UNIVERSITY of MARYLAND
THE FOUNDING CAMPUS

Date: Monday, October 12, 2020 11:43:51 AM

Print Close

HP-00062868

View: v2_Introduction Page

Introduction Page

1 * Abbreviated Title:
SRT4

2 * Full Title:
Neurophysiological and Kinematic Predictors of Response in Chronic Stroke

3

* Select Type of Submission:

- (●) **IRB Application**
- ( ) Humanitarian Use Device (for FDA approved Indication & non-research purposes ONLY)
- ( ) Single Patient Expanded Access (pre-use)
- ( ) Single Patient Emergency Use (post-use)
- ( ) Unsure if this proposal requires IRB review (Not Human Subject Research)

Note: The Type of Submission cannot be changed after this application has been submitted for review.

4 Original Version #:
Version 1

ID: VIEW4DF8709A33C00
Name: v2_Introduction Page

HP-00062868 View: v2_Research Team Information

Research Team Information

1 * Principal Investigator - Who is the PI for this study (person must have faculty status)? ***Faculty status is defined as being a full-time (>51% effort) faculty member holding one of the following titles at UM: Professor; Associate Professor; Assistant Professor.***
Michael Dimyan

CITI Training: ID00008911

1.1 * Does the Principal Investigator have a potential conflict of interest, financial or otherwise, related to this research?
◯ Yes ● **No**

2 Point of Contact - Who is the alternative point of contact for the PI? This person can be a study coordinator or any other study team member. In case the IRB cannot contact the PI, this person is a secondary person to contact:
Elsa Ermer

CITI Training: ID00007244

2.1 Does the Point of Contact have a potential conflict of interest, financial or otherwise, related to this research?
◯ Yes ● **No**

3 Other Team Members - list all additional members of the research team for this study. DO NOT include the PI or POC in this list:

	Name	Edit Submission	cc on Email	Research Role	Has SFI?	CITI Training
View	Linda Horn	no	no	Research Team Member	no	ID00005742
View	Jill Whitall	yes	no	Research Team Member	no	ID00008561
View	Susan Conroy	yes	yes	Sub-Investigator	no	ID00005518
View	Huichun Xu	yes	yes	Research Team Member	no	ID00006589

IMPORTANT NOTE: All research team members (including PI) must have current CITI and HIPAA training completed.

ID: VIEW4DF85C16F2800
Name: v2_Research Team Information

HP-00062868 View: v2_Resources

Resources

If this study is a collaborative UM/VA study, please clarify which resources are being used at each institution.

1 * Describe the time that the Principal Investigator will devote to conducting and completing the research:
The principal investigator will devote 25% of his time assigned to this study.

2 * Describe the facilities where research procedures are conducted:
Adequate facilities are available and in place to conduct the study procedures. Participants enrolled in Maryland will have all baseline and periodic evaluations including transcranial magnetic stimulation (TMS), questionnaires, and functional and robotic evaluations will be conducted at the Research on Arm Function and Therapy (RAFT) labs located on the 2nd floor of the Allied Health building of the University of Maryland School of Medicine at 100 Penn St, Baltimore, MD 21201, considered VA research space by memorandum of understanding. Training sessions will be performed at either the RAFT labs in the Allied Health Building or at the VAMHCS Loch Raven Exercise & Robotics Research Building located at 3901 The Alemeda, Baltimore, MD 21218. MRI scans will be conducted at the University of Maryland Medical Center research scanner which is located in the Paca Pratt Building at 110 S. Paca St., Baltimore, MD 21201. Saliva and blood samples will be collected at the GRECC lab at VAMHCS Baltimore.

3 * Describe the availability of medical and/or psychological resources that subjects might need as a result of anticipated consequences of the human research:
Every reasonable safety measure will be used to protect a participant's well-being. We do not anticipate the need for medical/psychological resources for this study. In case of any medical emergency, the Allied Health, Paca Pratt, and Loch Raven buildings have an AED available on-site. If any unanticipated medical emergencies arise study staff will call 911 for emergency care. If 911 is activated, participants will be taken to the nearest available hospital for care.

4 * Describe the process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions:
All persons assisting with the research will have access to the protocol through the CICERO website. Prior to the commencement of the study, the research team members will have an introductory meeting with the PI where they will be educated about the protocol, procedures and duties. In addition, regular study meetings will be organized where the team members will be updated about any changes in duties, functions, and responsibilities. Individualized training of study team members will be completed by the study coordinator for competency as needed. Study team members will also complete the necessary institutional training sessions necessary for compliance with policies and procedures.

ID: VIEW4DF83CB976400
Name: v2_Resources

Sites Where Research Activities Will Be Conducted

1 * Is this study a:

- (●) **Multi-Site**
- ( ) Single Site

2 * Are you relying on an external IRB (not UM) to be the IRB of Record for this study?

( ) Yes (●) **No**

3 * Are any other institutions/organizations relying on UM to be the IRB of Record for this study?

( ) Yes (●) **No**

3.1 Attach the applicable regulatory documents here (i.e., IRB Authorization Agreement (IAA), FWA, local ethics approval, other IRB approvals, etc.). Final UM approval will be contingent upon final execution of all required regulatory approvals:

Name	Created	Modified Date
There are no items to display		

4 * Is UM the Coordinating Center for this study? (Applicable for multi-site studies. A Coordinating Center is responsible for overall data management, monitoring and communication among all sites, and general oversight of conduct of the project.)

(●) **Yes** ( ) No

5 Is VA the Coordinating Center for this study? (Applicable for Collaborative studies between the VA, UM and other sites. A Coordinating Center is responsible for overall data management, monitoring and communication among all sites, and general oversight of conduct of the project)

( ) Yes (●) **No**

6 * Institution(s) where the research activities will be performed:

- [x] **University of Maryland Medical Center**
- [ ] University of Maryland, Baltimore
- [x] **VAMHCS**
- [ ] University of Maryland, Upper Chesapeake Kaufman Cancer Center
- [x] **UMB School of Medicine**
- [ ] Marlene and Stewart Greenebaum Cancer Center
- [ ] University Physicians Inc.
- [ ] Shock Trauma Center
- [ ] General Clinical Research Center (GCRC)
- [ ] Maryland Psychiatric Research Center (MPRC)
- [ ] Johns Hopkins
- [x] **University of Maryland Rehabilitation & Orthopaedic Institute (formerly Kernan Hospital)**
- [ ] International Sites
- [ ] UMB Dental Clinics
- [ ] Center for Vaccine Development
- [ ] Community Mental Health Centers
- [ ] Private Practice in the State of Maryland
- [ ] Institute of Human Virology (IHV) Clinical Research Unit
- [ ] Joslin Center

- [ ] UMB Student Classrooms
- [ ] National Institute of Drug Abuse (NIDA)
- [ ] National Study Center for Trauma and EMS
- [ ] Univ of MD Cardiology Physicians at Westminster
- [ ] Nursing Homes in Maryland
- [ ] University of Maryland Biotechnology Institute
- [ ] Department of Health and Mental Hygiene (DHMH)
- [ ] Capitol Region PG Hospital
- [ ] Maryland Proton Treatment Center
- [ ] Mount Washington Pediatric Hospital
- [x] **Other Sites**
- [ ] University of Maryland Medical System (Select below)

ID: VIEW4DF870DF2C000
Name: v2_Sites Where Research Activities Will Be Conducted

HP-00062868 View: v2_UM Coordinating Center

UM Coordinating Center

You indicated that UM is the Coordinating Center for this multi-site study.

2.1 *Describe the processes to ensure communication among sites.
Things to consider including in the communication plan:

- all sites have the most current version of the protocol, consent document, etc.
- all required approvals have been obtained at each site (including approval by the site's IRB of record).
- all modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.
- all engaged participating sites will safeguard data as required by local information security policies.
- all local site investigators conduct the study appropriately.
- all non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

The study uses FIPS140-2 and HIPAA/HITECH compliant, multi-factor authentication-protected electronic project management software and electronic telecommunications to share all protocol, consent and other relevant documents, including approvals.
The team has electronic and in-person team meetings approximately weekly and larger meetings monthly to discuss all issues within and between sites including regulatory, data collection, data quality and validation, data safeguarding, study conduct, non-compliance, and reporting.
All IRB submissions include details regarding data safeguarding.

2.2 *Describe the method for communicating to engaged participating sites including:

- reportable new information.
- problems.
- interim results.
- the closure of a study.

The study uses FIPS140-2 and HIPAA/HITECH compliant, multi-factor authentication-protected electronic project management software and electronic telecommunications to share all relevant communications.
The team has electronic and in-person team meetings approximately weekly and larger meetings monthly to discuss all issues within and between sites including reportable new information, problems, interim results, and study completion and closure.

ID: VIEW4DF737D4C2800
Name: v2_UM Coordinating Center

HP-00062868

View: v2_Other Sites Where Research Activities Will Be Conducted

Other Sites Where Research Activities Will Be Conducted

You selected "Other Sites," "Private Practice," "Community Mental Health Centers," and/or "Nursing Homes in Maryland" as a site where research will be conducted.

3.1 * Specify the name of the site(s):
VA Pittsburgh Healthcare System

3.2 * Contact Person(s) for Other Site:
Amy Boos

3.3 * Phone (if no phone available, input "none"):
412-648-4179

3.4 * Email Address (if no email available, input "none"):
amy.boos@pitt.edu

ID: VIEW4DF8712DB5800
Name: v2_Other Sites Where Research Activities Will Be Conducted

HP-00062868 View: v2_Funding Information

Funding Information

1 * Indicate who is funding the study:

- [x] **Federal**
- [ ] Industry
- [x] **Department / Division / Internal**
- [ ] Foundation
- [ ] Private
- [ ] State Agency

2 * What portion of the research is being funded? (Choose all that apply)

- [ ] Drug
- [x] **Device**
- [x] **Staff**
- [ ] Participant Compensation
- [x] **Procedures**
- [ ] Other

3 Please discuss any additional information regarding funding below:

Pepper Center Pilot funding is used to support the addition of blood RNA analysis to find biomarkers for optimal upper arm recovery.

ID: VIEW4DF85DF452400
Name: v2_Funding Information

HP-00062868 View: v2_DHHS Funded Study

DHHS Funded Study

You indicated that this is a Federally funded study.

1 * Is this study sponsored by a Department of Health and Human Services (DHHS) agency?

◯ Yes ● **No**

2 You may upload any grant documents here:

Name	Created	Modified Date
There are no items to display		

ID: VIEW4DF87B9560800
Name: v2_DHHS Funded Study

HP-00062868 View: v2_Federal Agency Sponsor Information

Federal Agency Sponsor Contact Information

You indicated that this is a Federally funded study.

1

* Agency Name:
Department of Veterans Affairs

* Address 1:
810 Vermont Ave NW

Address 2:

* City:
Washington

* State:
DC

* Zip Code:
20005

* Contact Person:
Patricia Dorn

* Phone Number:
(202) 461-1755

Grant Number 1 (if applicable):
B6935R / I01RX001667- OR - Check here if Grant 1 is not assigned a number. ☐

If Grant 1 has no number, please provide the following information:
Title of Grant 1:

PI of Grant 1:

Grant Number 2 (if applicable):
- OR - Check here if Grant 2 is not assigned a number. ☐

If Grant 2 has no number, please provide the following information:
Title of Grant 2:

PI of Grant 2:

Grant Number 3 (if applicable):
- OR - Check here if Grant 3 is not assigned a number ☐

If Grant 3 has no number, please provide the following information:
Title of Grant 3:

PI of Grant 3:

Grant Number 4 (if applicable):
- OR - Check here if Grant 4 is not assigned a number. ☐

If Grant 4 has no number, please provide the following information:
Title of Grant 4:

PI of Grant 4:

ID: VIEW4DF8584874400
Name: v2_Federal Agency Sponsor Information

HP-00062868 View: v2_Research Protocol

Research Protocol

1 * Do you have a research protocol to upload?

- (●) **Yes**
- ( ) No, I do not have a research protocol and will use the CICERO application to enter my study information

2 If Yes, upload the research protocol:

Name	Created	Modified Date
PepperPilotProtocolRNA_analysis(0.01)	3/13/2017 5:38 PM	3/13/2017 5:38 PM

ID: VIEW4E00563F8D000
Name: v2_Research Protocol

HP-00062868 View: v2_Risk Level

Risk Level

What is the risk level of your study? (Ultimately, the IRB will determine the appropriate risk level and your designation is subject to change.)

* Choose One:

- (●) **Minimal - The probability & magnitude of harm/discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations/tests.**
- ( ) Greater Than Minimal - Does not meet the definition of Minimal Risk.

ID: VIEW4E02805225800
Name: v2_Risk Level

HP-00062868 View: v2_Type of Research

Type of Research

1 * Indicate **ALL** of the types of research procedures involved in this study (Choose all that apply):

- [ ] Use of unapproved drug(s)/biologic(s) or approved drug(s)/biologic(s) whose use is specified in the protocol.
- [ ] Evaluation of food(s) or dietary supplement(s) to diagnose, cure, treat, or mitigate a disease or condition.
- [ ] Use of device(s) whose use is specified in the protocol
- [x] **Psychological/Behavioral/Educational Method or Procedure (i.e., survey, questionnaires, interviews, focus groups, educational tests).**
- [x] **Sample (Specimen) Collection and/or Analysis (including genetic analysis).**
- [x] **Data Collection or Record Review (i.e., chart review, datasets, secondary data analysis).**
- [ ] None of the above.

2 * Is this study a clinical trial OR will this study be registered at ClinicalTrials.gov?
A clinical trial is a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

○ Yes ● **No**

ID: VIEW4E0280569E000
Name: v2_Type of Research

HP-00062868

View: v2_Lay Summary

Lay Summary

1 * Provide a summary of the background and purpose of the study in language that can be understood by a person without a medical degree.

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. An ongoing study has shown value in adding task related training to robotic training to improve functional recovery. The proposed study will expand the current study to examine the ability to predict who will benefit from this optimized therapy approach as well as expand knowledge of what brain structures, genetic background, and activity are important for improvement.

ID: VIEW4E02805CF7000
Name: v2_Lay Summary

Justification, Objective, & Research Design

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * Describe the purpose, specific aims, or objectives of this research. State the hypothesis to be tested:

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 in the chronic phase. Recent clinical trials, including our own, (Evaluation of Robot Assisted Neuro-Rehabilitation HP-42797) have demonstrated significant but variable effects, of intensive interventions, with some individuals showing clinically significant improvements and others none. Ideally these interventions would be applied to those with a reasonable likelihood of improvement. While there have been successful methods to predict spontaneous motor recovery, there has been little published work on predicting response to specific interventions in chronic stroke.

Our long-range goal is the prescriptive application of intensive task practice to veterans who have suffered a stroke in order to maximize the cost-benefit ratio. We therefore plan to rigorously test the predictive value of potential biomarkers suggested by results of our past chronic stroke robotic rehabilitation trial, and further develop them over the first three years of the proposed study. These baseline biomarkers include genetic polymorphisms, blood RNA profiles, demographic data, clinical information, motor measures made both with and without the robotic device, transcranial magnetic stimulation responses that can be measured in most individuals, and resting-state connectivity of the motor system. Baseline structural and functional imaging will be used to determine the integrity of the motor system, in terms of the main white matter outflow tract, the internal capsule, and connectivity of the affected hemisphere primary motor cortex. We have identified an effective intervention for individuals with chronic stroke: robotic training with transition to task practice (Robot + TTT) and we now are able to rigorously formulate and test a predictive method in two sets of new participants. We propose the following three specific aims:

1. Design a predictive model based on baseline measure of movement ability and brain physiology. Working hypothesis: Baseline motor function, time after stroke, and preservation of the stroke-affected hemisphere motor system connectivity will correlate with practice-related effects of an optimized therapy method, but not always linearly. Additional factors such as interjoint coordination ability and plasticity-relevant genotype, and blood RNA expression profiles will be explored for predictive value. Expected outcome: A formula with weighted values in a non-linear model that predict s response in new participants. This formula will most likely include measures of preserved brain substrate for motor learning.

2. Rigorously test the predictive value of the model. Working hypothesis: As in Aim #1. Expected outcome: A revised predictive model that uses biomarkers of the substrate for recovery to estimate likelihood of meaningful clinical change in both function and ability. This will be confirmed by a rigorous resampling methodology that avoids biases based on participant selection.

3. Identify the changes in the cortical motor system that are associated with meaningful change in upper extremity motor function. Working hypothesis: Normalization of interhemispheric inhibitory interactions will be associated with reduction in impairment. Expected outcome: Resting-state connectivity will become a useful, reliable, and easily implemented method to monitor the interhemispheric motor network.

When we have completed the above aims, we will have more information about who benefits from intensive upper extremity training in the chronic period and an 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. We will also extend mechanistic knowledge about the response to intensive training on interhemispheric interactions, which has been noted to be altered after stroke and which strongly modulates motor activity. The value of baseline resting state connectivity of the motor system for prediction of response to therapy will also be known. Additionally, we will have better outcome assessment for the large population of significantly impaired individuals who are in the chronic phase after stroke.

One of the most important parts of therapy during the chronic phase is translation of motor ability into daily activities. The data from this study will build upon our previous work and measure the effects of combining an impairment-focused practice tool (the rehabilitation robot) with activity-based practice (transition to task.) We will have a better set of clinically meaningful, outcome measures to use in decision-making regarding administration of upper extremity practice-based therapy.

2 * Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc.:

The overall design is a one-arm, multiple baseline sequential, cohort study conducted over a four-year period in order to 1) define and 2) test a predictive clinical model of arm recovery after stroke. We intend to enroll 96 participants. All participants will receive the Robot+TTT intervention.

3 * Describe the relevant prior experience and gaps in current knowledge. Describe any relevant preliminary data:

Few studies have investigated predictors of response to a specific therapy in the chronic phase. In the acute phase, a recent systematic review/ meta-analysis of 58 studies (Coupar et al 2012) suggests that initial severity of motor impairment or function is the most important and consistent predictor of upper extremity recovery as measured by a variety of assessment measures, none of which are in the "participation of the paretic arm" category of the ICF (International Classification of Functioning, Disability and Health). In the chronic phase, two independent studies of constraint-induced therapy each found that finger extension ability was the only significant predictor of outcomes in the WMFT (Fitz et al. 2005) and the FM and Motor Activity Log (Lin et al. 2009) respectively. The latter finding is notable since one of the outcome variables assessed participation of the paretic arm. However, in a subsequent analysis of the same sample, using the outcome measure of the Stroke Impact Scale (SIS, a quality of life measure), only the Functional Independence Measure predicted the total SIS and the sub-domain of ADL/IADL(Huang 2010). None of the predictor variables (including Fugl-Meyer) predicted the SIS-hand domain.

These results are different from our own preliminary findings, that functional variables, including the Fugl-Meyer, are strong predictors for the participation outcome of SIS-Hand Domain improvement after Robot-TTT therapy. To our knowledge, no studies have used biomechanical analyses of motor control/learning parameters as predictors of response to a specific therapy in the chronic phase. We propose to investigate key clinical, biomechanical, and neurophysiological parameters, based on past literature and our preliminary results, as part of a comprehensive approach to predicting response to therapy.

Relatively few studies have investigated neurophysiological predictors of response to a specific therapy in the chronic phase. Recently, Stinear (2012) tested an algorithm (PREP) that uses four variables, in serial order, to predict functional outcomes after acute hemiparetic stroke: shoulder abduction, finger extension strength, presence/absence of a motor evoked potential (MEP) in response to TMS, and diffusion-weighted magnetic resonance imaging to assess the structural integrity of the posterior limbs of the internal capsules. With a similar strategy, but a longer-term focus, we propose to discover a new algorithm to predict how chronic patients respond to Robot-TTT therapy. We do not expect it to be identical to the PREP algorithm, for various reasons. In individuals with chronic stroke, using fMRI, Cramer found that larger functional gains after 6 weeks of different types of task-oriented training were predicted by lower levels of initial ipsilesional motor cortex activity, suggesting that these subjects had learned non-use of surviving cortical resources. Interestingly, brain factors such as infarct volume, site of activation or corticospinal tract atrophy have not been found to be good predictors of intervention outcome potential, but do correlate with initial deficits.

Our Investigations

The robot study (HP-42797) that this investigation is based on, tested two training paradigms in which there were hour-long sessions, 3X weekly for 12 weeks. The first 45 minutes of each session consisted of robotic arm training. The last 15 minutes were either further robotic arm training (in one group) or TTT training (in the other.) The primary outcome measures are Fugl-Meyer UE Test (FM), Wolf Motor Function Test for time (WMFT) and Stroke Impact Scale hand domain (SIS-hand) representing each level of the International Classification Framework.

Significant within group changes were found earlier during Robot+TTT therapy compared to Robot-alone for all outcomes (WMFT, FM, and SIS). Analysis of FM, WMFT data demonstrated significant earlier improvement of outcomes by Robot + TTT compared to Robot-alone program. For Robot+TTT, significant improvement can be observed as early as 4 weeks (FM as outcome measure) or 8 weeks (WMFT as outcome measure). Both groups maintained their gains upon completion of 12 weeks of training and no between-group differences occurred. Analysis of SIS-hand data demonstrated significant within-group changes for Robot+TTT achieved by 12 weeks that was retained at a 24 week follow-up. These data suggest both training groups are effective but the Robot+TTT group achieved significant gains earlier that may be more

tranferrable to real life activities.

As a prelude to a predictive model, we ran correlations of selected potential baseline predictors with changes in our three primary outcome variables at 12 weeks (n=20). The following baseline variables were significantly correlated with changes in FM, and SIS: WMFT, MEP presence and time after stroke. FM and wrist extension force were additionally correlated with SIS hand. Correlations with 24-week outcomes are generally consistent with the 12-week results. In contrast, a change in WMFT not correlated with any of these variables. These data provide evidence that clinical variables can be predictive of a positive outcome after the Robot + TTT training both at the impairment and the participation level. We propose to include a more comprehensive analysis of kinematic data from assistance-free robotic task evaluations that may provide additional predictor variables based on the quality of an individual's ability to move their whole arm rather than an isolated joint. Table 1 below shows correlations (r) from interim analysis from Robot+TTT group for 12-week outcomes. Improvements in the primary outcome, FM, and secondary outcome, SIS hand score, were related to less impairment (FM), better performance on Wolf, presence of MEP and shorter time after stroke as well as wrist extension force, a simple measure of motor function.

Post training at 12 weeks (n=20) P value * = <0.05; ** = <0.01.
Baseline variable FM change WMFT change SIS-hand change
FM 0.40 -0.30 0.61**
WMFT - 0.49* 0.16 -0.66**
MEP presence 0.63* -0.37 0.78**
Wrist Ext. Force 0.42 -0.40 0.57**
Time after stroke -0.56* 0.65**

Neurophysiological Findings
Our TMS findings in this population of stroke-affected individuals with moderate to severe impairment showed that about two thirds do not have motor-evoked potentials (MEP) in either biceps or extensor digitorum communis. Screening for MEP is a simple and rapid measure of the effectiveness of the motor cortex in producing movement. It correlates with response to the interventions, as seen in Table 1. As in acute studies of recovery, MEP presence provides an independent measure of the cortical substrate upon which repetitive task practice works. We have also measured the ipsilateral silent period and found that it is frequently absent in this group of patients. We are continuing to work on methodology for detecting small changes in interhemispheric inhibition when such impaired cortical control of upper extremity muscles exists.

Analysis of MRI from the previous study is in progress. Much of the resting state BOLD data has been analyzed using independent components analysis. This has demonstrated abnormalities in the motor network often out of proportion to the brain lesions. The best-responding subject in whom we have data showed better incorporation of the affected side primary motor cortex in the overall motor network. The representative slice that includes the motor cortex shows a network derived from an independent components analysis of over 11 minutes of resting state EPI BOLD. While there was no MEP present in this individual, both primary and non-primary motor cortices on the affected left side and unaffected right side were well-incorporated into this functional brain network. Functioally the FM change was > 3, WMFT change < -15 sec.This result indicates that having no MEP is not, by itself, an absolute predictor of poor outcome.

4 * Provide the scientific or scholarly background, rationale, and significance of the research and how it will add to existing knowledge:

The primary purpose of the current proposal is to develop predictors of response to the Robot + TTT (transition-to-task) therapy in the chronic population. By doing so, we will provide biomarkers and algorithms for a predictive model to guide future matching of patients to a therapy based on residual neural and motor function and other measureable factors. We also will contribute to understanding the mechanisms of recovery specifically by relating clinical, neurophysiological and kinematic markers to functional outcomes. While the ultimate goal is to personalize treatment during the sub-acute period when spontaneous recovery, optimal neuroplasticity and available rehabilitation coincide, the focus here on the chronic population has two advantages. First, it addresses the problem of an exponential growth in individuals aging with disabilities from stroke. Strokes are occurring earlier in the lifespan and individuals live longer with stroke 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 (Rothman 2013) and that rehabilitation can be effective years after the stroke e.g. (Van der Lee 1999), finding 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 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.

We will expand the impact of our investigation by including higher functioning individuals. Our first study with the planar robot showed better improvement for moderate-severe compared to mild-moderate impaired individuals (Macclellan 2005, Finley 20005), but we did not include training on the wrist robot or a TTT component. Both of these components were more likely to enhance the recovery of higher functioning individuals than solely practicing shoulder-elbow actions, which may be well preserved in those individuals. Moreover, other studies with the MIT-MANUS robot had positive results with higher functioning individuals (Fasoli 2004). The advantage of including higher functioning individuals is not only for generalizability to the larger population of individuals with chronic stroke, but also because we can compare our results in these individuals with those from the literature on Constraint-Induced Therapy (CIT) (Gauther 2009). In CIT, improvements are achieved through focused intensive repetitive shaping and task specific exercise of the paretic arm with physical restraint of the non-paretic arm in the laboratory and at home. Since our transition to task activities are similar to those used in CIT, it will be instructive to determine whether priming the neuromuscular system with robotic exercise before practicing specific functional tasks will produce comparable effect sizes. (In this respect, CIT is a standard to which Robot + TTT treatment can be compared.) Our preliminary data indicates that we have several factors that are associated with improved outcomes after Robot + TTT. We therefore propose continuing Robot + TTT as the single intervention, while increasing the baseline upper FM limit from 38 to 45 to take advantage of predicted higher impact in the better functioning individuals.

Impact on Health Care Delivery for Veterans:
The long-range goal of the proposed work is to meet the Veterans Health Administration Office of Research and Development Strategic Plan 2009-2014 listed objective 2.6 and transform the field of rehabilitation by developing evidence and procedures that selectively incorporate robot-assisted training into the routine management of stroke related upper extremity hemiparesis. Prevalence of stroke-induced disability in our veteran population is expected to rise since 64% of the population is aged 55 or older. 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 (Wagner 2011). We expect that the results from this study will provide objective evidence for choosing the Robot + TTT rehabilitation technique during the long time 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, findings should be generalizable to any intensive therapy oriented toward the impaired upper extremity, for example the intensive comparison therapy used in the VA Cooperative Study (Lo 2010). There will also be further insight gained into the issue of minimal clinically important difference (MCID) (Jaeschke 1989) in a range of outcome scales in the chronic period, when compensatory movement strategies become an important part of rehabilitation.

ID: VIEW4E02805EA0C00
Name: v2_Justification, Objective, & Research Design

HP-00062868 View: v2_Supporting Literature

Supporting Literature

1 * Provide a summary of current literature related to the research: ***If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer box below.***

Stroke is the primary cause of long-term disability in the United States with 795,000 new or recurrent strokes occurring each year. Weakness and spasticity of the upper extremity is a major cause of disability, and contributes to the related loss of quality of life. Following a hemiparetic stroke, only 5% regain full arm function and 20% regain no useful function at all. Although physical rehabilitation for post stroke recovery positively influences outcome, no one treatment strategy or protocol has demonstrated superiority. Results of rehabilitative robotic training studies for the upper extremity and constraint induced therapy (CIT) studies, such as the EXCITE trial, have confirmed that intervention can have a meaningful impact on motor function even many months post stroke. This has generated enthusiasm for further work in this area, but at the same time, an absence of wide range proven interventions, or scientific guidelines for the best method and timing of rehabilitation persists. See current literature list below:

2 If available, upload your applicable literature search:

Name	Created	Modified Date
Literature (0.01)	12/19/2014 12:06 PM	12/19/2014 12:06 PM

ID: VIEW4E02805A7E400
Name: v2_Supporting Literature

HP-00062868 View: v2_Study Procedures

Study Procedures

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below. (If this study is a collaborative UM/VA study please list each procedure that is being conducted and the locations where it is being conducted.)

1 * Describe all procedures being performed for research purposes only (these procedures would not be done if individuals were not in the study) and when they are performed, including procedures being performed to monitor subjects for safety or to minimize risks:

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

Participants enrolled in Maryland have baseline and periodic evaluations including transcranial magnetic stimulation (TMS), questionnaires, and functional and robotic evaluations conducted at the Research on Arm Function and Therapy (RAFT) labs located on the 2nd floor of the Allied Health building of the University of Maryland School of Medicine, considered VA research space by memorandum of understanding. Training sessions are performed at either the RAFT labs in the Allied Health Building or at the VAMHCS Loch Raven. MRI scans will be conducted at the University of Maryland Baltimore Magnetic Resonance Research Center. Saliva and blood samples will be collected at the VAMHCS Baltimore.

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 agree and who do not have any TMS or MRI exclusion criteria one baseline TMS evaluation and one baseline MRI will occur. Pain and expectation questionnaires will be given during the baseline period.

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. Using two separate robots which target different movements participants will progress through 3 robot programs sequentially with 12 sessions completed on the IMT wrist robot or the ArmeoPower, followed by 12 sessions on a shoulder-elbow robot, and the final 12 sessions will alternate between the wrist/Armeo Power and elbow-shoulder robot. Adjustments to this schedule may be made due to robot maintenance and availability. 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 agree and who do not have any TMS exclusion criteria one TMS evaluation will occur after final training and once 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.

Evaluation and test procedures may need to be repeated if there are technical difficulties with collection equipment.

PROCEDURES
A] Functional Upper Extremity Outcome Evaluations:
The outcome testing will be carried out by an experienced evaluator who is unaware of the potential predictors of response that we have identified and therefore unbiased. If a back-up tester is needed from the pool of trained testers, this person will similarly be unaware of the potential predictors. Upper extremity measures and evaluations of functional performance will be conducted at baseline, post training, and retention. The Standard Functional Evaluation will consist of: the Fugl-Meyer Upper Extremity Motor Performance Test (FM), the 6-Item Wolf Motor Function Test (WMFT), Stroke Impact Scale (SIS), Action Research Arm Test, isometric strength and range of motion evaluations of the shoulder, elbow, wrist, thumb, and grip (see below).

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 (Gladstone et al., 2002). In particular, it correlates well with interjoint coordination measures in the UE of stroke patients (Levin, 1996). The Fugl-Meyer (Fugl-Meyer et al., 1975) 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 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.

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 (Duncan et al., 1999). 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.

The 6-Item 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 (Morris et al., 2001). It has been modified for use with moderate to severely impaired patients (Liu et al., 2013). The time measure is a secondary variable because it measures function and we can compare to our previous work and other studies.

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 (Van der Lee et al., 2001). It is included as a secondary outcome for comparison to other studies and because we expect it to have neither floor nor ceiling problems in the target study population.

Isometric strength and range of motion:
Shoulder (flexion/extension/abduction), wrist (flexion/extension), and thumb opposition are tested using the BASELINE Hydraulic Hand Dynamometer. Although robot training does not include active movements of the fingers, or thumb, measurement of all joints is deemed necessary because subjects exert force to hold on to the machine handles and maintain hand position and the TTT training includes aspects of object manipulation. The hand-held dynamometer has been validated for use on stroke patients. Active range of motion is collected using standard goniometry.

Motion Monitoring:
The subject will be asked to wear a motion monitoring device with a three axis accelerometer on each wrist for a period of approximately four days. The monitoring will take place during the first and final weeks of the intervention.

B] Robotic Quantitative Measures:
The robot evaluation protocol involves the participant reaching for a series of point-to-point targets, clockwise around the circle pattern without robotic–assist in-between training sessions of 320 reaches. Robotic testing outcome variables include aiming error, movement time, movement units (directional changes in pathway), peak velocity, mean velocity, number of targets hit and path ratio. Repeated testing has demonstrated the reliability of these variables in stable stroke patients (Reinkensmeyer and Boninger, 2012). We will also compute three measures related to motor power and muscular strength: the direction-dependent magnitude of movement and force recorded as patients attempt to resist robot-imposed motion. The mechanical work done on the robot by the patient as the robot resists patient movement will also be calculated. We have shown that this can be mapped to the strength of specific muscles or muscle groups and our observations to date suggest that "quantization" may

be a basic feature of human motor behavior and the way it is recovered. Whether or not this hypothesis is confirmed by further experiment, quantification of submovements may still constitute a useful method to evaluate patients' recovery (Rohrer et al., 2002). We will decompose patients' movements into a sequence of submovements, quantify these speed profiles providing an estimate of movement sub-blending, giving an objective motor performance measure to augment the clinical evaluations. We can look at patient improvement during both training with the robot in assist mode and evaluation with the robot not assisting. The relationship between improvements in these measures and functional measures has not been explored previously but if they are strongly correlated then the robot settings might be a convenient way to track patient responses to therapy and to determine when therapy could be ended. In the new study we will investigate whether these variables (which reflect speed and accuracy) can achieve predictor status early during the course of each training period and also determine whether improvements reach a plateau and correlate with the measures of functional assessment using the Fugl-Meyer, WMFT and SIS-hand domain.

C] TMS Outcomes
On all participants who agree and who do not have any TMS exclusion criteria TMS evaluations will be conducted once at baseline, post-training, and post-retention periods. The purpose of these evaluations are mainly to measure baseline parameters that can enter the predictive model, but because evaluations are relatively brief and safe, post-training and post-retention measures can reveal changes in brain physiology that result from the intervention.

Stimulation of the nervous system may be performed using a magnetic stimulator. Magnetic stimulators are connected by cable to stimulator coils which are held in place by the experimenter or a mechanical coil holder on or near the scalp of the participant. When the magnetic stimulator is triggered, an electrical current passes through the coils, and brief magnetic field is produced surrounding the coil. This magnetic field is used to stimulate neuromuscular tissue underneath the coil, either in the brain, spinal cord, or periphery. Participants experience an auditory click, a mild vibration of the coil in some circumstances, and the excitation of underlying muscle or nervous tissue if the stimulation is above sensory or motor threshold. When central or peripheral motor systems are stimulated, motor evoked potentials (MEP) can be recorded unilaterally or bilaterally by EMG. Single, pairs, or groups of pulses can be delivered to briefly induce different types of nervous system circuit activity and record the output.

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 (Howard Leight, San Diego, CA) 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.

D] MRI evaluation:
MRI will be obtained on all participants who agree and who do not have any exclusion criteria. The MRI facility is located at the University of Maryland Medical Center, two blocks away from both the Allied Health Building and the VAMHCS. It consists of a 3T Siemens Tim-Trio scanner and includes a12-channel receive-only head coil. 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.

Normalization and Localization
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.

E] Genetic Polymorphism. Three polymorphisms that affect brain plasticity in some studies will be determined for each participant. They are BDNF, a growth factor, and two dopamine related genes: COMT, and DAT. A DNA-containing sample will be taken during baseline evaluations. A self-collection kit will be used to collect a saliva specimen. Participants will be told that the intent of the procedure is to collect a saliva sample from which DNA will be extracted for the purpose of obtaining genetic information for the study. Participants will be instructed not to eat or drink anything except water for 2 hours before the appointment and to not drink, smoke or chew gum for 60 minutes prior to the appointment. This will be verbally confirmed prior to providing the DNA sample. Participants will spit into a funnel until a 2mL liquid sample is provided. The sample will be combined with a stabilizing liquid, shaken for 5 seconds, and then tightly sealed. Participants will be provided access to drinking water and a snack at the completion of the procedure.

F] Blood RNA expression profiling and biobanking blood DNA for future blood DNA methylation profiling. DNA and RNA samples will be collected from peripheral blood of patients at 3 time points (Baseline, at the 6th week of the physical therapy, after the whole 12-week long physical therapy). The blood is usually drawn from the antecubital fossa with blood from the cephalic, basilic, or cubital veins. A total of THREE (3) whole blood vacutainers will be collected. This includes:
(1) Two 2.5 mL PAXgene® RNA blood vacutainers (BD, cat. no. 762165). Minimum volume requested is 2mL in each vacutainer;
(2) One 8.5 mL PAXgene® blood DNA tube: A minimum of 6 mL of blood is requested;
The sequence of filling the tubes is: one PAXgene® RNA tube, one PAXgene® DNA tube, the 2nd PAXgene® RNA tube. If blood amount is insufficient, please fully fill at least ONE of the two PAXgene® blood RNA tubes and then fill one PAXgene® blood DNA tube. Invert all blood collection tubes 10 times immediately following filling of the tube to ensure adequate mixing of the blood and additives. After inverting the filled tubes, store the tubes in -20C freezer between 2-5hr after blood drawing. The Tubes will then be transferred to -80C freezer for long term storage within 3 days. RNA will be extracted from PAXgene® blood tubes using PAXgene Blood miRNA Kit IVD (PreAnalytiX, a Qiagen/BD company). Paxgene blood DNA tubes will be biobanked for future purification of DNA.

G) Scalp Based Brain Activity Monitoring: Near-infrared spectroscopy (NIRS) and electroencephalography (EEG) are non-invasive scalp-based brain activity monitoring techniques that detect changes in brain blood oxygen and volume (NIRS) and electrical activity (EEG) that are associated with brain activity in different cortical regions. Participants who are asked to have scalp-based-brain-activity-monitoring performed will be asked to wear a fitted, elasticized cap embedded with sensors that detect and record these physiological changes. Preparation may require parting of the hair in the area of the sensors, or the use of washable gels or markers on the scalp and hair. Both techniques are non-invasive.

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 4 weeks completed on the IMT wrist robot or the ArmeoPower, followed by 4 weeks on the Shoulder-Elbow and completing with 4 weeks alternating sessions on the wrist/ArmeoPower and shoulder-elbow robot. Adjustments to this schedule may be made due to robot maintenance and availability. Participants will perform robot training for 45 minutes with each robot as described below followed by 15 minutes of TTT practice to complete their 60 minute intervention session.

Robotic Training: Each robot training session will require the participant to sit facing a workstation with their shoulder and upper thorax restrained by a racing style harness. Participants will interface with the robot manipulandum through a rigid support at the elbow, wrist and hand. They will perform a series of visually evoked, point-to-point, planar reaching or wrist placement tasks of increasing difficulty with the most affected limb (in the form of simple video games). The arm actions move an image on a computer screen providing visual feedback to the patient. Each session includes training with the robot in assistive and unassisted games. The assistive mode is responsive to the movement of the participant starting with low precision, which is progressively increased by reducing the radius of the target zone. In later trials, if the participant achieves high precision without robot guidance and/or assistance a progressively increasing (robot-generated) frictional load is added to oppose motion. To ensure there is adequate, but not excessive challenge in the task, the task difficulty will be increased and decreased automatically based on a running average of current performance. The maximum and minimum percent of successful trials is 90% and 70% respectively.

Description of Robots:
1) IMT InMotion2 Shoulder-Elbow or Planar Robot: This robot provides two translational degrees-of-freedom for elbow and forearm motion. It can move, guide or perturb the upper limb and record motions and mechanical quantities such as the position, velocity, and forces applied. The system uses impedance control and direct drive brushless motors specifically for rehabilitation. If a person is unable to move their arm, the robot guides the hand to the target in much the same way as a therapist

provides “hand-over-hand” assistance during conventional therapy. When a patient is able to initiate movement, the planar robot's low impedance control guarantees that the robot will not interfere with his/her attempts to move. It meets or exceeds applicable safety standards for operation in a clinical environment with use in a clinical rehabilitation context since 1991 without incident including the VA multi-site trial (Lo et al., 2010). The robot will provide assistance (in the adaptive mode) as follows: If the patient has not initiated movement within a specified interval after target presentation (e.g., 2 seconds), the robot will move the shoulder and elbow to drive the hand towards the target following a trajectory typical for normal human reaching movements (e.g., straight path, bell-shaped tangential speed profile). If the patient initiates motion within the specified interval, the robot will provide guidance and/or assistance to produce a straight, smooth motion to acquire the target with a specified radial precision.

2) Wrist Robot: This 3 degrees-of-freedom (DOF) robot also uses an impedance control system and can move, or guide the movement of the wrist as well as record mechanical quantities such as the position, velocity, and forces applied. It accommodates the range of motion of a normal wrist for everyday tasks, ie: flexion/extension 60˚/60˚, abduction/adduction 30˚/45˚, pronation/supination 70˚/70˚. The torque output from the drive is capable of lifting the patient's hand against gravity, accelerating against inertia, and can overcome most forms of hypertonicity and it has demonstrated its safety in numerous trials including the VA multi-site trial (Lo et al., 2010).

3) ArmeoPower Robot: The ArmeoPower is a rehabilitative exercise device for upper extremity therapy. The main component of the ArmeoPower is a motorized arm orthosis, which is able to support the weight of a patient's arm and to assist the patient during specific exercises in a large 3D workspace. The ArmeoPower is intended for patients who have lost the function or have restricted function in their upper extremities caused by central nervous or peripheral neurogenic, spinal, muscular or bone-related disorders. The ArmeoPower supports specific exercises for increasing the strength of muscles and the range of motion of joints in order to improve motor function. Furthermore, the ArmeoPower assists clinicians in evaluating these functions.

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.

2 * Describe all procedures already being performed for diagnostic or treatment purposes (if not applicable to the study, enter "N/A"):
N/A

3 * Describe the duration of an individual participant's participation in the study:
The participant's maximum study commitment including baseline testing and the retention follow-up will be 40 weeks.

4 * Describe the amount of time it will take to complete the entire study:
This study will be 4 years in length.

5 * Describe any additional participant requirements:
N/A

ID: VIEW4E0280585B400
Name: v2_Study Procedures

HP-00062868 View: v2_Sample Size and Data Analysis

Sample Size and Data Analysis

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * Provide the rationale and sample size calculations for the proposed target population:

Based on our record of recruitment and design feasibility, we propose to enroll 96 participants. Our previous 12-week study (HP-42797) has an attrition rate after enrollment of 12% so we anticipate completing about 85. We verify that with our sample size of 85, 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 WMFT of greater than 5. The table below displays the standard error (SE) of the estimated AUC for several values of the true AUC and different prevalence of responders [44]. The SE is less than 0.07 in all cases except when AUC is 0.7 and the proportion of responders is only 33%.

2 * Provide the plan for data analysis. Include in the description the types of comparisons that are planned (e.g., comparison of means, comparison of proportions, regressions, analysis of variance, etc.), which is the primary comparison/analysis, and how the analyses proposed will relate to the primary purposes of the study:

Analysis Plan for Aim #1.

We will develop a predictive model for the primary outcome, a (positive) change in FM of greater than four points at 12 weeks. A five point change in FM is considered to be a MCID [39]. With our proposed sample size of 96 subjects and 12% attrition rate, we expect to have 85 subjects completing the study. We will select potential predictors based on our prior research and clinical judgment. Then we want to select a smaller subset of variables from a large number of candidate predictors for predicting the primary outcome because including too many variables in the model (overfitting) will reduce predictive performance on new data. One traditional way of variable selection is by stepwise regression, which is easy to use but it does not impose any penalty for including too many variables. The regularization methods are a class of methods developed to improve the variable selection. These methods impose a penalty to overfitting, so they can find the best model not just for the current data (the training set), but for the data in the future. Ridge regression, LASSO and elastic net all fall into this class of regularization nmethods. Ridge regression imposes a penalty on the absolute size of the regression coefficients. The LASSO (Least Absolute Shrinkage and Selection Operator) regularization in logistic regression, penalizes the absolute size of the regression coefficients, so that some regression coefficients are shrunk to zero [40]. The elastic net, which penalizes both the absolute size of the regression coefficients and the squared regression coefficients, incorporates both ridge regression and LASSO. Elastic nets work well even for highly correlated predictors. We will develop several prediction models, with the first including only demographic variables, the second including demographic variables and baseline measures of movement ability, the third including variables in the second plus MRI data, and the fourth including variables in the third model plus genomics data .The prediction performance measures, including the C statistic, misclassification rate will be computed and compared across different models.

Aim #2

We will use K-fold cross validation method to perform cross-validation. In particular, we will stratify all subjects by our primary outcome (FM change >4), and split the data into K mutually exclusive and roughly equal-sized parts within each stratum. For the first time, we will use the first subset with ΔFM>4 and the first subset with ΔFM<=4 to form a validation set and use the rest of the data (K-1 fold) to form a training set. The regularized logistic regression models will be used to develop a prediction model based on the training set. We will apply the prediction model to the validation set in order to calculate the prediction error. We repeat this process for K times, each time choosing a different subset (one fold) as the validation set and the rest as the training set. Then the K estimated prediction errors will be combined to use as an overall measure of the prediction performance. The estimate of the area under the ROC curve (AUC) and its standard error will also be computed. In addition, as secondary analyses, we will also develop a predictive model for a change in SIS hand score of >17.8 at 12 weeks and at 24 weeks, as well as predicting a change in WMFT of < -10 sec at 12 weeks and 24 weeks. We will apply the predictive models in Aim 1 to the test data set to further assess the performance of the models. Estimate of the AUC and its standard error will be computed. AUCs from nested models will be compared using the test proposed by DeLong and others.

Aim #3

Ipsilateral silent period in triceps and extensor carpi radialis will be measured at each period. The MRI session will be only at baseline. Analysis Plan. We will apply mixed linear models to longitudinal outcome data, where the change in FM is the primary response variable, and the change in silent period is the primary independent variable. We will also include other risk factors and confounders in the model; correlation among changes in FM and other outcome variables will be handled by subject level random effects in the model. The regression coefficient corresponding to the change in silent period will be estimated along with its standard errors. P<0.05 is considered to be statistically significant. Analyses will be conducted using both SAS (SAS Institute Inc., NC, USA) and R (http://www.r-project.org/).

ID: VIEW4E02806052800
Name: v2_Sample Size and Data Analysis

HP-00062868 View: v2_Sharing of Results

Sharing of Results

1 * Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how it will be shared:

All participants will be receiving the same intervention protocol, however, we would not want to bias their participation prior to completion of the study, therefore the results of the individual assessments will be discussed with the curious participant upon completion of the study.

ID: VIEW4E02808CBD800
Name: v2_Sharing of Results

HP-00062868

View: v2_Psychological/Behavioral/Educational Methods and Procedures

Psychological/Behavioral/Educational Methods & Procedures

You indicated on the "Type of Research" page that your study involves a psychological/behavioral/educational method or procedure such as a survey, questionnaire, interview, or focus group.

1 * Select all behavioral methods and procedures which apply to this study:

- [x] **Surveys/questionnaires**
- [x] **Key informant or semi-structured individual interviews**
- [ ] Focus groups or semi-structured group discussions
- [x] **Audio or video recording/photographing**
- [ ] Educational tests or normal educational practices (education instructional strategies, techniques, curricula, or classroom management methods)
- [ ] Individual or group behavioral observations
- [ ] Psychosocial or behavioral interventions
- [ ] Neuropsychological or psychophysiological testing
- [ ] Deception
- [ ] Other psychosocial or behavioral procedures

ID: VIEW4E09416F57800
Name: v2_Psychological/Behavioral/Educational Methods and Procedures

HP-00062868 View: v2_Surveys/Questionnaires

Surveys/Questionnaires

You indicated that this study involves surveys and/or questionnaires.

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * List all questionnaires/surveys to be used in the study, including both standardized and non-standardized assessments:
Stroke Impact Scale, Brief Pain Inventory, and Therapy Expectation

2 * Upload a copy of all questionnaires/surveys:

Name	Created	Modified Date
Brief Pain Inventory(0.01)	6/23/2016 2:34 PM	6/23/2016 2:34 PM
Therapy Expectation(0.01)	6/23/2016 2:33 PM	6/23/2016 2:33 PM
Stroke Imapct Scale 3.0(0.01)	12/19/2014 2:04 PM	12/19/2014 2:04 PM

3 * What is the total length of time that each survey is expected to take?
The Stroke Impact Scale is a self-report of impairment, disabilities, and quality of life changes related to stroke which takes about 10 minutes to complete. The Therapy Expectation questionnaire is a three question self-report of anticipated results of the study which takes about 5 minutes. The Pain Inventory is a self-report of pain the subject is experiencing on a daily basis at the beginning of the research study and will take 10 minutes to complete. A member of the research team will be present to administer this scale in the case that some questions regarding emotions or function cause frustration.

4 * Are any of the questions likely to cause discomfort in participants or cause harm if their confidentiality were breached? (i.e., Illegal activities)
○ Yes ● **No**

5 * Do any questions elicit information related to the potential for harm to self or others?
○ Yes ● **No**

5.1 If Yes, what procedures are in place to assure safety?

ID: VIEW4E09460F5EC00
Name: v2_Surveys/Questionnaires

HP-00062868 View: v2_Interviews

Interviews

You indicated that this study involves key informant or semi-structured individual interviews.

1 * Are any of the questions likely to cause discomfort in participants or cause harm if their confidentiality were breached? (i.e., Illegal activities)

○ Yes ● **No**

2 * Upload a copy of the interview script or guide that will be used to guide the interviews:

Name	Created	Modified Date
Semi-Structured Interview(0.01)	5/23/2017 10:50 AM	5/23/2017 10:50 AM

3 * What is the individual duration of each interview and what is the entire duration of the interviews?

The semi-structured interview will take about 8-12 minutes to complete and will be recorded for later review.

4 * How will the interview responses be recorded and by whom?

The interview will be digitally recorded on a university computer for later review and transcription by a research team member.

5 * Do any questions elicit information related to the potential for harm to self or others?

○ Yes ● **No**

5.1 If Yes, what procedures are in place to assure safety?

ID: VIEW4E0947A633C00
Name: v2_Interviews

HP-00062868 View: v2_Audio or Video Recording / Photographs

Audio or Video Recording/Photographs

You indicated that this study involves audio or video recording/photographing.

1

* Indicate the type of recording (check all that apply):

- [ ] Video
- [x] **Audio**
- [ ] Still Photo
- [ ] Other

1.1

If Other, specify:

2

* What is the purpose of the recording? (i.e., for therapeutic purposes, to establish treatment fidelity, or to establish reliability of assessments)

During the semi-structured interview, the subject's responses will be recorded digitally for later transcription by a team member allowing the subject to speak at their own pace without interruption.

3

* Could the recording be likely to cause discomfort in participants or cause harm if their confidentiality were breached?

○ Yes ● **No**

4

* How will individuals' identities be protected?

The computer files of the audio recordings will be kept on password and firewall protected computers and servers. The files will be kept with the subject's ID number rather then their name.

ID: VIEW4E094C128C800
Name: v2_Audio or Video Recording / Photographs

HP-00062868 View: v2_Sample Collection/Analysis

Sample Collection/Analysis

You indicated on the "Type of Research" page that your study involves a sample (specimen) collection and/or analysis.

1 * What type of samples will be involved in this study? (Check all that apply)

- [x] **Prospective (will be collected)**
- [ ] Existing (previously collected at the time of initial IRB submission)

2 * Will genetic analysis/testing be done on any of the samples?

● **Yes** ○ No

3 * Will this study involve banking of samples (storing for future research use)?

● **Yes** ○ No

4 * What is the purpose of the sample collection and/or analysis?

We are attempting to find genetic markers that would aid in predictively determining whether a participant will positively respond to therapy. With the addition of RNA from whole blood, we are also examining gene expression profiles for a similar purpose, as well as examining the longitudinal response to treatment, correlating gene expression changes with outcomes.

5 * Is there the possibility that cell lines will be developed with any of the samples?

○ Yes ● **No**

6 * Will the samples be released to anyone not listed as an investigator on the protocol?

○ Yes ● **No**

6.1 If Yes, give name(s) and affiliation(s):

7 * Will the sample material be sold or given to any third parties?

○ Yes ● **No**

7.1 If Yes, give name(s) and address(es):

ID: VIEW4E0E1A4B80000
Name: v2_Sample Collection/Analysis

HP-00062868 View: v2_Prospective Samples

Prospective Samples

You indicated that the study involves collection of prospective samples (specimens).

1 * What type of sample will be collected? (Check all that apply)

- [x] **Blood**
- [ ] Bone Marrow Aspirate/Biopsy
- [ ] Cerebrospinal Fluid
- [x] **Saliva**
- [ ] Skin
- [ ] Sputum
- [ ] Stool
- [ ] Tissue
- [ ] Tumor
- [ ] Urine
- [ ] Other

1.1 If Other, specify:

2 For blood draws, specify the amount drawn, in teaspoons, at each visit and across the course of the subject's entire participation time:
2.7 teaspoons (13.5ml) at each visit for 3 visits; a total of 8.2 teaspoons (40.5 ml) blood will be drawn across the course of the subject's entire participation time.

3 * What type of samples will be collected? (Check all that apply)

- [x] **Samples obtained specifically for research purposes-obtained via a separate collection procedure done solely for the purposes of the study**
- [ ] Samples obtained specifically for research purposes-additional taken during a clinical procedure
- [ ] Leftover samples that were obtained for clinical purposes (no additional research procedures required)
- [ ] Commercial (for profit) samples
- [ ] Other

3.1 If Other, specify:

4 * How are these samples labeled? For example, do they contain name, initials, dates, Social Security number, medical record number, or other unique code?
Samples will be labelled with a study specific code and an encrypted date only.

5 * Will sample(s) be made available to the research subject (or his/her medical doctor) for other testing?
○ Yes ● **No**

6 * If a participant withdraws from the study, will that participant have the option to get the remaining portion of their sample(s) back?
○ Yes ● **No**

7 * If the participant withdraws, explain how their sample(s) will be handled (For example, will sample(s) be destroyed, anonymized, etc.):
Samples will be anonymized.

8 * Will the samples be destroyed after the study is over?
○ Yes ● **No**

8.1 If No, describe how the samples will be stored, where they will be stored, and for how long.
Samples will be stored in the VA Laboratory Research area as long as the study stays open.

ID: VIEW4E0E257D60C00
Name: v2_Prospective Samples

HP-00062868 View: v2_Genetics Research

Genetics Research

You indicated that genetic analysis/testing is being done on the samples.

1 * How would you classify your genetic study? (choose all that apply)

- [ ] Gene Transfer
- [ ] Pedigree Study (to discover the pattern of inheritance of a disease and to catalog the range of symptoms)
- [ ] Positional cloning (to localize and identify specific genes)
- [ ] DNA diagnostic study (to develop techniques for determining the presence of specific DNA mutations or polymorphisms)
- [x] **Other**

1.1 If Other, specify:
Determination of known polymorphisms by PCR amplification of specific gene segments and hybridization with polymorphism-specific probes; Determination of whole genome gene expression profiles in blood by microarray analysis.

2 * Discuss the potential for psychological, social, and/or physical harm that could result from participation in this research. In your discussion, consider the following aspects: risks to privacy, confidentiality, insurablity, employability, immigration status, paternity status, educational opportunities, or social stigma.
Since the data that is being collected is not being communicated to the subject or to identities outside of the research team, there is no risk to insurability, employability, immigration status, paternity status, educational opportunities, or social stigma. The genetic polymorphisms that are being evaluated have a weak relationship to personality, cognitive, and motor traits, but represent common variants present in the general population. Although they will be maintained in a confidential database, they are not related to risks of any of the listed aspects.

3 * Will subjects receive any information resulting from the genetic analysis?
○ Yes ● **No**

3.1 If Yes, describe the information that subjects will receive:
Please note: genetic analysis results should only be shared if the testing will be performed in a CLIA certified lab.

4 * Will participants be offered any type of genetic or educational counseling?
○ Yes ● **No**

4.1 If Yes, who will provide the education or counseling?

4.2 Under what conditions will education or counseling be provided?

5 * Is there the possibility that a family's pedigree will be presented or published?
○ Yes ● **No**

5.1 If Yes, describe how you will protect family members' confidentiality:

ID: VIEW4E0E7C50FBC00
Name: v2_Genetics Research

HP-00062868 View: v2_Sample Banking

Sample Banking

You indicated that the study involves banking of samples (storing for future research use).

1 * Where will the sample(s) be banked? (If this study involves the VA, please state the name of the registry/repository and the CICERO protocol number is was approved under.)
The blood samples will be banked in VA Baltimore GRECC facilities.

2 * Does the banking institution have an approved policy for the distribution of samples?
● **Yes** ○ No

3 How long will the sample(s) be kept?
as long as the quality being competent.

4 * Will sample(s) be made available to the research subject (or his/her medical doctor) for other testing?
○ Yes ● **No**

5 * If a participant withdraws from the study, will that participant have the option to get the remaining portion of their sample(s) back?
○ Yes ● **No**

6 * If the participant withdraws, explain how their sample(s) will be handled (For example, will sample(s) be destroyed, anonymized, etc.):
samples will be anonymized

7 * If the participant withdraws, explain how the data obtained from their sample(s) will be handled (e.g., will it be deleted?) ***(Please note that data for FDA regulated research cannot be deleted):***
Data will be anonymized.

ID: VIEW4E0E7E82B5800
Name: v2_Sample Banking

HP-00062868 View: v2_Data Collection / Record Review

Data Collection/Record Review

You indicated on the "Type of Research" page that your study involves data collection or record review (i.e., chart review, not self-report).

1 * What type of data will be collected/analyzed in this study? (Check all that apply)

- ☐ Retrospective/Secondary Analysis (data has already been collected at the time of initial IRB submission)
- ☑ **Prospective (data is not yet in existence and/or collected)**

2 * Will this study involve adding data to a registry or database for future use?

- ● **Yes** ○ No

3 * Will the data be released to anyone not listed as an investigator on the protocol?

- ○ Yes ● **No**

3.1 If Yes, give name(s) & affiliation(s):

ID: VIEW4E0E25A8CA400
Name: v2_Data Collection / Record Review

HP-00062868 View: v2_Prospective Data

Prospective Data

You indicated that the study involves the collection of prospective data.

1 * Where is the data being collected from? (Check all that apply)

- [x] **Medical records**
- [x] **Medical images**
- [ ] Commercial (for profit) entity
- [ ] Publicly available records
- [ ] Schools
- [x] **Other**

1.1 If Other, please specify:
Physiological and neurophysiological data from the subject

2 * What data fields will you have access to/collect for the study? For example, name, initials, date of birth, Social Security number, income, demographic information, family units, housing, etc.
Name
Date of birth
Soc Sec (for VA forms only)
EMG
MRI
kinematic data

You can also upload a copy of the data fields/variables to be collected for the study:

Name	Created	Modified Date

There are no items to display

ID: VIEW4E0E25B643800
Name: v2_Prospective Data

HP-00062868 View: v2_Data Registry

Data Registry

You indicated that the study involves adding data to a registry or database for future use.

1 * What is the name of the registry/database to which data will be added? (If this study involves the VA, please state the name of the registry/repository and the CICERO protocol number it was approved under.)
The Baltimore GRECC GERI database

2 * What is the purpose of the registry/database?
GERI is a secure password protected database behind the VA firewall that serves as a data repository for GRECC data.

3 * Who has oversight and controls access to the registry/database?
The GERI biostatistics core provides oversight and control over access to the database.

4 * Who will have access to the registry/database?
Study team members. If a team member leaves the study their access wil be revoked immediately.

5 * How long will the data be stored in the registry/database?
Indefinitely as VA research data can not be destroyed. We wil follow the VA RCS10.1 data retention/destruction policy.

6 * Are participants in the study allowed to request that their data be removed?
◯ Yes ● **No**

6.1 If No, explain why subjects will not be able to request that their data be removed:
Data will not be removed from the data base, however participants will have the option to not be enrolled in the database at the time of consent.

ID: VIEW4E0E25BCFA400
Name: v2_Data Registry

HP-00062868 View: v2_Participant Selection

Participant Selection

1 * How many local potential participants (or specimens/charts) do you anticipate will be screened for this study? ***Screening includes determining potential participants' initial eligibility for and/or interest in a study.***
200

2 * How many participants (or specimens, or charts) will be enrolled/used for this study? ***A local prospective participant is considered enrolled in the study when a UM-approved Informed Consent Document (not including separate screening consent forms) is signed.***

Local - the number being enrolled at this site:
80

Worldwide - the number being enrolled total at all sites (including local enrollment):
96

3 * Gender:

- [x] **Male**
- [x] **Female**

4 * Age(s):

- [ ] 0 to 27 days (newborn infants)
- [ ] 28 days to 12 months (Infant)
- [ ] 13 months to 23 months (Toddler)
- [ ] 2 to 5 years (Preschool)
- [ ] 6 to 11 years (Child)
- [ ] 12 to 17 (Adolescents)
- [x] **18 years and older (Adult)**
- [ ] 89 years and older

5 * Race/Ethnicity:

- [x] **All Races Included**
- [ ] American Indian or Alaskan Native
- [ ] Asian/Other Asian
- [ ] Asian/Vietnamese
- [ ] Black or African American
- [ ] Hispanic or Latino
- [ ] Mixed Race or Ethnicity
- [ ] Native Hawaiian or Pacific Islander
- [ ] White or Caucasian

6

* Language(s):

- [x] **English**
- [ ] Chinese
- [ ] French
- [ ] Italian
- [ ] Japanese
- [ ] Korean
- [ ] Local Dialect

- [ ] Spanish
- [ ] Vietnamese
- [ ] Other

6.1 Specify Other:

7

* Are you excluding a specific population, sub-group, or class?

◯ Yes ● **No**

7.1

If Yes, indicate your justification for excluding a specific population, sub-group, class, etc.:

ID: VIEW4E0E519C1D000
Name: v2_Participant Selection

HP-00062868 View: v2_Vulnerable Populations

Vulnerable Populations

1 * Will you be targeting ANY of the following Vulnerable Populations for enrollment? (Select all that apply)

- [ ] Employees or Lab Personnel
- [ ] Children (Minors)
- [ ] Cognitively Impaired/ Impaired Decision Making Capacity
- [ ] Pregnant Women/Fetuses
- [ ] Wards of the State
- [ ] Students
- [ ] Prisoners
- [ ] Nonviable Neonates or Neonates of Uncertain Viability
- [ ] Economically/Educationally Disadvantaged
- [x] **None of the above**

Only select populations which you will be targeting for enrollment. Do not include populations that may be enrolled incidentally. Enrollment of a vulnerable population is considered to be "targeted" if the study team will be aware that a subject is from a vulnerable group as a result of interaction with the subject or collection of specific information about the subject, and the research team does not wish to exclude them. "Incidental" enrollment is limited to situations where a study team is unaware that a subject is from a vulnerable group.

ID: VIEW4E0E519917800
Name: v2_Vulnerable Populations

HP-00062868 View: v2_Eligibility

Eligibility

1 * Do you have an existing Eligibility checklist(s) for this study?

◯ Yes ● **No**

1.1 If Yes, upload here. If you need a template, you can download it by clicking **HERE**. The checklists you upload will also be available under the Documents tab of this application.

Name	Created	Modified Date
There are no items to display		

1.2 If No, create an eligibility checklist below:

List inclusion criteria (List each Inclusion Criteria individually, using the ADD button):

	Number	Criteria
View	1	Clinically defined, unilateral, hemiparetic stroke with radiologic exclusion of other possible diagnosis
View	2	Stroke onset at least 6 months before enrollment
View	3	Present with Mild/Moderate to Severe arm dysfunction (based on Fugl-Meyer scores of 10 to 45)
View	4	Be medically stable to participate in the study and not have contractures or other impairments that would interfere with the interventional training.

List exclusion criteria (List each Exclusion Criteria individually, using the ADD button):

	Number	Criteria
View	1	Unable to give informed consent
View	2	Have a serious complicating medical illness that would preclude participation.
View	3	Contractures or othopedic problems limiting range of joint motion in the potential study arm
View	4	Visual loss such that the subject would not be able to see the test patterns on the robot computer monitor
View	5	Botulinum toxin to study arm within four months of baseline testing or if received during the study period
View	6	Unable to comply with requirements of the study

After entering the inclusion and exclusion criteria above, click the Save link. CICERO will automatically generate a printable Eligibility Checklist for you to use in your research. To review the checklist, click on the resulting link below. This checklist is also available under the Documents tab of this application.

Eligibility Checklist for HP-00062868_20 v1-30-2018-1517346128014(0.01)

ID: VIEW4E0E5185F9000
Name: v2_Eligibility

HP-00062868 View: v2_Recruitment

Recruitment

1 * Describe plans for recruitment, including the identification of potential participants (or acquisition of charts/records/samples) and initial interactions with them: (If this study involves the VA please list all sites at which recruitment will take place.):

Recruitment will occur from within the VAMHCS (e.g. Baltimore, Perry Point, and Loch Raven locations) through the outpatient stroke and rehabilitation clinics as well as the University of Maryland Rehabilitation and Orthopaedics Institute (UMROI). Subjects with upper extremity weakness due to hemiparetic stroke will be recruited at and screened for eligibility. Three primary mechanisms will be used:

1. Initial contact will be made through the VAMHCS occupational and physical therapy department or VA stroke clinic. The clinician will explain the study purpose and ask the patient if they would like to find out more information about participation. If a patient is determined to be a potential study candidate, name and phone number will be recorded so that the patient can be contacted. The study coordinator will either be contacted by the clinician or by the interested patient for an initial screening. Before participation, the research team member and the participant will discuss the major aspects of the study, complete an "evaluation to sign the informed consent form" and proceed to signing the informed consent.

Other avenues of recruitment include inservices to health providers (therapists, MD's, and nurses) within the VAMHC and community hospitals, and newspaper advertisment.

2. The Kernan Stroke Database (HP-00040358) will also be used as a recruitment mechanism. 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 and first contact will follow the standards listed above.

3. The PEPPER center registry--please see below:
People who respond to our advertisements will be contacted by telephone and informed about the general aspects of the studies. If interested in participating in this study they will then be contacted via telephone by the research study staff who will inform them about the general aspects of the study and go through an initial telephone screening process. The information we obtain from participants during the telephone screening will be entered into the IRB approved Pepper Center Registry (H-28418). This registry is designed to collect and store information across research studies undertaken by investigators in the VA and University of Maryland. Information in the registry will be used to screen participants for entry into this research project, as well as serve as a source of participants for future recruitment into new IRB approved studies carried out by UMB and VA researchers. As described in the Pepper Center Registry IRB application (H-28418), the only data that will be stored in the registry will be data that has previously been approved for collection by the IRB under this IRB application. Thus, we are not requesting permission to collect new data. Only those subjects who approve having their information entered into the registry and agree to be re-contacted in the future for new studies will be entered in the registry. If at some time in the future participants wish to have their data removed from the registry, the data will be removed. The design and procedures related to the entry of data in the registry and their protection are detailed in section F1 of H-28418, including the protection of PHI data by encryption and limiting access to the registry (i.e. by requiring a user name and password as well as access to the secured VA local area network). A few questions will be asked over the phone about their height, weight, general health and prescribed medications as this will help clarify whether they are eligible for the study. At the first visit, the PI, co-investigator or a member of the research staff will review the study with the participant and answer their questions. Informed consent will be obtained, HIPAA regulations reviewed, and all forms signed. Results of tests will be given to, and reviewed with participants in a private area by the PI, co-investigator and/or research staff.

2 * Describe measures that will be implemented to avoid participant coercion or undue influence (if not applicable to the study, enter "N/A"):

Participants will be informed that the study is voluntary and that they have a right to withdraw from the study at any time for any reason. It will be emphasized upon withdrawal that they will not lose eligibility for medical care or services at the VA or University of Maryland Medical Center, nor will they lose eligibility to participate in any future research studies. Informed consent will follow institutionally approved guidelines, including protection of confidential information relating to medical history and other information gathered to determine eligibility criteria.

3 * Who will recruit participants (or acquire charts/records/samples) for this study? (Check all that apply)

- [x] **PI**
- [x] **Study Staff**
- [ ] Third Party

3.1 If you are using a third party, specify Third Party Recruiters:

4 Upload any recruitment tools such as screening/telephone scripts and introductory letters (do not upload advertisements here):

Name	Created	Modified Date
SRT4 Participant Phone Screening(0.01)	10/1/2018 10:37 AM	10/1/2018 10:37 AM

ID: VIEW4E0BCAA0A6C00
Name: v2_Recruitment

HP-00062868 View: v2_Advertising

Advertising

1 * Will you be using advertisements to recruit potential participants?

● **Yes** ○ No

ID: VIEW4E0BCCF811000
Name: v2_Advertising

HP-00062868 View: v2_Advertising Detail

Advertising Detail

You indicated that you will be using advertisements to recruit potential participants.

1.1 * Select the mode(s) of advertising (check all that apply):

- [ ] Radio
- [ ] Internet
- [x] **Print**
- [ ] Television
- [ ] Other

1.1.1 If Other, specify:

1.2 * Provide exact text of all proposed advertisement(s):

What is the goal of this Chronic Stroke Study?
Recent VA studies have shown that robot-assisted rehabilitation can benefit patients who have difficulty using their arm even at 6 months or more after experiencing a stroke.
Doctors at the VA and University of Maryland are conducting a study to examine predictors of recovery and potential mechanisms of recovery in participants enrolled in an exercise program that combines “hands on” task specific arm training with robot therapy.
Additionally, information on brain anatomy and brain activity will be gathered using non-invasive techniques of magnetic resonance imaging (MRI) and transcranial magnetic stimulation (TMS)
Who is eligible?
To be eligible you must:
• have had a stroke > 6 months ago
• be 18 years of age or older
• have weakness in one of your arms
• be able to follow directions
• be Seizure-free (for TMS portion of study)

What is involved if I take part in the Study?
If eligible, you will receive a medical exam, arm evaluations, TMS and MRI testing. These evaluations will assess your ability to use and control your arm for the robot-assisted exercise as well as examine the excitability of your brain.
Evaluations will be performed:
• Prior to the start of the study
• During and after robot training
• At the completion of all robot exercise training
• At a 12 week follow-up visit

Training:
Once enrolled, you will be assigned to our robot-assisted arm therapy that includes 45 minutes of robot training combined with 15 minutes of “hands on” task specific arm training.
These treatments will last one hour and will be held three times a week for 12 weeks.

Procedures & training will take place at Baltimore VA Medical Center and The University of Maryland.
This study has been approved by the University of Maryland Human Studies Committee.

1.3 * Upload advertisement(s) here:

Name	Created	Modified Date
SRT4 Pamphlet(0.06)	10/7/2015 1:43 PM	5/18/2018 2:44 PM

ID: VIEW4E0BCE82B8C00
Name: v2_Advertising Detail

HP-00062868 View: v2_Research Related Risks

Research Related Risks

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer box below.

1 * Individually list each research-related risk, using a separate line for each. Next to each risk, delineate the likelihood/seriousness of the risk, and the provisions for minimizing the risk:

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 therapist 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 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.

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. 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.

6. The MRI scanner is loud. The risk of hearing loss from the scanning is minimized by having you wear earplugs or headphones. Some people experience anxiety (claustrophobia) when they get in the MRI. If this happens wave your hand and we will remove you from the scanner. The MRI may pose a risk to certain metallic or implanted electronic devices (pacemaker) or identify problems in your head that will require follow-up from your doctor.

7. Unexpected MRI findings. 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.

8. 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 in the Allied Health Building.

9. Blood-draw related risks. The risks of taking blood include pain, a bruise at the point where the blood is taken, redness and swelling of the vein and infection, and a rare risk of fainting. Subjects are being asked to fast for only 2 hours for the laboratory appointment, less than the gap between most meals and less than what is required for most routine clinical lab tests. There is an unlikely risk of feeling fatigued, lightheaded/faint, dizzy, or other discomfort, which will be reduced by offering a snack after the laboratory appointment. If subject has diabetes, they are asked to adjust their diet and medications according to their doctor's instructions, if needed.

10. 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, light-headedness, and dizziness.

11. Risks of Scalp Based Brain Activity Monitoring. The risks of scalp based brain activity monitoring or low frequency, low severity, and short duration and include discomfort from the preparation (parting of hair very finely, application of gels/tapes/marker/adhesives), discomfort from the sensors which must sit with pressure applied to the scalp, discomfort from any cap or material used to prevent movement of sensors, discomfort from holding the head relatively still for accurate measurements. All of these risks will be reduced by frequent checks with the participant regarding their comfort level, adjustment of the equipment, and removal if necessary.

ID: VIEW4E1B52509F000
Name: v2_Research Related Risks

HP-00062868

View: v2_Potential Benefits and Alternatives

Potential Benefits and Alternatives

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * Describe the potential direct benefit(s) to participants:
There is no direct benefit from participation in this study.

2 * Describe the importance of the knowledge expected to result from the study:
The delivery of rehabilitation has not benefited from improvements in information technology and robotics. The robot devices and therapeutic intervention being tested have the potential to provide therapy that is more focused and prescriptive for patients with arm weakness due to stroke. Participation may help the investigators better understand and improve the rehabilitation of arm problems in stroke patients.

3 * Describe how the potential risks to participants are reasonable in relationship to the potential benefits:
The risks are minimal and well controlled. The potential long term study benefits include the development of new therapies for stroke survivors that will reduce upper extremity disability and promote independence.

4 * Describe the alternatives to participation in this study. If there are no alternatives, state that participation is voluntary and the alternative is not to participate. For intervention studies, describe appropriate alternative clinical procedures or courses of treatment available to subjects.
Participation is voluntary and the alternative is not to participate.

ID: VIEW4E1B5251B0400
Name: v2_Potential Benefits and Alternatives

HP-00062868 View: v2_Withdrawal of Participants

Withdrawal of Participants

If the questions below are not applicable to the research (i.e., chart review), enter "N/A".

1 * Describe anticipated circumstances under which subjects will be withdrawn from the research without their agreement:

The investigator in charge of the research study can withdraw you from the study at any time without your approval. Possible reasons for removal include:
1) Failure to follow study related directions given by study team members.
2) Inability to contact for follow-up visits.
3) Inability to perform the tasks as required per the protocol.
4) Repeated missed appointments without contacting study staff.
6) Serious reaction to engagement in study related tasks.
7) A treatment option becomes available that may result in a better response for the participant.
8) The PI feels that the study is no longer in the patient's best interests
9) The entire study may be stopped by the sponsor, the study investigator or the Institutional Review Board for reasons not related to your participation. In that case, your participation will end unless another investigator is identified and approved by the Institutional Review Board. You will be informed by the study staff should this situation arise and provide you with the opportunity to ask questions.

2 * Describe procedures for orderly termination:

Orderly termination of a participant's involvement will occur when the end point of the investigation and subsequent evaluative sessions have concluded. The decision to withdraw a participant from the study will be based upon an individual's actions. If any of the above circumstances arise, a decision whether to withdraw a person will be made. The study participant and any regulatory agencies will be notified accordingly.

3 * Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection:

In the event of adverse events, these will be recorded and acted upon depending on the type of event. If partial withdrawal from procedures is desired by the participant, the PI will make a decision about whether the data can still be used or whether to censor the data from further analysis. Also, withdrawals for personal reasons with no adverse events will be noted. With all these situations, the appropriate regulatory agencies will be notifified accordingly.

ID: VIEW4E1B52531F800
Name: v2_Withdrawal of Participants

HP-00062868 View: v2_Privacy of Participants

Privacy of Participants

If the study does not involve interaction with participants, answer "N/A" to the questions below.

1 * Describe how you will ensure the privacy of potential participants throughout the study ***(privacy refers to persons and their interest in controlling access to themselves):***

Paper data collected by research team members will be secured in research specific binders. Physical data will be stored in locked cabinets in locked offices in Allied Health Building, considered VA research space by memorandum of understanding, and Bressler Research Building.

Electronic data will be stored either on VA or UMB electronic data storage.Combined data will be stored on UMB electronic data storage. All electronic data storage is FIPS-140-2 and HIPAA compliant and accessed via multi-factor authentication by authorized research team members only.

De-identified copies of electronic data will be stored on CD's in a locked file and/or on a secure research drive on university or VA servers. Appointments will not be scheduled or confirmed via email. Only de-identified data will be shared across study sites.

2 * Describe the location where potential participants will receive research information and detail the specific actions the study team will take to ensure adequate privacy areas:

All discussions with participants will be conducted in University of Maryland office or lab spaces with doors can be shut for privacy.

3 * Describe potential environmental stressors that may be associated with the research:

All participants that need assistance with directions or navigating the Allied Health Building will be escorted from the lobby to the lab.

4 * Will this study have a site based in the European Union?

◯ Yes ● **No**

5 * Will the study have planned recruitment or data collection from participants while they are located in the European Union?

◯ Yes ● **No**

Access link below for information about the EU General Data Protection Regulations to assist in answering these questions.
https://www.umaryland.edu/oac/general-data-protection-regulation/

ID: VIEW4E1B525B87C00
Name: v2_Privacy of Participants

HP-00062868 View: v2_Confidentiality of Data

Confidentiality of Data

1 * Will stored research data contain identifiers or be able to be linked to and identify individual participants (either directly or through a code/research ID)?

- (●) **Yes**
- ( ) No, the data will be stored de-identified/anonymous (stripped of all identifiers, no way to identify individual participants)

2 * Where will research data be kept (address electronic and paper data as applicable)? (If this is a VA study please list specific sites that data will be kept.)

Paper data collected by research team members will be secured in research specific binders. The research binders will be maintained in locked file cabinets in locked offices or in the locked robot room at the Allied Health Building when not in use. Data in electronic format will be stored behind the VA firewall on password protected VA servers, on university owned, password protected servers behind university firewalls, or on computers or devices with FIPS-140-2 certified encryption. De-identified copies of electronic data will be stored on CD's in a locked file and/or on a secure research drive on university or VA servers. Only de-identified data will be shared across study sites.

3 * How will such data be secured?

All research subjects are assigned a unique identifying number and all data processing is done utilizing this number rather than name, social security number, birth date or other specific individual identifying information. All data with identifiers are kept in locked cabinets in a locked room or on research computers protected by network firewalls and passwords. Any electronic data transmissions will consist of de-identified and/or encrypted data. As per current VA policy, in accordance with the VA records control schedule, no research data collected in this study will be destroyed. If at a later date the VA policy changes data will be destroyed using the most current approved methods available. If there is a loss of data, unauthorized access to sensitive data, or non-compliance with security controls it will be immediately reported to the PI and the appropriate VAMHCS Privacy Office and Information Security Personnel. The VA Research Compliance Office and IRB will also be notified.

Patient identifiers including the social security number are requested at the first enrollment visit in order to enter them into the VA medical system. This information is given to the VA enrollment office and the research copy is destroyed in the VA approved locked "shred-it" boxes. The research data itself is de-identified. Each participant is given a study # not related to their name or social security number for VA enrollment purposes. The research intervention file is de-indenfied with a study number on all pages except for one page in the emergency contact section. This section includes the patient's name and emergency contact information for use in an emergent situation during the intervention appointments.

Electronic data will be stored either on VA or UMB electronic data storage.Combined data will be stored on UMB electronic data storage. All electronic data storage is FIPS-140-2 and HIPAA compliant and accessed via multi-factor authentication by authorized research team members only. De-identified electronic data will not linked to the patients name, social security number or any other identifiying info. Any data that is extracted for analysis has all patient identifiers removed.

If there is a loss of data, unauthorized access to sensitive data, or non-compliance with security controls it will be immediately reported to the PI and the appropriate VAMHCS Privacy Office and Information Security Personnel. The VA Research Compliance Office and the IRB will also be notified.

4 * Who will have access to research data?

The PI and the study research staff will have access to the data. Any data sent to a non-va research team member (i.e. a statistician) will be de-identified. When a staff member leaves employment or is no longer a member of the research team, their access to data will be terminated via password or permission changes.

5 * Will study data or test results be recorded in the participant's medical records?

- ( ) Yes
- (●) **No**

6 * Will any data be destroyed? ***(Please note that data for FDA regulated research and VA research cannot be deleted)***

- ( ) Yes
- (●) **No**

6.1 If Yes, what data (e.g., all data, some recordings, interview notes), when and how?

7 Do you plan to obtain a Certificate of Confidentiality?

- ( ) Yes
- (●) **No**

7.1 If Yes, upload your Certificate of Confidentiality. If you have not yet obtained the Certificate, please note that once it is obtained, you will need to submit an amendment to attach the document, make any needed changes to the submission and make needed changes to the Informed Consent Document.

Name	Created	Modified Date
There are no items to display		

8 * Discuss any other potential confidentiality issues related to this study:

Confidentiality issues have been addressed above and other potential confidentiality issues are not anticipated.

ID: VIEW4E1B5265E0400
Name: v2_Confidentiality of Data

HP-00062868 View: v2_Monitoring Plan Selection

Monitoring Plan Selection

1 * Type of data safety monitoring plan for the study:

- ○ Will use/defer to the external sponsor's Data Safety Monitoring Plan
- ○ Data Safety Monitoring by a Committee
- ● **Data Safety Monitoring by an Individual**
- ○ There is no data safety monitoring plan in place

ID: VIEW4E1B00E30D400
Name: v2_Monitoring Plan Selection

HP-00062868 View: v2_Monitoring Plan - Individual

Monitoring Plan - Individual

You indicated that the monitoring will be done by an Individual.

1 * Identify the individual who will be performing the safety monitoring:
Michael Dimyan, MD

2 * Describe this individual's role in relation to the protocol:
Michael Dimyan is the PI for this protocol and the site PI for the Baltimore study site.

3 * What data will be reviewed?

- [x] **Adverse Events**
- [x] **Enrollment Numbers**
- [x] **Patient Charts/Clinical Summaries**
- [ ] Laboratory Tests
- [x] **Medical Compliance**
- [ ] Procedure Reports
- [ ] Raw Data
- [ ] Outcomes (Primary, Secondary)
- [ ] Preliminary Analyses
- [ ] Other

3.1 If Other, specify:

4 * What will be the frequency of the review?

- (●) **Annually**
- ( ) Bi-Annually
- ( ) Other

4.1 If Other, specify:

5 * Safety monitoring results will be reported to:

- [x] **IRB**
- [ ] GCRC
- [ ] Sponsor
- [ ] Other

5.1 If Other, specify:

ID: VIEW4E1B026A2A400
Name: v2_Monitoring Plan - Individual

HP-00062868 View: v2_Research Related Costs

Research-Related Costs

1 * Is the study's financial supporter (e.g., commercial sponsor, federal or state grant or contract, private foundation, physician-sponsor) covering any research-related costs?

- ○ No
- ● **Yes**

1.1 If Yes, check all that apply:

- ☑ **Research-Related Services (personnel costs, tests, supplies, exams, x-rays, or consultations required in the study)**
- ☑ **Investigational or Study Device**
- ☐ Investigational or Study Drug
- ☑ **Investigational Procedure(s)**

1.2 If No, who is responsible for payment?

2 * Who is responsible for the uncovered research-related costs?

- ☑ **Participant**
- ☐ Sponsor
- ☐ UM
- ☐ Other
- ☐ There will be no uncovered research-related costs

2.1 If Other, specify:

3 If the participant is responsible for any research-related costs, identify and estimate the dollar amount:
The participant is required to provide their own transportation to and from the testing / training. They do not have to pay for parking costs or Mobility services.

ID: VIEW4E1B5D9641800
Name: v2_Research Related Costs

HP-00062868 View: v2_Compensation for Research-Related Injury

Compensation for Research-Related Injury

1 * Is this study under a master agreement that includes a provision requiring the sponsor to provide compensation to participants for research-related injury?

○ Yes ● **No**

1.1 If Yes, please provide the date and title of the agreement and upload the portion of the contract language relevant to compensation for research-related injury:

Name	Created	Modified Date
There are no items to display		

1.2 If No (the study is not under a master agreement), is there proposed contract language concerning payment to participants for treatment in the event of a research-related injury?

○ Yes ● **No**

1.2.1 If Yes, indicate the status of the contract review/approval with the ORD and upload the proposed language relevant to compensation for research-related injury:

1.2.2

Name	Created	Modified Date
There are no items to display		

ID: VIEW4E1B629EEC000
Name: v2_Compensation for Research-Related Injury

HP-00062868 View: v2_Payment to Participants

Payment/Reimbursement to Participants

1 * Will participants receive payment (money, gift certificates, coupons, etc.) or reimbursement for their participation in this research?

● **Yes** ○ No

ID: VIEW4E1C52A5D7800
Name: v2_Payment to Participants

HP-00062868 View: v2_Payment Detail

Payment/Reimbursement Detail

You indicated that participants will receive payment (money, gift certificates, coupons, etc.) or reimbursement for their participation in this research.

1 * Payment/reimbursement to participants will be for: (check all that apply)

- [x] **Travel**
- [x] **Parking**
- [ ] Meals
- [ ] Lodging
- [ ] Time and effort
- [ ] Other

1.1 If Other, specify:

2 * What is the total dollar value of the payments/reimbursements over the duration of the study? ***Total payment(s) for participation in research of $600 or more is required to be reported on an IRS Form 1099.***
Up to $400

3 * Describe the timing and distribution plan for the payment/reimbursement (schedule, means, etc.)?
For participants that drive or are driven to the study, parking vouchers to the University garage next door will be given after each visit to cover the amount of time that was used in the study (2 or 3 hours at $8 or $9). Participants that take the Maryland Transit Authority (MTA) Mobility services will receive a voucher ($1.90) to cover the price of the trip home and one for return trip for the next visit.

4 * Method(s) of payment/reimbursement to be Used:

- [ ] Cash
- [ ] Check
- [ ] Money Order
- [ ] Gift Certificate/Gift Card
- [x] **Other**

4.1 If Other, specify:
Parking vouchers are obtained from the University of Maryland traffic office. The MTA mobility vouchers are obtained from the MTA directly.

ID: VIEW4E1C54A6ACC00
Name: v2_Payment Detail

HP-00062868 View: v2_HIPAA

HIPAA (Health Insurance Portability and Accountability Act)

1 * HIPAA applies to the University of Maryland School of Medicine, the University of Maryland School of Dentistry and the VA. Are you affiliated with, or will be accessing data from, any of these places? ● **Yes** ○ No

2 If Yes, will the study view, access, share, collect, use, or analyze health information that is individually identifiable under HIPAA? ● **Yes** ○ No

ID: VIEW4E1B0A2114400
Name: v2_HIPAA

HP-00062868 View: v2_Protected Health Information

Protected Health Information (PHI)

You indicated that HIPAA applies and the study will view, access, share, collect, use, or analyze health information that is individually identifiable.

1 * Which PHI elements will be used or disclosed in this study? (Check all that apply)

- [x] **Name**
- [x] **Address (if more specific than Zip Code)**
- [x] **Dates**
- [ ] Ages over age 89
- [x] **Telephone numbers**
- [ ] Fax numbers
- [ ] Email addresses
- [x] **Social Security numbers**
- [x] **Medical record numbers**
- [ ] Health plan beneficiary numbers
- [ ] Account numbers
- [ ] Certificate/license numbers
- [ ] Vehicle identifiers and serial numbers, including license plate numbers
- [ ] Device identifiers and serial numbers
- [ ] Web universal resource locators (URLs)
- [ ] Internet protocol (IP) address numbers
- [ ] Biometric identifiers, including fingerprints and voiceprints
- [ ] Full-face photographic images and any comparable images
- [ ] Any other unique identifying number, characteristic, or code, unless otherwise permitted by the Privacy Rule for re-identification
- [ ] None

2 * Why is the PHI necessary for this research?
If SSNs are going to be used, describe the specific use and type of SSN to be used (real, scrambled, last 4 digits).
The full social security number, date of birth, and name are required for enrollment into the VA medical record (CPRS system) and the GERI database. This information will be recorded on VA Form 1010-EZ which is submitted to the VA for entry into CPRS by authorized VA personnel and stored in their chart. We do not retain a copy of this form but we do store the last four of the SS# in the participant's HIPAA/Consent file as it is a required entry on the form.

3 * What is the source(s) of the PHI?
The source of the PHI would be from patient report and medical records.

4 * Provide written assurance that Protected Health Information will not be reused. (Note: this refers to re-use on another study or for a purpose which has not been approved, not to the re-use of screening data during the current study).
The PHI collected for the conduct of this study will not be used for another study or for any other purpose that has not been approved.

5 * How will permission to allow the use/disclosure of the individual's protected health information (PHI) be obtained? (Choose all that apply:)

- [x] **Obtain written authorization *(upload authorization form at the end of the application under "Consent and HIPAA Authorization Forms")***
- [x] **Requesting waiver/alteration of authorization (includes waiver of authorization for recruitment only)**
- [ ] Qualifies as a limited data set (LDS)

5.1 If you are using a limited data set (LDS), please attach the Data Use Agreement (DUA):

Name	Created	Modified Date

There are no items to display

ID: VIEW4E1B0A24AA400
Name: v2_Protected Health Information

HP-00062868 View: v2_Waiver/Alteration of Authorization

Waiver/Alteration of Authorization

You indicated that a waiver/alteration of authorization is requested.

1 * Provide rationale for how the research presents no more than minimal risk to the privacy of individuals:

The partial HIPAA privacy waiver will be used for recruitment purposes only. This information does not present an increase risk to the privacy of research participants as compared to the general population as the PHI parameters to be used for recruiting purposes are identifiers used by the general population on a daily basis.
The policies and procedures in place, and detailed below, also aide in the effort to minimize the potential risk to the privacy of individuals. The PI and study personnel will take every reasonable step to protect PHI. All PHI will be stored in locked room within a locked file cabinet. Only authorized study personnel who have completed HIPAA, Privacy and Information Security, and CITI training will have access to PHI. Research compliance officers of the VA R&D conduct routine audits to ensure proper usage and destruction of PHI. Full social security numbers are only used to enroll participants into the VA medical CPRS system. The last 4 of the social secruity numbers are present on the VA HIPAA form which will be stored separately from the participant file and be located in the study HIPAA/Consent form binder locked in the study coordinator's office. Because of these measures taken, our research does not present more than a minimal risk to the privacy of individuals.

2 * Describe the plan to ensure the protection of PHI collected during this study from improper use and disclosure:

All study procedures take place in a study team members office and/or the robot room. All paper study information will be kept in a locked file cabinet in the study personnel's locked office. Electronic files are kept on a secured research drive on the VA server. Appointments will not be scheduled or confirmed via email.

3 * Describe the plan to destroy the PHI collected during this study at the earliest opportunity consistent with the conduct of the research. If there is a need to retain PHI, provide a justification:

All data, including the investigator's research records and any participant identifiers will be retained until the maximum retention period is reached as defined by the Dept. of Veterans Affairs Records Control Schedule (RCS 10-1). When the maximum retention period is reached, the data will be destroyed using the most current electronic data destruction methodologies that are available at the time of data destruction.

4 * Why could the research not practicably be done without access to and use of this PHI?

PHI is needed to establish that potential participants listed in these registries meet basic inclusion criteria. Alternatively, exclusion criteria may also be determined at this time. Not all individuals who are stroke survivors will be considered for this study based on inclusion/exclusion criteria. The waiver is necessary to evaluate the basic clinical and demographic information to establish if a person is initially eligible, medically safe, and meets inclusion/exclusion criteria. The waiver gives us the practical ability to conduct the study and provides an alternative to an in-person evaluation to determine if subjects' are medically eligible and safe to enter; a process that would increase participant burden.

5 * Why could the research not practicably be done without the waiver or alteration?

Present recruitment methods are not generating the participant flow needed to meet our aims in a timely manner. Since eligibility is determined through the clinical findings (PHI), we could not practically conduct the study without access to this information. Without a waiver we could not identify potential participants nor contact them to assess their interest in participating in the study. The waiver will allow access to the Kernan Stroke Registry (HP-42797) and the Pepper Center Registry thus providing names of potential participants.

6 * Will the subjects' PHI be disclosed to (or shared with) any individuals or entities outside of UM?

◯ Yes ● **No**

6.1 If Yes, describe the individuals or entities outside of UM to whom PHI will be disclosed.

ID: VIEW4E1B0A2896400
Name: v2_Waiver/Alteration of Authorization

HP-00062868 View: v2_Informed Consent Process

Informed Consent Process

If the study does not involve interaction with participants or a waiver of consent is being requested , answer "N/A" to the questions below.

1 * Indicate the type(s) of consent that will be involved in this study: (check all that apply)

- [ ] Not applicable (study may qualify as exempt)
- [x] **Request to Waive Consent/Parