site principal investigator for VA CSP #558, which involved robotic rehabilitation.

ID: Pro00003161 View: 1.2 VA Involvement

VA Involvement

1.0 Does the proposed research involve any of the following?:

	Name
☑	**VA Funding**
☑	**VA Personnel Funded Effort**
☑	**VA Patients or their Private Health Information**
☐	Other VA Resources: Central IRB
☑	**Other VA Resources: VA Equipment**
☑	**Other VA Resources: VA Property (Including space leased to, or used by VA)**
☐	Other VA Resources: VA Databases
☐	None of the Above apply to this research

ID: Pro00003161 View: 1.3 Study Funding Information

Study Funding Information

1.0 * **Funding Sources:**

	Funding Source	(Other)	Code
View	Merit Review (CC 103)		9003

2.0 **Upload Grant Application, if applicable (If NIH, VA, voluntary agency, must upload):**

Name	Modified Date
Grant Application	7/12/2019 1:45 PM

ID: Pro00003161 View: 1.4 Resources

1.0 * **Do you currently have adequate resources (e.g., staff, physical space, information technology, etc.) to protect the safety of participants, staff, and the confidentiality of subjects' data during the conduct of this study?**

◉ **Yes** ○ No

If yes, include a listing of the VAPHS resources that will be used for this study and are necessary to protect participants.
The main laboratory area is the Laboratory for Research on Arm Function and Therapy (RAFT) which is located in the Keystone building, a commercial building leased by the University of Pittsburgh, with a pending Memorandum of Understanding regarding its use as VA Research Space. There is an off-site waiver for the current study-related activities in RAFT, which is part of the Rehab Neural Engineering Labs (RNEL.) The laboratory contains a variety of devices designed around upper extremity motor function. This includes transcranial magnetic stimulation (TMS) equipment (a rapid stimulator capable of modulating brain activity for several minutes, standard TMS stimulators and Bistim device), and Brainsight Neuronavigation systems. There is a unimanual exoskeleton robot (Armeo Power) and a bimanual KINARM exoskeleton robotic system (B·Kin / KINARM, Kingston, ON.)

University Drive VAPHS: All veterans will have their functional evaluations in the occupational therapy area at this facility.

Human Engineering Research Laboratories (HERL) are a part of the U.S. Department of Veterans Affairs as the Center for Wheelchairs and Associated Rehabilitation Engineering. Dr. Wittenberg has office space in this facility and receives administrative and scientific support from its faculty and staff. Sensitive data will be stored within its VA resources.

If no, please describe the resources that will be needed and explain how the resources will be obtained before the study is initiated:

2.0 * **VAPHS requires that either the PI or co-PI have a *physical presence* at VAPHS. Please describe the role the PI and/or co-PI have at VAPHS with respect to clinical responsibilities or in relation to other research activities.**
The P.I. is a 5/8 part-time employee of VAPHS, with an appointment as Neurologist in the Medicine Service. He has 2/8 of clinical effort, which is on the Outpatient Neurology service, seeing consultations and follow-up patients preferentially with stroke and movement disorders, as well as other general neurological disorders. The remainder of his effort is devoted to VA specific research.

3.0 * **Will off-site ancillary service facilities (e.g., radiology services, central labs, non VA space, etc) be used for this study?**

◉ **Yes** ○ No

If yes, please provide the location and a brief description of the project activities to be conducted at the off-site ancillary facilities:
MRI scans will be conducted at the Magnetic Resonance Research Center, which houses and operates two 3T Siemens Prisma systems and has research staff and technologists to support our project.

The Main Laboratory Area is the Laboratory for Research on Arm Function and Therapy (RAFT) part of the Rehab Neural Engineering Labs (RNEL.) The laboratory is in the Keystone Building,

second floor, in one suite that contains a variety of devices designed around upper extremity motor function. This includes transcranial magnetic stimulation (TMS) equipment (a rapid stimulator capable of modulating brain activity for several minutes, standard TMS stimulators and Bistim device), Brainsight Neuronavigation systems. There is a bimanual KINARM exoskeleton robotic system (B·Kin, Kingston, ON.).

4.0 * **Will a firm be contracted to obtain consent from subjects, collect private individually identifiable information from human subjects, or be involved in activities that would institutionally engage the firm in human subjects' research?**

○ Yes ◉ **No**

If yes, please provide a description of the contracted service(s):

* Please specify the IRB that has oversight of the firm's activity(ies):

Name of Site / Institution	IRB Approval Document	FWA Number
There are no items to display		

5.0 **Collaborations**

Please list any non-VAPHS institutions or individuals (i.e. co-authors, mentors, etc.) that you will collaborate with and describe their specific role in the research:
Dr. Amit Sethi will supervise the clinical evaluations of upper extremity function and TMS studies. As Assistant Professor in the Department of Occupational Therapy at the University of Pittsburgh, he is a clinical investigator who is experienced in the assessment of upper extremity function and the training of stroke survivors in upper extremity functional use.

Dr. Tae Kim's specific role is designing acquisition and analysis methods for the MRI portion of the proposed work. He is an Assistant Professor in the departments of Radiology and Bioengineering at the University of Pittsburgh. Research interests include brain perfusion modeling, cerebrovascular regulation mechanisms, and technical development and quantification of functional MRI, all relevant for this study.

5.1 If this is not Multi-Site Research, please upload the appropriate written agreement(s) here:

Name
There are no items to display

ID: Pro00003161 View: 1.5 Project Information

1.0 Does the project involve any of the following (check all that apply):

Type
☐ Biological Hazards (including human biological specimens)
☐ Chemicals
☐ Ionizing radiation or use of radioactive materials
☐ Drug, Biological, or Nutritional (e.g. herbal or dietary) Supplement

2.0 Project Focus (check if applicable):

Type
☐ Traumatic Brain Injury (TBI)
☐ Post Traumatic/Post Deployment Stress Disorder (PTSD/PDSD)
☐ Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF)

3.0 KEYWORDS

Please provide a minimum of 3, maximum of 6 keywords. Please use MeSH terms.

* stroke
* rehabilitation
* robotics

4.0 * Please describe the type of study:

one-arm, multiple baseline sequential, cohort study

5.0 * Will any of the research being conducted as a part of this study be used to fulfill academic requirements (e.g., master's thesis, dissertation, or other academic program requirements necessary to obtain a degree/certification, etc.)? ○ Yes ◉ **No**

ID: Pro00003161 View: 1.6 (CR) Study Locations

Study Locations

1.0 * **Please add the local sites where this study will be conducted:**

	Location
View	VAPHS University Drive Division
View	Other

If Other, Please Specify:
The Laboratory for Research on Arm Function and Therapy (RAFT).

The Human Engineering Research Laboratories (HERL), part of the U.S. Department of Veterans Affairs as the Center for Wheelchairs and Associated Rehabilitation Engineering.

ID: Pro00003161 View: 1.6.1 (CR) Multi-Site Study

1.6.1 Multi-Site Study

1.0 * **Is this a multi-site study:**

(●) **Yes** ( ) No

ID: Pro00003161 View: 1.6.1.1 (CR) Multi-Site Study

1.6.1.1 Type of Multi-Site Research

1.0 * **Type of Multi-Site Research:**
Research NOT Conducted Under a Cooperative Research and Development Agreement (CRADA) with a Pharmaceutical Company or other Non-Federal Entity ("Collaborative Research").

ID: Pro00003161 View: 1.6.1.1.2 (CR) Multi-Site Not Conducted Under CRADA

1.6.1.1.2 Multi-Site Not Conducted Under CRADA

1.0 * **Status of the PI in Proposal (check all that apply):**

Coordinating Investigator in multi-site study (includes studies conducted both at VAPHS and Pitt)

Provide Further Details (if needed):

ID: Pro00003161 View: 1.6.1.1.2.1 (CR) Coordinating Investigator

1.6.1.1.2.1 Coordinating Investigator

1.0 * **Number of currently participating institutions/sites (including VAPHS and international sites, if applicable):**
2

2.0 * **Does this study involve international/transnational research?**
○ Yes ◉ **No**

Please answer the questions below for all research conducted **within** the United States, its territories, or Commonwealth:

3.0 * **Specify other research sites where this research will be conducted:**

Name of Site / Institution	IRB Approval Document
University of Pittsburgh	

4.0 **Provide details with regards to coordinating center responsibilities:**
As both sites in the study are the RAFT Lab and the research is being overseen by identical study staff, once the VA protocol is approved, the University of Pittsburgh protocol will be modified to reflect the coordinating site protocol. The study coordinator will ensure that all study documents and amendments are performed to reflect the coordinating site. The PI and study coordinator will assure that the University of Pittsburgh will safeguard VA data as required by VA information security policies. The study coordinator will communicate to engaged participating sites SAEs that have the potential to affect of the study and study events and interim results (if appropriate). The study coordinator and PI will report all non-compliance with the study protocol or applicable requirements is reported in accordance with VHA Handbook 1058.01.

5.0 **Please upload the study-wide sample informed consent form(s), protocol, and another other relevant documents, as applicable.**
Name
There are no items to display

6.0 **Upload applicable agreement(s) with non-VA collaborators (e.g., Research Data Use Agreement) that address such issues as the responsibilities of each party, the ownership of the data, and the reuse of the data for other research and any other relevant documents.**
Name
VA MRI contract
RDUA with MRRC
Provide further details (if necessary):

ID: Pro00003161 View: 1.7 Section Chief and Service Line VP approvals

Please upload the approval of the Section Chief, if applicable and the Service Line VP.

1.0 * **Institutional Approval Document:**
Institutional Approval Document(0.02)

ID: Pro00003161 View: 2 Study Objectives & Design

Study Summary

1.0 Funding End Date:

2.0 * Abstract. Please provide a brief description of the study.

Stroke is the leading cause of neurological disability in the veteran population and problems with arm movement are a major cause of loss of functional ability. The costs of rehabilitation are significant and effectively limit therapy to the first few months after stroke onset. Recent results show clearly that patients with chronic stroke (> 6 months) benefit from intensive arm practice. Robot assisted therapy followed by task related training offers a cost-effective approach to this type of practice that also results in better arm function in daily life. A previous study has shown that it is possible to predict who will benefit from this kind of treatment, specifically what individual characteristics are related to a clinically meaningful improvement in arm movement. This next phase of the study will test whether the prediction method is reproducible and independent of the type of robot being used. It will also expand knowledge of how the brain area most important for movement changes its connections with other brain areas and the muscles in the arm.

3.0 * Describe the study objectives. Please include primary aim and hypothesis, if applicable any secondary aims and hypotheses.

Chronic upper extremity dysfunction after stroke is a leading cause of disability and has been the target of many therapeutic methods that involve repetitive task practice. Clinical trials of intensive practice-based interventions have demonstrated significant changes in mean impairment in a group, but variable effects among individuals, with clinically significant improvements in only a fraction of the population. This is true of our previous Merit Review study, which showed good mean gains in several areas, and about half of participants having clinically significant changes in the primary outcome of motor impairment. The basis for these variable responses is not known, i.e. we do not know the biological mechanisms that moderate response to these standardized interventions. And while recovery of function is associated with normalization of brain network interactions and task-related brain activation, the causal role of these changes is not well understood. In our current project period, we are continuing to address both issues with construction of a predictive model that uses demographics, functional status, genomics, neurophysiology, neuroanatomy, and other potential biomarkers to predict the likelihood of a clinically significant change in impairment at the end of the intervention.

Our long-range goal is the prescriptive application of intensive task practice to veterans who have suffered a stroke, maximizing the cost-benefit ratio. We therefore plan to externally validate the predictive value of biomarkers as incorporated in the model resulting from our previous chronic stroke robotic rehabilitation trial. We will not only validate the predictive model in a new cohort, we will now quantify the *changes* in functional connectivity of the affected hemisphere's primary motor cortex with other brain areas and with the spinal cord, in order to uncover the mechanisms by which intensive task practice leads to increased motor ability. We will continue to use an effective intervention for individuals with chronic stroke, robotic training

with transition to task practice (Robot + TTT,) now focusing on use of an *exoskeleton platform,* which has already been part of our intervention. We propose the following two specific aims in the proposed renewal of this award:

1. ***To validate a predictive model based on baseline measures of biological and functional biomarkers.*** *Working hypothesis: Baseline factors that include functional and physiological status will predict clinically significant responses to therapy.* Change from use of end-effector and exoskeleton robots to solely exoskeleton will not significantly affect the prediction model. The rationale for the hypothesis is that the effects of assisted repetitive task practice is not dependent on a particular technology but does depend on a biological substrate. Expected outcomes: The predictive model will be externally validated, a receiver operating curve described, and the intervention and model validated on an exoskeleton platform for delivering therapy.

2. *To identify the changes in the input and output of the affected primary motor cortex associated with change in motor impairment.* *Working hypothesis: Increased input into the motor cortex, increased output from the motor cortex, or both, underlies the treatment effect of repetitive task practice.* Normalization (increase) in connectivity of affected primary motor cortex to other motor brain areas of both sides of the brain will be associated with reduction of motor impairment. In a subpopulation of treatment responders an increased effectiveness of the motor cortex in directly activating muscles will be demonstrated. Expected outcome: The causal role of task practice in changing a brain region's connectivity will be known, with potential uses as a surrogate measure of outcome in rehabilitation trials. Resting state BOLD MRI, transcranial magnetic stimulation, and clinical electrophysiology will be used to provide data regarding the mechanisms of training-related gains.

When we have completed the above aims, we will have a validated algorithm by which a set of baseline variables (biomarkers) can be used to inform both the clinician and patient regarding the likelihood of successful training, in an appealing exoskeleton robotic rehabilitation platform, for upper extremity disability in the chronic period after stroke. This algorithm can be modified to consider those biomarkers that are more practical in VA clinical settings. We will also extend mechanistic knowledge about the response to intensive training on brain connectivity, which has been noted to be altered after stroke and which may relate to learned non-use of the affected limb and loss of spinal response to descending input. We will have new efficacy data on the use of assisted mass practice followed by assisted task practice on multiple dimensions of functioning and disability, including use of the arms in daily life.

4.0 *** Provide a summary of the background of the study, and explain how this research will contribute to existing knowledge. Describe previous studies that provides a basis to show that the proposed research can be carried out without undue risk to human subjects.**

Stroke is the leading cause of long-term disability [1] costing an estimated $38.6 billion a year [2] and stroke-related disability is becoming more prevalent [3], even as overall rate of stroke is in slight decline. Recent evidence indicates that the brain can remodel after stroke, even years later, through neuroplasticity (including changes in excitability and synaptic strength) and synaptogenesis [4-6]. Behavioral remodeling also occurs and allows compensatory movement patterns to accomplish

task goals [7-9]. Interventions incorporating strategies of task specificity, challenge, and repetition appear to be key factors in promoting these two types of remodeling and are central elements in rehabilitation of motor weakness following stroke [11]. Since our initial project period, the value of robot-assisted therapy to improve upper extremity function has become more established but there are still questions about many aspects of implementation, including patient selection, dose, and type of treatment [12]. There are two basic types of rehabilitation robots, *endeffector*, in which the patient engages with the tip of the limb, and *exoskeleton*, in which a powered framework encloses the limb. Both types have demonstrated efficacy [13] with some potential advantage in full use of exoskeleton capabilities in training joint coordination [14], and we have used both types in our ongoing study. Robot-assisted and other types of upper extremity treatment studies in chronic stroke report relatively modest *average* gains in motor function that typically fail to translate into meaningful change in everyday use of the paretic arm [15]. This has prompted us to directly address issues of predicting response, promoting and measuring translation to daily use and determining optimal scheduling for that therapy. Therefore, there is now a critical need for research that: 1. predicts response to hybrid robotic and functional task oriented therapies in chronic stroke and 2. determines the brain mechanisms of response to such therapies so that we better understand why such therapies work for some, but not all, stroke survivors.

5.0 * **Describe the overall significance of the research in terms of the problem to be studied and potential findings, as well as its relevance to the care of veterans, the VAPHS, and the VHA:**

Importance and Impact

The primary purpose of the current proposal is to externally validate predictors of response to Robot + TTT (transition-to-task) therapy in the chronic stroke population. By doing so, we will validate biomarkers and algorithms for a predictive model to guide matching of patients to a therapy based on residual neural and motor function and other measurable factors. We have been contributing to understanding the mechanisms of recovery specifically by relating baseline clinical, neurophysiological and kinematic markers to functional outcomes. We are now proposing to go beyond this contribution by measuring specific changes in connectivity of the primary motor cortex, the hub of voluntary movement function in the human brain.

While we, and others, have as a goal personalized treatment during the *sub-acute* period when spontaneous recovery, optimal neuroplasticity and available rehabilitation coincide, the field has been turning to **chronic** populations for a few reasons. First, doing so addresses the problem of an exponential growth in individuals aging with disabilities from stroke. Strokes are occurring earlier in the lifespan [16] and individuals live longer with stroke [17] therefore causing increased costs to society as a public health concern as well as increased costs to the individuals who face more years with a lower quality of life. Since it is known that neuroplasticity continues across the lifespan [18] and that rehabilitation can be effective years after the stroke e.g. [19], validating biomarkers and algorithms that best *match individuals with a specific therapy will maximize recovery of function and reduce health care resource utilization over the long term*. *Second, providing further evidence*

for optimal use of robotic therapy in the chronic period may provide an impetus for the installation of robots and other arm exercise programs into health clubs and veteran's service organizations where rehabilitation and exercise can usefully combine.

Impact on Health Care Delivery for Veterans:

The long-range goal of the proposed work is to meet the Department of Veterans Affairs Strategic Plan 2014-2020 listed objective 1.1 and create evidence-based rehabilitation methods for veterans with stroke related upper extremity hemiparesis that focus resources more efficiently. Prevalence of stroke-induced disability in our veteran population is expected to rise since 64% of the population is aged 55 or older [20]. Robotic devices provide a cost-effective method to automate parts of therapeutic practice, allowing more efficient use of therapist time while providing high doses of training [21]. We expect that the results from this study will validate and possibly refine our method for choosing the Robot + TTT rehabilitation technique during the long period following sub-acute recovery. It will also bring insights for the science of predicting outcomes and optimally matching therapeutic techniques in this period. While use of robotic training is a key part of the treatment in this trial, we take steps toward generalization with the use of an advanced robotic rehabilitation system piloted in the current study. Inclusion of an exoskeleton robot is also in line with the RR&D service's call for studies of such devices.

6.0 Please upload any additional documents:

Name	Version
There are no items to display	

ID: Pro00003161 View: 2.1 Required Reviews

Required Reviews

1.0 **Type of Submission:**

New study

If this is a 'New Paper Conversion' please include the MIRB Number:

Please upload a letter certifying that you have made no modifications or amendments in converting this research study from paper to electronic:

2.0 * **Requested Review Type:**

Name
◯ Exempt
◯ Expedited
◉ **Full IRB Review**
◯ Not Human Subject Research

3.0

	Please check which of the following Service Lines/Departments/Entities will be impacted or used in the conduct of this study	**Upload Letter of Support**
☐	Clinical Support	
☐	Medical Specialty	
☐	Investigational Drug Service	
☐	Imaging	
☐	Community Based Care	
☐	Patient Care Services	
☐	Behavioral Health	
☐	Primary Care	
☐	Surgical Specialty	
☐	Critical Care	
☐	Clinical Trials Center	
	☐ Regulatory Coordinator Support Core	
	☐ Clinical Coordinator Support Core	
	☐ Ancillary Support Core	
	☐ Data Support Core	
☐	Research Registry Registry Number:	
☐	Other	

If Other, please specify:

ID: Pro00003161 View: 3 Research Design

Methods & Procedures

1.0

* **Does this research study involve any of the following:**

Name	
Deception	☐
Interview/Focus Groups	☐
Use of Drug, biological, or nutritional (e.g., herbal or dietary) supplement (investigational or FDA approved)?	☐
Use of medical devices	☑
Prospective Analysis of Specimens	☐
Banking of Specimens-Data	☐
Retrospective use of specimens	☐
Audio/Video Recordings or Photographs	☐
Honest Broker or other similar service	☐
None of the Above	☐

ID: Pro00003161 View: 3.4 Use of Medical Devices

Medical Devices

1.0 * **Specify all devices used on this study:**

Device Name	Manufacturer	Use of Device	IDE Number (if Applicable)	Device Brochure	Description of Use	Risk Level Determined by Sponsor
The MagStim 200	MagStim	FDA Approved but used in unapproved way				Non-Significant Risk

2.0 * **Describe your plan for storage and control of devices:**

The device will be stored in a secure laboratory environment only accessible by research study staff. Use is restricted to individuals who have been educated and trained.

ID: Pro00003161 View: 4 Research study methods

Research Study Methods

Describe all study related procedures following enrollment of a subject in this study.

Please see Section 6 for where the study team defines when a subject will be considered enrolled in the study.

1.0

*** Research Procedures/Interventions:**

After obtaining informed consent and a review of medical records, participants will be seen for a neurological exam visit by the PI and initiation of study evaluations.

All baseline testing will occur within a 6 week time frame and will include 2 separate baseline functional upper extremity outcome evaluations and one baseline robot evaluation with the rehabilitation robots in measurement mode for quantitative measures of upper extremity kinematics and strength. If participants have differences in Fugl-Meyer scores greater than 2, one additional baseline may be administered to establish the more stable result with only two baseline datasets used for analysis. On all participants who do not have any TMS or MRI medical exclusion criteria one baseline TMS evaluation and one baseline MRI will occur.

After completion of the baseline evaluations, the intervention phase of the study will begin. During this time, participants will complete a total of 36 intervention sessions of Robot +TTT training. These will occur 3 times per week for 12 weeks. If scheduling conflicts arise, changes will be allowed with sessions occurring up to 4 times per week but will not exceed 18 total weeks. The intervention sessions will be one hour in duration. During each session, participants will complete 45 minutes of robotic intervention followed by 15 minutes of TTT. Participants will progress through 3 robot programs sequentially with 12 sessions focused on distal upper extremity function, 12 sessions focused on proximal upper extremity function and the final 12 sessions alternating between a distal and proximal focus. Functional outcome and robot evaluations will occur after each robot block, at final training, and at a 12 week retention follow-up. On all participants who do not have any TMS or MRI exclusion criteria one TMS evaluation and one MRI will occur after final training. Also, one TMS evaluation and one MRI will occur at the 12 week retention follow-up. The retention follow-up visit must occur within 4 weeks of when it is due. All procedures are routinely done within clinical practice.

Baseline/Outcome evaluations:

Upper extremity measures and evaluations will consist of: the Fugl-Meyer Upper Extremity Motor Assessment (FMA), the Wolf Motor Function Test (WMFT), Stroke Impact Scale (SIS), Action Research Arm Test, isometric strength and range of motion evaluations of the shoulder, wrist, thumb, and grip. The *Activity Monitor* wearing schedule will occur at baseline (3 days), and post-training.

The Fugl-Meyer Upper Extremity Motor Performance Section Test:

Selected because it assesses impairments and has been shown to be valid and has high inter-rater reliability and test/retest reliability [46]. In particular, it correlates well with interjoint coordination measures in the UE of stroke patients [47]. The Fugl-Meyer [48] has been shown to be both internally and externally valid. According to Duncan et al., it is probably the most widely known scale of motor recovery after stroke and can be considered a *gold standard* for motor impairment measures [49] but its relationship to task performance is not clear. It is a primary outcome variable because it measures impairment and we can it compare to other studies.

The Wolf Motor Function Test:

Selected because it measures functional capability in terms of performance time, quality of movement, and ability to hold weight. The test appears to be more sensitive than other UE tools such as the Frenchay Arm Test and is commonly used in the CI studies of UE rehabilitation. It has high interrater reliability, high test-retest reliability and good concurrent validity with the Fugl-Meyer with patients who have mild deficits [50]. It has been modified for use with moderate to severely impaired patients [51] and streamlined to reduce testing time [52]. The time measure is the primary variable used because it continuously measures functional ability and we can compare to our previous work and other studies.

Stroke Impact Scale (disability):

The short version of this test contains 50 questions and is designed to assess changes in impairments, disabilities and handicaps following stroke [53]. This tool assesses physical, mental, and emotional changes that occur as a result of stroke and that can contribute to a change in quality of life. The Stroke Impact Scale has been tested for and found to be reliable, valid, and sensitive to change in the stroke population. The hand domain is a primary variable because it measures participation in daily life and captures the addition of TTT to robot training.

Action Research Arm Test:

This has been suggested to be more responsive in chronic stroke than the Fugl Meyer and is also more rapid to administer [54, 55]. It is included for comparison to other studies and because we expected it to have neither floor nor ceiling problems in the target study population. Our experience so far has confirmed this. However, it is not the primary outcome variable because it has not been as sensitive to change as the FMA.

Isometric strength and range of motion:

Manual muscle testing is done for finger extension and shoulder abduction and grip strength is measured with a Dynamometer. The hand-held dynamometer has been validated for use on stroke patients. Active and passive range of motion is collected using standard goniometry. Shoulder (flexion/abduction), wrist (extension), and thumb opposition are tested.

KINARM and finger load cell evaluations.

A set of standard sensory, motor, and cognitive-motor evaluations will be performed. These tests, which have been normed, will provide multiple secondary outcomes. They will relate connectivity measures and unimanual function to bimanual sensorimotor function. Since the KINARM only allows shoulder-elbow movement, finger movements will be evaluated using a custom-made load-cell array developed by Dr. Collinger. Due to altered finger biomechanics, we may not be able to collect data from a subject's impaired hand with the custom load-cell device at baseline. For these individuals, we will not collect this data at future testing time points.

Physical Activity Monitors of arm use:

To complement the self-report measures of using the paretic arm in daily life, we will continue to use low cost, portable 3D accelerometers (ActiGraph, Pensacola, FL) to objectively quantify arm movement. Such accelerometers have good rater and test-retest reliability [56, 57] as well as sensitivity to change and convergent validity with standardized measures of impairment, performance and activity (see [58, 59] for recent reviews). We will coach the participant and caregiver on how to attach and detach a sensor to each arm before allowing them to leave our facility and return in 3 days at baseline, after training and at retention. The schedule will be Monday-Thursday or Tuesday-Friday to avoid the weekend (potentially more variable within/between participants). Arm use will be collected and classified in 1-second epochs, summed over 24 hours and averaged over the three days using an established

software program. Reporting a ratio of paretic to non-paretic arm use will reduce the effect of mobility activity such as walking that provides common kinematic drive to both arms. The results of accelerometry analysis will be correlated with the measures of functional assessment using the Fugl-Meyer, WMFT and SIS-hand domain.

TMS Outcomes

Transcranial magnetic stimulation of the motor cortex is performed using a MagStim 200 Magnetic Stimulator (MagStim Ltd., Wales, UK) to assess changes in brain physiology and MEP in arm muscles. Surface electromyography (B&L Engineering, Santa Ana, CA) is used to record muscle activity from three muscles (first dorsal interosseous [FDI], extensor carpi radialis [ECR], the anterior deltoid [AD]) on both the paretic and non-paretic arms. SIGNAL (CED, Oxford, UK) scripts are used to drive single pulse TMS and collect simultaneous EMG data through a Power 1401 (CED) system. TMS sessions are completed at three time points: baseline, post-training, and at the 12-week follow-up visit. Soft foam earplugs are inserted into each ear canal for hearing protection.

Prior to the initial TMS session, a skin and whole-brain reconstruction are created from the participant's high resolution anatomical MRI scan, using neuronavigation software (BrainSight, Rogue Research, Montréal, QC, Canada). The hand knob in each hemisphere is identified from the anatomical scan and used as the center point for hotspot grid (described below). The neuronavigation software records three-dimensional coordinates of each TMS stimulation site, measured using an optical digitizing device (Vicra, Northern Digital Inc.). Thus, this technique ensures reproducible locations at each session.

MRI Evaluation:

Participants will lay down and be positioned in the scanner by MRRC staff with supervision from study staff. They will be given a device to communicate any discomfort to staff and the procedure can be paused or discontinued at any time. The MRI procedure will take approximately 1.5 hours. The MRI facility is located at the UPMC MR Research Center. It consists of two 3T Siemens Prisma scanners.

A high resolution MPRAGE (TE 3.44 ms, TR 2250 ms, T1 900 ms, flip angle 9°, 1.5 mm isotropic voxels) will be obtained. Two resting state BOLD (T2*) scans will be obtained, with TE=30 ms, TR = 2000 ms, FOV=220mm, resolution=64X64 with 36 4 mm axial slices over 10 min to yield 380 volumes each. Diffusion tensor images for fractional isotropy (FA) analysis will be obtained using the most up to date Siemens protocols to maximize resolution and will be optimized for determination of FA rather than tractography. An ROI and seed based method will be used to determine the FA value for the posterior limb of the internal capsule on each side and a voxel -based correlation of a seed in the arm area of the primary motor cortex with the rest of the brain. A Z transformed score for mean correlation of the seed ROI with the rest of the brain will be obtained and will serve as a variable for the prediction model. This will also lead to an exploration of the relationship of this connectivity measure with lesion and function. Volumetric data will be normalized and right hemisphere strokes mirrored so that all images are in the same space, with the affected hemisphere on the left. But the ROI and seed-based approaches will be carried out in individuals to avoid most of the blurring effects of normalization. The spatial normalization itself will be purely linear affine transformations, with masking of large lesions to reduce normalization error. An atlas- based approach to the internal capsule and primary motor cortex UE representation will be used (e.g. WFU Pick-atlas, Maldjian et al., 2003, NeuroImage 19, 1233 9.) In general we will use a combination of

public domain tools for image analysis, include AFNI, SPM, FSL, and MRIcron, all listed at http://www.nitrc.org.

INTERVENTION (Robot + TTT)
All participants will be enrolled in the same intervention: Robot + TTT. The intervention proposed will be completed 3x/week for 12 weeks. The training progression will be sequential with 12 sessions focused on distal upper extremity function, 12 sessions focused on proximal upper extremity function and the final 12 sessions alternating between a distal and proximal focus. Participants will perform robot training on an FDA-approved robot for 45 minutes followed by 15 minutes of TTT practice to complete their 60 minute intervention session.

Transition to Task Training (TTT):
Participants will receive robotic training in the sequence described above. The intervention session will be 60 minutes long; however, 15 minutes will focus on TTT. This transition to task training is functionally based within four domains of real world tasks: homemaking, hygiene, feeding and dressing skills. Two tasks are designed for each session and they are matched to the patient's type of robot therapy (wrist or shoulder/elbow) as well as to their severity level.
The task design is progressive in nature with difficulty added by changing the parameters and demands to promote generalization. The tasks are performed with the participant sitting for tabletop activities with therapist supervision to prevent substitution and promote the use of available arm motor control and motion for a more normal reaching pattern. The minimization of compensatory trunk movements during reach-to-grasp movements has been shown to improve inter-joint coordination and active arm joint ranges in patients with hemiparesis due to chronic stroke The TTT activities proposed include tasks that promote both stabilizing and active use of the hemiparetic upper extremity. Active arm tasks however will be emphasized more than stabilizing tasks.

Please upload a table of procedures if applicable.
The study procedures table must be completed for:
- All Greater than Minimal Risk (GTM) studies; and
- All Minimal Risk studies that use Standard of Care or Usual Care/Interventions.

Name	Modified Date
Study Procedures Table	7/15/2019 1:19 PM

2.0 * **Will Usual Care Procedures/Interventions be used?"**
○ Yes ◉ **No**

If yes, please specify and include a description of what the usual care or expected level of care is at VAPHS (e.g., medications, testing, timing, etc.) for patients, similar to those individuals that meet the inclusion/exclusion criteria for this research study:

2.1 If Usual Care Procedures/Interventions will be used, who is the individual or entity responsible for relevant aspects of the usual care (i.e., which of the above usual care activities will the research study team be responsible for)?:

2.2 Does the usual care at VAPHS for the condition of interest in this research study differ from national guidelines/recommendations (i.e. standard of care)?

○ Yes ◉ **No**

If yes, please describe the differences:

2.3 Are any procedures that are considered standard for this patient population performed more frequently than usual care?

○ Yes ◉ **No**

If yes, please indicate which time points are considered usual care and which are considered research.

2.4 If there is more than one standard, does VAPHS limit which one is followed (e.g. warfarin use for atrial fibrillation vs. one of the newer anticoagulants).

○ Yes ◉ **No**

If yes, please explain:

3.0 * **Does clinical expertise need to be enlisted?**

○ Yes ◉ **No**

If yes, please provide the provisions for enlisting the services of a clinician with appropriate expertise and privileges to perform duties, if the investigator is not a clinician [i.e. reviewing the data, adverse events, and new study findings; also making required decisions to protect the health of the subject (e.g., stopping the participant's involvement in the study or determining when to notify the subject or the subject's health care provider of information that may affect the health of the subject)]:

4.0 **Please upload any surveys, questionnaires, and data collection forms.**

Document	Description	Version Number
View ARAT Scoring(0.01)		0.01
View Demographics(0.01)		0.01
View Dynamometry and ROM Scoring(0.01)		0.01
View Finger Assessment Form(0.01)		0.01
View Fugl-Meyer Scoring(0.01)		0.01
View Inclusion Exclusion Checklist(0.01)		0.01
View Medical History Form(0.01)		0.01
View Stroke History Form(0.01)		0.01
View Stroke Impact Scale(0.01)		0.01
View Wolf Scoring(0.01)		0.01

ID: Pro00003161 View: 4.1 Research study methods: analysis Plan

1.0 * **Please describe the analysis plan for the study** *(it is acceptable to refer to the sponsor/multi-site protocol for section if applicable):*

Analysis Plan for Aim #1.

We will determine the receiver operating curve (ROC, sensitivity vs 1-specificity) of the predictive model for the primary outcome, a (positive) change in FMA of greater than four points at 12 weeks. (A five-point change in FMA is a MCSD [34].) The ROC will be compared to the SRT4 model [35]. With our proposed sample size of 64 subjects and 12% attrition rate, we expect to have 57 subjects completing the study, a validation set of similar size to the original set from which the model was derived.

Further analysis, validation and refinement of the predictive model will be performed using the random decision forest technique [36]. This would also result in an algorithm like the PREP [30] that can be used for step-wise decision-making about embarking on the 12-week program of robot+TTT.

Analysis Plan for Aim #2.

The primary analysis with be correlation between change in physiological parameters (e.g. affected M1 connectivity, recruitment curve slope) and change in FMA. Analysis of H-reflex changes will be compared to recruitment curve changes to rule out a general change in lower motor neuron excitability. Secondarily, there will be correlations of these parameters at baseline with baseline motor function measures. A more detailed analysis of the MRI data will also examine individual interregional connections to determine whether any of them are more sensitive to the intervention than others. There will be exploration of whether the predictive model also predicts changes in physiological measures, which could lead to more efficient studies in the future.

ID: Pro00003161 View: 5 Sub-Studies

1.0 * **Is there a sub-study or are there sub-studies associated with this study?**
There is no sub-study associated with this study.

ID: Pro00003161 View: 6 Study Population Summary

Study Population Summary

1.0 * **What is the maximum number of subjects you plan to enroll at VAPHS?**
80

2.0 * **Do you plan on enrolling patients into different categories:**
○ Yes ◉ **No**

If yes, please explain:

3.0 **If this is a multi-site study, indicate the projected total subject accrual:**
70

4.0 * **Please provide a justification for the sample size:**
Based on our record of recruitment and design feasibility, we propose to enroll 64 participants. Our current 12-week study has an attrition rate after enrollment of 12% so we anticipate completing about 57. We verify that with our sample size of 57, we will be able to estimate the area under the Receiver operating characteristic (ROC) curve (AUC) with an adequate precision (that is, the standard error is reasonably small). The AUC is an important measure to describe the performance of a predictive model for a binary outcome such as the change in FMA of greater than 4. The table below displays the standard error (SE) of the estimated AUC for several values of the true AUC and different prevalence of responders [10]. The SE is less than 0.07 in all cases except when AUC is 0.7 and the proportion of responders is only 33%. (This is the current situation in the preliminary analysis, providing an upper bound on our AUC measure.)

For Aim #2, which is based on correlations, a sample size of 57 would allow detection of Pearson correlations $r > 0.365$, which is comparable to individual correlations found in the Robot Biology study, assuming alpha = 0.05, beta = 0.2 [41]. This was confirmed by the Statistics Core using that data and PASS (v14.0) software.

ID: Pro00003161 View: 6.1 Study Population

Study Population

1.0 * **Check all that apply to describe your study population:**

Study Population
☑ **Non-Veterans**
☐ Special Populations
☑ **Veterans**
☐ Vulnerable populations
☐ Other

2.0 * **Indicate the inclusion criteria for enrollment:**

1. Clinically defined, unilateral, hemiparetic stroke with radiologic exclusion of other possible diagnosis
2. Stroke onset at least 6 months before enrollment
3. Present with Mild/Moderate to Severe arm dysfunction (based on Fugl-Meyer scores of 10 to 45)
4. Be medically stable to participate in the study
5. Be English speaking

3.0 * **Indicate exclusion criteria for enrollment:**

1. Unable to give informed consent
2. Have a serious complicating medical illness that would preclude participation.
3. Contractures, orthopedic problems, or other impairments that would interfere with the interventional training or limit the range of joint motion in the potential study arm
4. Visual loss such that the subject would not be able to see the test patterns on the robot computer monitor
5. Botulinum toxin to study arm within four months of baseline testing or if received during the study period
6. Unable to comply with requirements of the study
7. <21 years of age
8. Enrollment in another greater-than-minimal risk study
9. Presence of medical condition or implant that prevents safe administration of TMS (history of seizures, and/or currently taking any of the following medications: lamotrigine (Lamictal), levetiracetam (Keppra), oscarbazepine (Trileptal), topiramate (Topamax), phenytoin (Dilantin), arbamazepine (Tegretol), valproic acid (Depakote), phenobarbital (Barbita, Luminal, Solfoton) and/or metallic implant in the head and/or neck area including aneurysm clips or coils, stents, deep brain stimulators, electrodes, shrapnel/bullets, facial tattoos with metallic or magnetic-sensitive ink) or MRI. If participants have a medical condition or implant mentioned above, this only makes them ineligible for TMS and/or MRI, not for other parts of the study.
10. Pregnancy

4.0 **If there are any age, ethnic, language, or gender-based exclusion criteria, including the exclusion of any pregnant or lactating women, or those of child-bearing potential, please provide justification:**

Participants must be English speaking to ensure that all study procedures and interventions are understood and performed safely.

5.0 **Please specify why vulnerable subjects and/or special populations will not be enrolled:**

6.0 **With some exceptions as listed in VHA Handbook 1200.05, incompetent subjects cannot be enrolled in VAPHS approved research. Specify that you will not enroll incompetent subjects and the general rules to be used in making that determination:**

Incompetent subjects will not be enrolled in this study because they would not meet the inclusion/exclusion
criteria for the study.

ID: Pro00003161 View: 6.1.1 Non-Veterans

Non-Veterans

1.0 * **Target number of participants:**
25

2.0 * **Describe why you cannot complete enrollment in this study without the use of Non-Veterans:**
As stated in our study objectives, our long-range goal is the prescriptive application of intensive task practice to individuals who have suffered a stroke, maximizing the cost-benefit ratio. Our predictive model must be validated with a large and heterogeneous group of subjects having varied demographics, functional status and neurophysiology. Considering the inclusion/exclusion criteria, it is possible that we would not recruit a sufficient number of veteran subjects required to complete the proposed study in accordance with 38 CFR 17.45 and 38 CFR 17.92. For eligible subjects, their stroke must be their main health deficit. Participants may be excluded from the study if they have orthopedic and/or joint problems in the arm affected by their stroke. They cannot have any other injuries to the brain such as traumatic brain injury diagnosis. Therefore, we will recruit non-veteran subjects in order to achieve our goal of validating our predictive model. Nearly 40 subjects have completed the previous version of the study without any major study-related adverse events, therefore we expect future participants will have a low likelihood of injury from the study procedures.

According to the CDC, 795,000 Americans have a stroke every year. Only 15,000 of those are US Veterans. This is 1.89% of the total number. During recruitment for other studies in our lab, only one individual out of the 19 screened was a veteran. Stroke research is, however, very relevant to present and former military personnel and should be pursued. By including nonveterans, this will allow for a larger subject pool which will increase the strength of the study statistically speaking. We will make every effort to actively recruit veterans into this study, including posting of approved advertisements at VAPHS, staffing recruitment tables at VA Research Week events and requesting direct referrals from VA staff. The PI of the study is a practicing neurologist at VAPHS and may provide information about the study to patients.

The long-range goal of the proposed work is to meet the Department of Veterans Affairs Strategic Plan 2014-2020 listed objective 1.1 and create evidence-based rehabilitation methods for veterans with stroke related upper extremity hemiparesis that focus resources more efficiently. By increasing our sample size, the inclusion of non-veterans will help us to validate evidence-based treatment methods for the veteran population.

The goal of our study is the prescriptive application of intensive task practice to individuals who have suffered a stroke. Once we have validated this predictive model, it can be directly utilized in the rehabilitation plans for veterans who have had a stroke. By establishing a larger, more heterogeneous subject pool with the inclusion of non-veterans, the statistical strength of the study will increase, which will improve the prediction ability of the model.

Please upload the Inclusion of Non-Veterans Worksheet here:

3.0 * **If your study is a clinical trial, please indicate where the VHA Notice of Privacy Practices (VA Form 10-0483) will be stored once signed:**
This form will be stored in the secured file room in the VA Human Engineering Research Laboratory at Bakery Square.

ID: Pro00003161 View: 7 Risk/Benefit Assessment-Risks

Risk/Benefit Assessment-Risks

1.0 * **Risk classification for this study (select one).**

Name

- ○ Minimal Risk
- ◉ **Greater than Minimal Risk**

2.0 * **Basis for making the above recommendation:**

Transcranial Magnetic Stimulation is categorized as a greater than minimal risk procedure by the VAPHS.

3.0 * **Describe the safety precautions that will be taken to minimize risks/harms:**

There are potential risks associated with some of the procedures included in this study. However, the procedures have been planned by the investigators to minimize the danger of any major complications. All study procedures will be supervised by qualified personnel who will carefully monitor the participants. All participants will undergo a medical and history interview with the PI at entry into the study to assure that it is safe for them to participate.

1. Risk of injury by the robot. The possible injuries from a malfunctioning robot include bruises, pinching, strain, lacerations, dislocations, or bone fractures. The robot has not caused dislocation or bone fracture in any of our ongoing robot studies. The risk of injury is minimized by the design of the robot allowing the participant to stop it as well as oversight by a staff member who can also stop the robot if there is any potential for injury.

2. Risk of injury from TTT. The is minimal risk of muscle fatigue and/or soreness, and joint pain, from the repetitive exercise. In order to minimize this risk the participant will be supervised throughout the activity and given rest breaks as needed. The participant will be made aware that they can stop the task at anytime.

3. Seizures. Transcranial magnetic stimulation at low frequency (< 1 Hz) has been used for over 30 years in a variety of normal subjects and in subjects with neurological conditions and has generally been found to be safe. In a review of 38 studies involving 850 subjects, there were no seizures or other major adverse events (Gilbert et al. 2004). For non-neurologically impaired subjects and for subjects with stroke, the risk is considered minimal. Although TMS is not used in subjects with implanted metallic devices, it is thought to be safe in patients with hydrocephalus and ventricular shunts. Although high-rate, repetitive TMS has the potential to induce seizures (Wassermann et al. 1996), TMS rates of 0.2 Hz or less are safe in epileptic patients and even higher rates may have a protective effect in the case of intractable seizures (Tergau et al. 1999). ONLY rates < 0.2 Hz will be used in this study.

4. Discomfort. 1000 TMS stimuli are an upper limit that will not be exceeded during any session. Usually, it will be far fewer stimuli provided. But in any case, this number (1000) of stimuli not likely to be stressful or uncomfortable, as they are spread out over time. There is no cumulative effect, besides potentially a slight headache. The participant may always ask for a break, and if this is done in between mapping different locations, causes no loss of validity of data collection. Since the investigator is literally inches away from the participant, participant comfort is monitored closely.

5. The risk of hearing loss from the MRI scanning is minimized by having the subject wear earplugs or headphones. If a subject feels anxiety in the scanner, they will be removed from the scanner. For those participants who have an MRI that reveals a potential condition, previously unknown, having the MRI may lead to further medical work up. This is likely beneficial, as a condition may be revealed earlier in its course than it otherwise would have been, but may cause psychological distress to the participant. The MRI will be reviewed by the PI, a neurologist experienced in reading brain MRI, and any need for follow up will be communicated directly to the participant.

7. Breach of confidentiality. To minimize risk all files and information is maintained in a locked file

cabinet in the study coordinator's locked office or the Principle Investigator's office.

8. There are also general risks associated with using any piece of equipment and with any exercise involving moving, standing, sitting, or lying in place for prolonged periods of time. These risks include skin wounds like abrasions, bruises, or irritations; body stiffness, soreness, aches, and trembling; and general symptoms like upset stomach, chills, fatigue, mood changes, lightheadedness, and dizziness. The subject will be monitored by a staff member while using any equipment and will be encouraged to voice any discomfort or fatigue to the study staff to take appropriate breaks and precautions as needed.

4.0 * **Provide details regarding the nature of each risk using the area provided below:**

	Risk Name
View	Intervention and Testing
View	Data Collection -Confidentiality

5.0 * **Do you plan on using the research answering service:** (●) **Yes** ( ) No

If yes, please Upload the research answering service form:
Answering Service Form(0.01)

6.0 **If your study involves a treatment or intervention, please upload the Patient ID Card:**
Subject ID Card(0.01)

ID: Pro00003161 View: 7.1 Risk/Benefit Analysis-Potential Benefits and Alternatives

Risk/Benefit Analysis-Potential Benefits and Alternatives

Describe any potential for benefits to participants in this study:

1.0 * **Direct and Indirect Benefits to Subjects:**
There may be no direct benefit from participation in this study but they will receive many sessions of arm rehabilitation that has previously been shown to be effective in improving arm function. Subjects may receive indirect benefit given that they are contributing to medical science or helping to advance future understanding of rehabilitation after stroke.

2.0 * **Describe alternatives (research or non-research) that are available to subjects if they choose not to participate in this study:**
Participation is voluntary and the alternative is not to participate.

ID: Pro00003161 View: 8 Methods of Recruitment and Retention

Recruitment Methods and Materials used for Retention

1.0 * **Select recruitment methods used on this study:**

Name	
☐	Mail Campaign
☑	**Referral by independent source**
☑	**Advertising such as fliers, letters, or ads (newspaper, TV, radio)**
☐	Web Site
☑	**Research registry**
☑	**Selected from pre-existing records**
☑	**Pre-existing relationship with participants**
☐	Other

If Other Methods Specify:

2.0 * **Specify how subjects will be identified and how study eligibility will be determined:**
Recruitment will occur from within the VAPHS through the neurology and rehabilitation clinical services as well as the University of Pittsburgh Medical Center (UPMC). Two primary mechanisms will be used:

1. The Western Pennsylvania Patient Registry (Pitt IRB# PRO07080061) will be used as a recruitment mechanism. This registry draws from patients admitted to the UPMC Stroke Institute, and area rehabilitation hospitals plus ongoing contact from Stroke Survivor Support Groups. The purpose of the database is to provide a way to contact appropriate patients to discuss possible inclusion in research projects. Our investigators will inform the database coordinator of any recruitment through the database and of any requests to opt out. All information will be kept confidential. The database is maintained by the Co-Directors who are University of Pittsburgh and Carnegie Mellon University professors.

2. UPMC Department of Physical Medicine and Rehabilitation (Pitt IRB #12030122). All registry participants have provided informed consent to be contacted for future research studies. The IRB approved flyer for this study will be provided to the registry investigators to distribute to potential subjects according to the procedures established in the registry IRB approved protocols. In response to the flyer, potential subjects will directly contact the research team if interested in participating.

Veteran participants may also be identified through screening medical records in CPRS and/or VISTA. To identify potential participants, we would do a search for a diagnosis of stroke over 6 months ago and identify which VA clinics the individual attends. We may then contact providers so that information about the study can be passed along to the potential subjects. We will also regularly provide study pamphlets to VAPHS rehab supervisors for electronic distribution on their "Rehab Recap" email listserv. Physical and occupational therapists can then identify appropriate Veteran patients that may be candidates for the study and provide them with information. In addition we may staff recruitment tables at VAPHS Research Week events, providing written and verbal study information directly to Veterans. VA researchers who attend Stroke Rehabilitation Research Network quarterly meetings may also be approached directly regarding potential participants appropriate for this study. Study pamphlets will also be placed at the University Drive campus registration desk area.

Potential participants will receive the study pamphlet where brochures are displayed at the VA Human Engineering Research Laboratories, and areas where brochures are displayed at the Rehab and Neural Engineering Labs on the University of Pittsburgh campus. The study pamphlet may also be distributed at local stroke support groups.

A phone pre-screening will be administered to determine potential study eligibility. After written consent is obtained, eligibility will be formally determined based upon the inclusion/exclusion criteria.

3.0 * **Provide the location (or locations) of the sites where participants will be recruited:**
VPAHS, HERL- Bakery Square, UPMC, RNEL/ RAFT Labs, University of Pittsburgh, off-site recruitment events (stroke support groups, public speaking events by staff, etc.)

4.0 **Please include information regarding any advertisements (print, TV, radio, etc) that will be used to recruit subjects including a general description of where this information will be posted:**
Our approved study pamphlet has been uploaded in question 5.0. This will be posted at VPAHS, the VA Human Engineering Research Laboratories, and areas where brochures are displayed at the Rehab and Neural Engineering Labs on the University of Pittsburgh campus. The study pamphlet may also be distributed at local stroke support groups/events to provide information to individuals interested in research participation.

5.0 **Please UPLOAD the documents that will be used for recruitment and an introductory statement or letter to accompany consent for those studies obtaining written informed consent using methods such as fax, email or mail (if applicable). Please also upload any screening/recruitment questions that will be verbally asked of potential research subjects. Also, if you will be providing any retention materials, please upload them here.**

Name	Reviewer	Modified Date	Version Number
Public Affairs email	Boos, Amy	9/20/2019 10:09 AM	0.02
Study Pamphlet	Boos, Amy	9/20/2019 10:09 AM	0.02

ID: Pro00003161 View: 9 Informed Consent

Informed Consent

1.0

* **Indicate the types of consent that will be involved in this study (check any or all that apply):**

Informed Consent Category
Written/signed consent by subject
Waivers are being requested.

2.0 * **Waivers: If you are applying for any waivers of consent (check any or all that apply):**

	Name
☐	Waiver of Informed Consent
☑	**Waiver of HIPAA Authorization**
☑	**Waiver of Documentation of Informed Consent (telephone consent, verbal script)**
☐	No Waiver at all

3.0 * **Will this study include non-English speaking participants?**

○ Yes ◉ **No**

ID: Pro00003161 View: 9.1 Waiver of HIPAA

You have indicated you are requesting a waiver of HIPAA.

1.0 * **Is the request only for Screening/Recruitment purposes?**

◉ **Yes** ○ No

If yes, please describe your screening/recruitment method:
We will use a phone screening script to explain the study and ask eligibility questions over the phone. The waiver is for the verbal screening and review of medical records after verbal consent.

If no, the request is for the full study (e.g. retrospective chart reviews and certain observational studies)

Please describe the types of records and/or databases to be accessed:
We will access the discharge summary and MRI report from when an individual had their stroke relating to the current study.

THE IDENTIFIABLE INFORMATION BEING REQUESTED:
Note: If participants will be receiving payment and HIPAA Authorization is not being obtained, you must select Names, Addresses and Social Security Numbers as that information will be disclosed for payment purposes.

2.0 * **Identifiable Information per HIPAA Definition**

Name
☐ None
☐ Account numbers
☐ Biometric identifiers, including finger and voice prints
☐ Certificate/license numbers
☐ Device identifiers and serial numbers
☑ **Elements of dates (except year, for example, date of birth, admission date, discharge date, date of death, date of procedures; and all ages over 89)**
☐ Email Address
☐ Fax Numbers
☐ Full-face photographic images or any comparable images
☑ **Geographical subdivisions smaller than a State (street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code)**
☐ Health plan beneficiary numbers
☐ Internet Protocol (IP) address numbers
☐ Medical Record Numbers
☑ **Name or any derivative of name such as initials**
☐ Social Security Numbers
☑ **Telephone Numbers**
☐ URLs (Web Universal Resource Locators)
☐ Vehicle identifiers and serial numbers, including license plate numbers
☐ Any other unique identifying number, characteristic, or code (Note: The study ID number, code or other means of record identification is not considered one of the identifiers that must be excluded for de-identification)

3.0 * **Patient Protected Health Information:**

	Name
☑	**Demographic Information (e.g., Name, Address, Phone Number, Social Security Number**
☐	Billing and Payment Information
☑	**Hospital or Medical Records**
☐	History and Physical Exam Notes
☐	Mental Health Records
☐	Data Previously Collected for Research Purposes
☐	Progress Notes
☐	Consultation Reports
☐	Laboratory Test Results
☐	Operative Reports
☑	**Other**

Please indicate the 'Other' Patient Protected Health Information:
Answers to phone screen

4.0 **Other Health Information:**

Name

There are no items to display

ID: Pro00003161 View: 9.1.1 Waiver of HIPAA - More Information

Waiver of HIPAA- More Information

1.0 * **Describe how the identifiable information is to be used and/or disclosed only by members of the research team and the following persons *(identify with specificity and justify the need to disclose the information to anyone outside the VHA.)* Note: If participants will be receiving payment and HIPAA Authorization is not being obtained, you must also describe this disclosure to representatives of the VA for administrative purposes here.**

Also describe how this activity meets the "minimum necessary standard" described in the HIPAA Privacy Rule:
All registry participants have provided informed consent to be contacted for research studies. Individuals will be contacted according to the procedures established in the registry IRB approved protocols. Research staff will be provided with contact information for individuals from the registry who may be eligible for the study. Recruitment materials will be sent to individuals from the registry.
Identified information will be used to screen prospective subjects for eligibility. Subjects can choose to answer the phone screening questions with a yes or no. The phone screen is performed in an effort to reduce the burden of travel on individuals who may not be eligible for the study. If an individual agrees to schedule a consent visit, then their name and contact information will be recorded.

The proposed study poses minimal risk to the privacy of the subjects because...

2.0 * **Describe how the identifiable information will be protected from improper use or disclosure by (detail how this will be accomplished including the limitations of physical or electronic access to the information and other protections):**
Registry information will not be shared with anyone not involved in the recruitment process. Information will be recorded on the phone screening paper form and stored in a locked file room with other identifiable data.

3.0 * **Describe how the identifiers will be destroyed at the earliest opportunity consistent with the research (discuss the timeframe or the reasons the identifiers must be retained, including health or research justifications or any legal requirement to retain them) (Note: At this time, identifiers used for research screening and all other screening records must be retained indefinitely and this must be documented by checking "Other" below):**
All research records will be maintained in accordance with the Veterans Health Administration (VHA) Records Control Schedule. Paper records will be disposed of using methods deemed appropriate by the VAPHS Privacy Officer, and all electronic data will be sanitized using methods rendered appropriate by the VAPHS ISO.

* **When will screening data be de-identified or destroyed:**
Name

Other
If Other, please describe:
All research records will be maintained in accordance with the Veterans Health Administration (VHA) Records Control Schedule. Paper records will be disposed of using methods deemed appropriate by the VAPHS Privacy Officer, and all electronic data will be sanitized using methods rendered appropriate by the VAPHS ISO.

4.0 * **Describe how the identifiable information will not be reused or disclosed to any other person or entity outside the VHA other than the manner described in the protocol, except as a required by law, for authorized oversight of this research study, or as specifically approved for used in another study by an IRB:**
Information (including any medical records) will remain in locked file storage as described in our protocol along with other identifiable study information. It will not be reused or disclosed to any other person or entity not directly involved in the study, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

5.0 * **Describe why the proposed study cannot be practicably conducted without a waiver of authorization: (discuss reasons why it would not be possible to obtain authorization from individual subjects. Time constraints themselves are generally not considered adequate for this justification:**

The phone screening is conducted to minimize the burden of travel for people who may not be eligible for the study. Since initial screening is conducted over the phone, providing written authorization prior to asking the screening questions is not practical. Verbal authorization also allows medical record screening which will help identify participants who may not be eligible for the study. The anticipated discomfort in answering the screening questions is not greater than what is encountered in daily life. People can choose not to answer the questions in the phone screening. If they choose not to answer these questions, we will inform them that eligibility criteria will be verified after informed consent.

6.0 * **Describe why the proposed study cannot be done without the specified identifiable information: Discuss reasons why it would not be possible to conduct the research without the identifiable information being collected.**

The phone screening is conducted to minimize the burden of travel for people who may not be eligible for the study. Since initial screening is conducted over the phone, providing written authorization prior to asking the screening questions is not practical. The anticipated discomfort in answering the screening questions is not greater than what is encountered in daily life. People can choose not to answer the questions in the phone screening. If they choose not to answer these questions, we will inform them that eligibility criteria will be verified after informed consent.

ID: Pro00003161 View: 9.3 Waiver of Documentation of Informed Consent

Waiver of Documentation of Informed Consent

You have selected a waiver of Documentation of Informed Consent

1.0 **This is a request for Waiver of Documentation of Informed Consent because this research study conforms to either A and/or B (Check if 'yes' and provide the verifying information requested):**

* A: The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern. ○ Yes ◉ **No**

AND/OR

* B: The proposed study poses minimal risk to the subjects. ◉ **Yes** ○ No

If yes, please explain why the proposed study poses minimal risks to the subjects. (Outline the subject's involvement in the project and why the study poses minimal risk) :
The anticipated discomfort in answering the screening questions is not greater than what is expected to be encountered in daily life.

2.0 * **The research involves no procedures for which written consent is normally required outside of the research context. Research procedures include:**
Questions will be asked over the phone to determine if the potential participant meets the eligibility criteria for this study.

3.0 * **Explain how whenever appropriate, the subjects will be provided with additional pertinent information (e.g. an information sheet):**
If the subject is interested in participating in the study after screening, then they will be scheduled for an in-person consent process.

4.0 **Please upload SCRIPT here:**

	Document	Description	Version Number
View	Phone Screening Script(0.04)		0.04

ID: Pro00003161 View: 9.4 Consent Forms & Process of Consent

Consent Forms & Process of Consent

1.0 Upload the completed forms into the correct lists below.

1.1 **Informed Consent Form (clean copy):**

	Document	Modified Date	Version Number
View	Consent Form(0.09)	12/3/2019 12:00 AM	0.09

1.2 **Provider Behavior Informed Consent Form (clean copy):**

Document	Modified Date	Version Number
There are no items to display		

1.3 **Screening Informed Consent Form (clean copy):**

Document	Modified Date	Version Number
There are no items to display		

2.0 **Consent Forms (modified copy):**

	Document	Modified Date	Version Number
View	ICF with tracked changes(0.05)	1/29/2020 10:45 AM	0.05

3.0 * **Describe how, where, when, and by whom the consent process will be initiated:**
Potential subjects will be provided an explanation of the purpose of the research, why they are being asked to participate, and the duration of the study. In addition, the potential participant will be made aware of any foreseeable risks associated with the study as well as any potential benefits. Potential participants will be made aware of the alternative to participation in the study and the methods used to protect the confidentiality of the records during the study. Also, subjects will be told that their participation in this study is completely voluntary and that they can withdraw at any time. Information on who to contact if they were to have any questions, concerns, or complaints about this research will also be provided. Subjects will also be asked if they understand the purpose, risks and benefits, procedures, and their rights as a research subject. Any questions the subjects have at any time will be answered by one of the listed study team members. The entire process will occur prior to obtaining written informed consent. The principal investigator or a team member of this study will be involved in the consent process described above. The consent process will take place in a private location.

4.0 * **Will you be maintaining a Master List of Subjects?**
Yes

5.0 * **Describe when the subject's name will be added to the master list and how the list will be maintained in a secure fashion.**
Only once informed consent has been obtained from the subject and it has been documented using an IRB approved consent form, will the study subject's name be added to the master list of subjects. The electronic master list will be secured in compliance with all VA confidentiality and information security requirements at \\vhapthmulherl07.v04.med.va.gov\herl\HERL Projects Wittenberg\3161.SRT5.

ID: Pro00003161 View: 10.0.0 Data Security and Privacy: Data Types Storing

10.0 Data Types Collecting and Storing

1.0 **Click the add button (below) to open an entry form to indicate the types and/or sources of the data that will be collected/stored as part of the project.**

Instructions: **For each type/source of data that will be collected as part of the project, this includes screening data, click the add button to open an entry form that lists the types and/or sources of data. Select a source/type of the data that will be collected/stored. Then indicate what, if any, identifiers or sensitive information will be collected/stored from the source/type (None is an option). To add another source/type click "OK Add Another" button to open up a new entry form to repeat the process.**

Example 1: You are collecting data from VA Medical records including names, last 4 of SSN, and addresses. Therefore, you would select "VA medical record data" as the source, and then select in the identifiers: "Name or any derivative of name, such as initials," "Social Security Numbers," and "Geographical subdivisions smaller than a State (street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code)" as the identifiers being collected.

Example 2: You are screening VA Medical Records and recording the information you use to screen (i.e.: names, last 4 of SSN, and addresses, etc.) Note: This information must be treated as a Source document, please select "Screening" as the source and then select the identifiers "Name or any derivative of name, such as initials," "Social Security Numbers,", as applicable.

*

	Data Type/Source	Collection Details	Identifiers
View	Other *Robotic Quantitative Measures*	The Armeo Power robot has the ability to precisely record a subject's performance during assisted and unassisted modes. We may use this data to provide an objective motor performance measure to augment the clinical evaluations. The KINARM robot may also be used to perform a set of standard sensory, motor, and cognitive-motor evaluations.	None
View	Questionnaires/Surveys, paper	Demographic and questionnaire data will be recorded on the attached data collection sheets by approved research staff. Subjects will be assigned a subject number for labeling the data collection sheets. Prior to data entry, all data will be reviewed for inconsistencies and checked for missing values.	Telephone Numbers Geographical subdivisions smaller than a State (street address, city, county, precinct, zip code, and their equivalent geocodes, except for the

	Data Type/Source	Collection Details	Identifiers initial three digits of a zip code) Name or any derivative of name such as initials
View	Other *TMS*	Magnetic stimulation will be performed at each examination according to the following general experimental procedure: The target muscle will be at rest during the entire procedure with the participant resting on a pillow in the lap. Audio monitoring of muscle activity is performed during the study through the EMG amplifier to ensure that muscles are at rest. Soft foam earplugs are inserted into each ear canal for hearing protection. The three dimensional coordinates of each TMS stimulation site will be measured using an optical digitizing device (Vicra, Northern Digital Inc.) with localization software (BrainSight, Rogue Research, Montreal, Canada.) This technique ensures reproducible locations at each session, without having to search for the hotspot each time.	None
View	Other *MRI*	The data will be collected and recorded at the MRRC by research staff and study staff. Data will be transferred via a VA-encrypted hard drive to the VAPHS server.	None
View	Other *Social Security Number*	Social Security numbers will be collected and then destroyed after creation of the VA CPRS health record, which is required for study enrollment and progress notes for this intervention study.	Social Security Numbers

ID: Pro00003161 View: 10.0.1 Data Security and Privacy: Social Security Numbers

10.0.1 Data Security and Privacy: Social Security Numbers

1.0 You indicated that you will be using all or some part of the research subjects' SSNs as part of this study. Which of the following will you be using:

Real Social Security numbers	*	(●) **Yes** ( ) No
Scrambled Social Security numbers	*	( ) Yes (●) **No**
Last 4 digits of Social Security Number	*	(●) **Yes** ( ) No
Other (some derivation of the SSN)	*	( ) Yes (●) **No**

If other, please explain:

2.0 * Please describe how subjects' Social Security numbers will be used in this study:
The SS number is required for CPRS documentation in this intervention study as well as for processing payment. The last 4 digits are required on the HIPAA form, which will be stored in a secure file room with other paper documents at the Human Engineering Research Laboratories. HERL is located at Bakery Square, 6425 Penn Avenue, Pittsburgh, PA 15206. The secure file room is Suite 401, Room 4103. This is a locked room inside a locked office, inside a locked suite. Documents are transported under an approved Authorization to Transport and Utilize VA Sensitive Information Outside Protected Environments form.

3.0 * Please describe the security measures that will be taken to protect SSNs.
The SS number will be destroyed after the CPRS record is created.

ID: Pro00003161 View: 10.1.0 Data Security and Privacy: Incoming Data

10.1.0 Incoming Data

1.0 * **Will data be transferred into VAPHS?**

Yes. Data is being obtained from a non-VA source and will be transferred to VAPHS

ID: Pro00003161 View: 10.1.1 Data Security and Privacy: Incoming Data - Identifiable Data

10.1.1 Incoming Data - Identifiable Data

1.0 * **Is any of the data being transferred *into* VAPHS identifiable?** ○ Yes ◉ **No**

If yes, please describe what the identifiable data is and where it is coming from:

ID: Pro00003161 View: 10.2.0 Data Security and Privacy: Outgoing Data

10.2.0 Outgoing Data

1.0 * **Will any of the data being collected/stored be transferred outside of VAPHS?**
Yes. The data will be transferred to a non-VA entity.

ID: Pro00003161 View: 10.3.0 Data Security and Privacy: Local Data Storage Types

10.3.0 Local Data Storage Types

1.0 * **How will data be stored on this project? (Select all that apply)**

On Paper

Electronically

ID: Pro00003161 View: 10.3.1 Data Security and Privacy: Local Data Storage Types - Paper

10.3.1 Local Data Storage Types - Paper

1.0 * **All VA research data collected in paper must be stored in a locked room at VAPHS. List the room number(s) and the campus(es) where data will be stored in the text box below.**

Paper documents will be stored in a secure file room at the Human Engineering Research Laboratories. HERL is located at Bakery Square, 6425 Penn Avenue, Pittsburgh, PA 15206. The secure file room is Suite 401, Room 4103. This is a locked room inside a locked office, inside a locked suite.

ID: Pro00003161 View: 10.3.2 Data Security and Privacy: Local Data Storage Types - Electronic

10.3.2 Local Data Storage Types - Electronic

1.0 * **Where is the electronic data being stored? Select all that apply.**

VAPHS Network (shared drive)

VA Encrypted VA external drive or thumb drive

Other

If "Other" please describe OR if you would like to provide additional information for clarification, please elaborate in the text box below.

Non-identifiable data may be collected and analyzed using a non-VA (Pitt) computer with any identifiable data being stored on the VAPHS shared drive. The equipment used in this study may require specific software that is available on non-VA (Pitt) computers. All data will ultimately be transferred and stored on the VAPHS network using an encrypted hard drive. All data being transferred will be non-identifiable. Access will be restricted to only those associated with this research study. Data may include kinematic, neurophysiological and robot-generated metrics.

If you selected VAPHS or VA Network (Shared Drive), please provide the name of the drive (i.e. "MySharedDriveName (\\vapthshsare) (X:)"):

\\oitpthhsmsvm200.v04.med.va.gov\Research\Wittenberg_Pro3161_PSRT5

ID: Pro00003161 View: 10.4.0 Data Security and Privacy: Reusing Data

10.4.0 Data Security and Privacy: Reusing Data

1.0 * **Will the data collected in this study be reused in other studies?** ○ Yes ◉ **No**

If yes, please describe where the data to be reused will be stored and how access to that data will be provided and monitored:

2.0 **If this research is part of a grant, please upload the Data Management Access Plan (DMAP) or Resource Sharing Plan for this study.**

Name	Modified Date
DMAP	7/15/2019 1:59 PM

ID: Pro00003161 View: 10.5.0 Data Security and Privacy: Off-Site Storage and Transfer of Data

10.5.0 Off-Site Storage and Transfer of Data

1.0 * **You indicated that data collected as part of this study will be transferred outside of VA/VAPHS. Please provide a justification for why the data must be stored, transmitted, and/or transferred off-site:**
Data may be transferred to the Magnetic Resonance Research Center, where MRI scans will be performed.

Click here for Research Data Security and Privacy Frequently Asked Questions

Specify in detail how data will be collected, entered, and analyzed. For multisite studies, if no data entry and/or analysis will occur on site, this should be specified. Specify how long each phase of the study will take to complete and provide a time line for each aspect of the study ending with the final analyses and projected publication/presentation timeframe. If you are seeking exempt status on the basis of retrospective medical records review, please include the start and end dates (dates of creation) of the medical records you wish to use (Note: In order for the study to be granted exempt status the data must have already been collected prior to the date of submission of the application for exempt status) Also, provide all data entry forms or a complete list of the variables you will be collecting.

2.0 **Please list all locations or individuals who will receive/be provided with the data, including sponsor, site monitors, coordinating center, University of Pittsburgh, non-VA investigators/collaborators, reading centers, core laboratories, other research laboratories, data monitoring committee, etc.**

* **Data Recipients and Identifiers:**

Recipient and Description	Identifier	Identifier Description	Transfer Methods
University of Pittsburgh *Magnetic Resonance Research Center (MRRC)*	Elements of dates (except year, for example, date of birth, admission date,	Date of Birth	Direct entry into electronic website (Provide URL Below) *mrctr.upmc.edu/mrsched/*

Any identifiable information that is being shared with these individuals/entities must be described in the HIPAA authorization (in the disclosure section).

Recipient and Description	Identifier	Identifier Description	Transfer Methods
	discharge date, date of death, date of procedures; and all ages over 89)		
	Telephone Numbers	Telephone number	Direct entry into electronic website (Provide URL Below) *mrctr.upmc.edu/mrsched/*
	Name or any derivative of name such as initials	First name, Last name	Direct entry into electronic website (Provide URL Below) *mrctr.upmc.edu/mrsched/*

ID: Pro00003161 View: 10.5.1 Data Security and Privacy: Keeping a Copy of the Data

10.5.1 Data Security and Privacy: Keeping a Copy of the Data

1.0 * **How will the study team keep a copy of the data at VAPHS that is being transferred?**

Name

Paper (copies of CRFs, questionnaires, etc.)

Specify other method of maintaining a copy of the data being transferred:

The data will be stored on the subject demographic forms, which will be stored in a secure file room with other paper documents at the Human Engineering Research Laboratories. HERL is located at Bakery Square, 6425 Penn Avenue, Pittsburgh, PA 15206. The secure file room is Suite 401, Room 4103. This is a locked room inside a locked office, inside a locked suite.

2.0 * **Upload the VA Data Storage and Retrieval Worksheet:**

ID: Pro00003161 View: 10.6.0 Data Security and Privacy: HIPAA

10.6.0 Data Security and Privacy: HIPAA

The Healthcare Insurance Portability and Accountability Act (HIPAA) prohibits the use of a person's Protected Health Information without a valid authorization.

1.0 * **Select the option which fits this study:**

Name
○ Not applicable: No PHI is being used or disclosed by VAPHS
○ Not applicable: Waiver has been requested
○ HIPAA Authorization (Combined Consent and HIPAA Authorization)
◉ **HIPAA Authorization (Standalone)**

Upload HIPAA authorization (Standalone) here:

Document	Modified Date	Version Number
View Placeholder Document(0.02)	8/2/2019 3:14 PM	0.02

2.0 **At screening will clinical personnel be asked to share potential participants PHI:**

○ Yes ◉ **No**

If yes, please upload the 10-5345:

ID: Pro00003161 View: 10.7.0 Data Security and Privacy: Additional Information

10.7.0 Data Security and Privacy: Additional Information

1.0 **Does this research involve...**

* **...specially obtained software?** ◉ **Yes** ○ No

If yes, please describe the software and what it is being used for:

Actilife software is the proprietary software associated with the Actigraph activity monitors. It is the only software that can export the data from the monitors and convert it to a .csv or .dat file that can then be used for majority of the analysis.

SIGNAL is required to administer Transcranial Magnetic Stimulation according to the study protocol. MATLAB is required for data analysis.

The Armeo Power and KINARM robots run on proprietary software that allows safe use with human subjects.

The ActiLife software license was previously purchased from the company ActiGraph. A SIGNAL software license has also been purchased from the company A-M Systems. Only coded data will be stored in temporary files on the computer's hard drive as data is collected.

The Armeo Power robot runs on proprietary software that was included in the original purchase of the robotic system from the company Hocoma. The KINARM robot runs on proprietary software that was included in the original purchase of the robotic system from the company BKin / KINARM. The robot computers will not be connected to the VA or Pitt networks. MATLAB software will only be used for analysis and is licensed through the RNEL.

* **...one or more Web-based applications?** ○ Yes ◉ **No**

If yes, please describe the application and what it is being used for:

* **...mobile devices?** ○ Yes ◉ **No**

If yes, please describe:

2.0

* **Will a Certificate of Confidentiality be obtained for this study?** ○ Yes ◉ **No**

If yes, please attach the Certificate of Confidentiality:

3.0

* **Will VA sensitive information be transported and utilized outside protected environments?** ◉ **Yes** ○ No

If you answered yes above, please upload a fully executed VAPHS Memo to Take VA Sensitive Information Outside a Protected Environment by following **these instructions** .

ID: Pro00003161 View: 10.8.0 Data Security and Privacy: Certifications

10.8.0 Certifications

1.0 * **I certify that all study staff are up-to-date and will remain up-to-date with Information Security Awareness Training, Rules of Behavior, and VHA Privacy Training.**
(●) **Yes** ( ) No

2.0 * **I also certify that when an individual is no longer part of the study team, access will be removed to research study data.** (●) **Yes** ( ) No

3.0 * **I certify that all research records will be maintained in accordance with the Veterans Health Administration (VHA)Records Control Schedule. Paper records will be disposed of using methods deemed appropriate by the VAPHS Privacy Officer, and all electronic data will be sanitized using methods rendered appropriate by the VAPHS ISO.** (●) **Yes** ( ) No

4.0 * **I certify that any loss or compromise of any VA sensitive information (including research data), VA equipment or device, or any non-VA equipment or device that is used to transport, access, or store VA information will be reported in accordance with the reporting requirements outlined in VA Handbook 6500.** (●) **Yes** ( ) No

5.0 * **I certify that, in accordance with VA Handbook 6500, no personal laptops will be used for official VA business in conjunction with this study.** (●) **Yes** ( ) No

ID: Pro00003161 View: 11 Local Data Safety Monitoring Plan

Local Data Safety Monitoring Plan

For local studies, a data and safety monitoring plan (DSMP) must be established.

1.0 * **Please describe how the study procedures and data being collected will be continuously monitored so that changes in the risk/benefit ratio can be determined in a timely fashion during the course of the study:**

A data and safety monitoring plan will be implemented to insure that there are no changes in the benefit/risk ratio during the study and that confidentiality of research data is maintained. These meetings are overseen by the Directors of HERL or their designees. Any instances of adverse events will be reported immediately using the standard forms and/or procedures set forth by the Institutional Review Board. In addition, clinical coordinators from HERL may periodically review study documentation and/or consent forms to ensure that subject's confidentiality is maintained. Reporting of adverse events will be done as outlined by the VAPHS IRB. A data safety and monitoring report will be sent to the IRB at the time of renewal.

2.0 * **Describe how frequently Investigators, study personnel, and the clinical coordinators involved in the study will meet and/or review study data.**

Investigators, study personnel, and the clinical coordinators involved in the study will meet quarterly to discuss the study (e.g. study goals, progress, modifications, documentation, recruitment, retention, data analysis, and confidentiality) and address any issues or concerns at this time.

3.0 * **Will this study use a Data Safety Monitoring Board or Data Monitoring committee?**

○ Yes ◉ **No**

4.0 * **Will this study use a Medical Monitor?**

○ Yes ◉ **No**

ID: Pro00003161 View: 12 Costs and Payments

Costs and Payments

1.0 * **Does this study have a budget?:**

(●) **Yes** ( ) No

If yes, please upload the current budget:

Budget(0.01)

2.0 * **Will patients receive payments for this study?**

(●) **Yes** ( ) No

If yes, please upload the financial letter of support (either from the Business Service line or the Veterans Health Foundation) or documentation waiving the requirement of a letter of support:

Financial LOS Memo 0.01

3.0 * **Are you paying patients using the WePay system?**

no

ID: Pro00003161 View: 12.1 Costs

Costs

1.0 * **Will subjects be required to pay for any services outside of the VHA that may be required as part of participating in this research study?**
No.

ID: Pro00003161 View: 12.2 Participant Payments

Participant Payments

1.0 * **Please explain how the proposed payments are reasonable and commensurate with the expected contributions of the subject:**
Participants will receive payment for time and effort for their study participation, commensurate with their expected contributions to the research study. Participants will be attending over 40 sessions that involve attention and effort, especially during the exercise sessions. They will be contributing a significant amount of time and the information gathered from each individual contributes to the validation of the predictive model and is therefore very valuable to the study outcomes.

2.0 * **Please provide information on how the subject payments are fair and appropriate, and that they do not constitute (or appear to constitute) undue pressure or influence on the prospective research subjects to volunteer for, or to continue to participate in, the research study. In additional the payments do not constitute (or appear to constitute) coercion to participate in, or continue to participate in, the research study:**
The payment is a small amount and as such does not appear to constitute coercion to participate in the research study. Payments are approximately the same as that of other researcher studies in the building and area where the study is conducted. Payment is designed to approximate the cost of transportation plus time and effort of the participants.

3.0 * **Specify the amount, form of payment and the specific disbursement schedule of payments:**
Payment of $20 per visit will be made once a month while participants are enrolled in the study. Except in limited circumstances, payments issued through VA are generated by Electronic Funds Transfer (EFT). If participants are not able to receive payment through EFT, the Direct Express Debit MasterCard may be issued. The Direct Express Debit MasterCard is a prepaid debit card.

4.0 * **Are the subjects being paid employees?**
no
If yes, please describe how it will be in accordance with the SOP:

ID: Pro00003161 View: 14 References

References:

1.0

* **Please provide a list of references** *(Multi-site protocols: You may reference the page numbers in the original protocol):*

1. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. Circulation. 2017;135 (10):e146-e603.
2. Go A, Mozaffarian D, Roger V, Benjamin E, Berry J, Borden W, et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. Circulation. 2013;127 (1):e6-e245.
3. Krishnamurthi RV, Feigin VL, Forouzanfar MH, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet Glob Health. 2013;1(5):e259-81.
4. Gauthier L, Taub E, Perkins C, Ortmann M, Mark V, Uswatte G. Remodeling the brain: plastic structural brain changes produced by different motor therapies after stroke. Stroke. 2008;39 (5):1520-5.
5. Wittenberg GF, Chen R, Ishii K, Bushara KO, Eckloff S, Croarkin E, et al. Constraint-induced therapy in stroke: magnetic-stimulation motor maps and cerebral activation. Neurorehabil Neural Repair. 2003;17(1):48-57.
6. Wittenberg G, Bastings E, Fowlkes A, Morgan T, Good D, Pons T. Dynamic course of intracortical TMS pairedpulse responses during recovery of motor function after stroke. Neurorehabil Neural Repair. 2007;21(6):568-73.
7. Raghavan P, Santello M, Gordon A, Krakauer J. Compensatory motor control after stroke: an alternative joint strategy for object-dependent shaping of hand posture. J Neurophysiol. 2010;103 (6):3034-43.
8. Boyeson M, Jones JL, Harmon RL. Sparing of motor function after cortical injury: a new perspective on underlying mechanisms. Archives of Neurology. 1994;51:405-14.
9. Kwakkel G, Meskers C, van Wegen E, Lankhorst G, Geurts A, van Kuijk A, et al. Impact of early applied upper limb stimulation: the EXPLICIT-stroke programme design. BMC Neurol. 2008;8:49.
10. Hanley J, McNeil B. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology. 1982;143(1):29-36.
11. O'Dell M, Lin C, Harrison V. Stroke rehabilitation: strategies to enhance motor recovery. Annu Rev Med. 2009;60:55-68.
12. Mehrholz J, Pohl M, Platz T, Kugler J, Elsner B. Electromechanical and robot-assisted arm training for improving activities of daily living, arm function, and arm muscle strength after stroke. Cochrane Database Syst Rev. 2018;9:CD006876.
13. Colombo R, Pisano F, Delconte C, Mazzone A, Grioni G, Castagna M, et al. Comparison of exercise training effect with different robotic devices for upper limb rehabilitation: a retrospective study. Eur J Phys Rehabil Med. 2017;53(2):240-8.
14. Brokaw EB, Holley RJ, Lum PS. Comparison of joint space and end point space robotic training modalities for rehabilitation of interjoint coordination in individuals with moderate to severe impairment from chronic stroke. IEEE Trans Neural Syst Rehabil Eng. 2013;21(5):787-95.
15. Kwakkel G, Kollen BJ, Krebs HI. Effects of Robot-Assisted Therapy on Upper Limb Recovery After Stroke: A Systematic Review. Neurorehabil Neural Repair. 2008;22(2):111-21.
16. Kissela B, Khoury J, Alwell K, Moomaw C, Woo D, Adeoye O, et al. Age at stroke: temporal trends in stroke incidence in a large, biracial population. Neurology. 2012;79(17):1781-7.
17. Murray CJ, Atkinson C, Bhalla K, Birbeck G, Burstein R, Chou D, et al. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. JAMA. 2013;310(6):591-608.
18. Rothman S, Mattson M. Activity-dependent, stress-responsive BDNF signaling and the quest for optimal brain health and resilience throughout the lifespan. Neuroscience. 2013;239:228-40.

19. van der Lee JH, Wagenaar RC, Lankhorst GJ, Vogelaar TW, Deville WL, Bouter LM. Forced use of the upper extremity in chronic stroke patients: results from a single-blind randomized clinical trial. Stroke. 1999;30(11):2369-75.
20. Westat. National Survey of Veterans, Active Duty Service Members, Demobilized National Guard and Reserve Members, Family Members and Surviving Spouses. 2010. p. Contract GS-23F-8144H.
21. Wagner TH, Lo AC, Peduzzi P, Bravata DM, Huang GD, Krebs HI, et al. An Economic Analysis of Robot-Assisted Therapy for Long-Term Upper-Limb Impairment After Stroke. Stroke. 2011;42 (9):2630-U422.
22. Wittenberg G, Bastian A, Dromerick A, Thach W, Powers W. Mirror movements complicate interpretation of cerebral activation changes during recovery from subcortical infarction. Neurorehabil Neural Repair. 2000;14(3):213-21.
23. Wolf S, Winstein C, Miller J, Taub E, Uswatte G, Morris D, et al. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. JAMA. 2006;296(17):2095- 104.
24. Lo A, Guarino P, Richards L, Haselkorn J, Wittenberg G, Federman D, et al. Robot-assisted therapy for long-term upper-limb impairment after stroke. N Engl J Med. 2010;362(19):1772-83.
25. Kwakkel G, Winters C, van Wegen EE, Nijland RH, van Kuijk AA, Visser-Meily A, et al. Effects of Unilateral Upper Limb Training in Two Distinct Prognostic Groups Early After Stroke: The EXPLICIT-Stroke Randomized Clinical Trial. Neurorehabil Neural Repair. 2016;30(9):804-16.
26. Sawaki L, Butler A, Xiaoyan L, Wassenaar P, Mohammad Y, Blanton S, et al. Constraint-induced movement therapy results in increased motor map area in subjects 3 to 9 months after stroke. Neurorehabil Neural Repair. 2008;22(5):505-13.
27. Sawaki L, Butler A, Leng X, Wassenaar P, Mohammad Y, Blanton S, et al. Differential patterns of cortical reorganization following constraint-induced movement therapy during early and late period after stroke: A preliminary study. NeuroRehabilitation. 2014.
28. Wittenberg GF, Richards LG, Jones-Lush LM, Roys SR, Gullapalli RP, Yang S, et al. Predictors and brain connectivity changes associated with arm motor function improvement from intensive practice in chronic stroke. F1000Res. 2016;5:2119.
29. Frohlich H, Balling R, Beerenwinkel N, Kohlbacher O, Kumar S, Lengauer T, et al. From hype to reality: data science enabling personalized medicine. BMC Med. 2018;16(1):150.
30. Stinear C, Barber P, Petoe M, Anwar S, Byblow W. The PREP algorithm predicts potential for upper limb recovery after stroke. Brain. 2012;135(Pt 8):2527-35.
31. Stinear CM, Byblow WD, Ackerley SJ, Barber PA, Smith MC. Predicting Recovery Potential for Individual Stroke Patients Increases Rehabilitation Efficiency. Stroke. 2017;48(4):1011-9.
32. Connell LA, Smith MC, Byblow WD, Stinear CM. Implementing biomarkers to predict motor recovery after stroke. NeuroRehabilitation. 2018;43(1):41-50.
33. Gauthier L, Taub E, Mark V, Perkins C, Uswatte G. Improvement after constraint-induced movement therapy is independent of infarct location in chronic stroke patients. Stroke. 2009;40 (7):2468-72.
34. Lin K, Hsieh Y, Wu C, Chen C, Jang Y, Liu J. Minimal detectable change and clinically important difference of the Wolf Motor Function Test in stroke patients. Neurorehabil Neural Repair. 2009;23 (5):429-34.
35. DeLong ER, DeLong DM. Comparing the areas under two or more correlated receiver operating characteristic curves: A non-parametric approach. Biometrics. 1988;44:837-45.
36. Breiman L. Random forests. Mach Learn. 2001;45(1):5-32.
37. Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect. 2012;2(3):125-41.
38. Busan P, Barbera C, Semenic M, Monti F, Pizzolato G, Pelamatti G, et al. Effect of transcranial magnetic stimulation (TMS) on parietal and premotor cortex during planning of reaching

movements. PLoS One. 2009;4(2):e4621.
39. Procacci NM, Stanford TR, Wittenberg GF. The relationship between visual orienting and interlimb synchrony in a patient with a superior parietal infarction: A case study. Neurocase. 2009;15(2):73-88.
40. Schieppati M, Trompetto C, Abbruzzese G. Selective facilitation of responses to cortical stimulation of proximal and distal arm muscles by precision tasks in man. J Physiol. 1996;491 (Pt 2):551-62.
41. Hulley SB. Designing clinical research. 4th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2013. p. p.
42. Roger V, Go A, Lloyd-Jones D, Benjamin E, Berry J, Borden W, et al. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. Circulation. 2012;125 (1):e2-e220.
43. CDC. Summary Health Statistics for U.S. Adults. 2011.
44. O'Brien S, Xue Y. Predicting goal achievement during stroke rehabilitation for Medicare beneficiaries. Disabil Rehabil. 2013.
45. Levin M, Desrosiers J, Beauchemin D, Bergeron N, Rochette A. Development and validation of a scale for rating motor compensations used for reaching in patients with hemiparesis: the reaching performance scale. Phys Ther. 2004;84(1):8-22.
46. Gladstone D, Danells C, Black S. The fugl-meyer assessment of motor recovery after stroke: a critical review of its measurement properties. Neurorehabil Neural Repair. 2002;16(3):232-40.
47. Levin M. Interjoint coordination during pointing movements is disrupted in spastic hemiparesis. Brain. 1996;119(Pt 1):281-93.
48. Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. Scand J Rehabil Med. 1975;7(1):13-31.
49. Duncan P, Bode R, Min Lai S, Perera S. Rasch analysis of a new stroke-specific outcome scale: the Stroke Impact Scale. Arch Phys Med Rehabil. 2003;84(7):950-63.
50. Morris D, Uswatte G, Crago J, Cook E, Taub E. The reliability of the Wolf motor function test for assessing upper extremity function following stroke. Arch Phys Med Rehabil. 2001;in press.
51. Liu W, McCombe Waller S, Kepple T, Whitall J. Compensatory arm reaching strategies after stroke: induced position analysis. J Rehabil Res Dev. 2013;50(1):71-84.
52. Bogard K, Wolf S, Zhang Q, Thompson P, Morris D, Nichols-Larsen D. Can the Wolf Motor Function Test be streamlined? Neurorehabil Neural Repair. 2009;23(5):422-8.
53. Duncan PW, Wallace D, Lai SM, Johnson D, Embretson S, Laster LJ. The stroke impact scale version 2.0. Evaluation of reliability, validity, and sensitivity to change. Stroke. 1999;30 (10):2131-40.
54. van der Lee J, Beckerman H, Lankhorst G, Bouter L. The responsiveness of the Action Research Arm test and the Fugl-Meyer Assessment scale in chronic stroke patients. J Rehabil Med. 2001;33(3):110-3.
55. Van der Lee J, De Groot V, Beckerman H, Wagenaar R, Lankhorst G, Bouter L. The intra- and interrater reliability of the action research arm test: a practical test of upper extremity function in patients with stroke. Arch Phys Med Rehabil. 2001;82(1):14-9.
56. Uswatte G, Taub E, Morris D, Vignolo M, McCulloch K. Reliability and validity of the upper-extremity Motor Activity Log-14 for measuring real-world arm use. Stroke. 2005;36(11):2493-6.
57. Welk G, Schaben J, Morrow JJ. Reliability of accelerometry-based activity monitors: a generalizability study. Med Sci Sports Exerc. 2004;36(9):1637-45.
58. Gebruers N, Vanroy C, Truijen S, Engelborghs S, De Deyn P. Monitoring of physical activity after stroke: a systematic review of accelerometry-based measures. Arch Phys Med Rehabil. 2010;91(2):288-97.
59. Lang C, Bland M, Bailey R, Schaefer S, Birkenmeier R. Assessment of upper extremity impairment, function, and activity after stroke: foundations for clinical decision making. J Hand

Ther. 2013; 26(2):104-14;quiz 15.
60. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonicatlas-based interrogation of fMRI data sets. NeuroImage. 2003;19(3):1233-9.

ID: Pro00003161 View: 15 Miscellaneous Documents

Miscellaneous Documents

If you have any documents that need to be included in this submission, but do not fit in any of the previous sections please upload them here.

Document	Description	Version Number
There are no items to display		

ID: Pro00003161 View: SF - Final Page

Final Page

You have completed your application!

Please hit "Finish" to save and exit the application. Doing so will NOT submit the application for review.

Please note that a submission may only be forwarded to the IRB by the Principal Investigator. To do this, the Principal Investigator must press the "SUBMIT STUDY" button in My Activities for this Study ID:Pro00003161.

You can track the ongoing status of your submission by logging into the study workspace.

Please feel free to contact the IRB with any questions or concerns.

ID: Pro00003161 View: Create/Edit

Study Funding Source

1.0 * **Funding Source Name:**
Merit Review (CC 103)
If you can't find the Funding Source above, choose "Other" and enter it here:

ID: Pro00003161 View: Print View

Name of Site / Institution:
University of Pittsburgh

Are the study-related research activities at this site defined as engagement?
Yes

Investigator Name:
George Wittenberg

Investigator Address:
3520 Fifth Ave, Suite 201, Pittsburgh, PA 15213

Investigator Email:
george.wittenberg@va.gov

Investigator Phone:
412-648-4178

IRB-of-Record Contact Name:

Contact Address:

Contact Email:

Contact Phone:

FWA:

ID: Pro00003161 View: VA Create-Edit

* **Device Name:** The MagStim 200
* **Use of Device:** FDA Approved but used in unapproved way
Manufacturer: MagStim
IDE Class:
IDE Number(if Applicable):
Risk Level Determined by Sponsor: Non-Significant Risk

Upload Device Brochure

Provide any other notes about how this device will be used or justification for lack of IDE number

Is the investigator hold the IDE for this device?

○ Yes ◉ **No**

If yes please provide a basis for risk level.

ID: Pro00003161 View: Risk Detail Entry

Address for each screening procedure, research intervention/interatction, and follow-up/monitoring procedure:

* Research Activity:
Intervention and Testing

Common Risks:

Infrequent Risks:
Risk of injury by the robot. The possible injuries from a malfunctioning robot include bruises, pinching, strain, lacerations, dislocations, or bone fractures. The robot has not caused dislocation or bone fracture in any of our ongoing robot studies. The risk of injury is minimized by the design of the robot allowing the participant to stop it as well as oversight by a therapist who can also stop the robot if there is any potential for injury.

Risk of injury from TTT. The is minimal risk of muscle fatigue and/or soreness, and joint pain, from the repetitive exercise. In order to minimize this risk the participant will be supervised throughout the activity and given rest breaks as needed. The participant will be made aware that they can stop the task at anytime.

Seizures. Transcranial magnetic stimulation at low frequency (< 1 Hz) has been used for over 20 years in a variety of normal subjects and in subjects with neurological conditions and has generally been found to be safe. In a review of 38 studies involving 850 subjects, there were no seizures or other major adverse events (Gilbert et al. 2004 - attached). For non-neurologically impaired subjects and for subjects with stroke, the risk is considered minimal. Although TMS is not used in subjects with implanted metallic devices, it is thought to be safe in patients with hydrocephalus and ventricular shunts. Although high-rate, repetitive TMS has the potential to induce seizures (Wassermann et al. 1996),TMS rates of 0.2 Hz or less are safe in epileptic patients and even higher rates may have a protective effect in the case of intractable seizures (Tergau et al. 1999). ONLY rates < 0.2 Hz will be used in this study.

Some people experience anxiety (claustrophobia) when they get in the MRI. The MRI may pose a risk to certain metallic or implanted electronic devices (pacemaker) or identify problems that will require follow up. Risk of hearing loss from the scanning. For those participants who have an MRI that reveals a potential condition, previously unknown, having the MRI may lead to further medical work up. This is likely beneficial, as a condition may be revealed earlier in its course than it otherwise would have been, but may cause psychological distress to the participant.

Discomfort. 1000 TMS stimuli are an upper limit that will not be exceeded during any session. Usually, it will be far fewer stimuli provided. But in any case, this number (1000) of stimuli not likely to be stressful or uncomfortable, as they are spread out over time. There is no cumulative effect, besides potentially a slight headache. The participant may always ask for a break, and if this is done in between mapping different locations, causes no loss of validity of data collection. Since the investigator is literally inches away from the participant, participant comfort is monitored closely.

Other TMS risks. There is no known risk to participating in multiple low-frequency TMS studies. There are no known adverse effects of TMS in pregnancy, but studies have been limited to a single case report in which there were no adverse effects of high-rate stimulation. There is also the risk of skin irritation at the site of the EMG electrodes used for TMS data collection and the chance of electrical current (DC) less than what would be experience with a nine-volt battery.

Other Risks:

ID: Pro00003161 View: Risk Detail Entry

Address for each screening procedure, research intervention/interatction, and follow-up/monitoring procedure:

* Research Activity:
Data Collection -Confidentiality

Common Risks:

Infrequent Risks:
Breach of confidentiality. To minimize risk all files and information is maintained in a locked file cabinet in the study coordinator's office or the Principal Investigator's office in the Keystone Building. All sensitive documents are stored at HERL in a secure file room.

Other Risks: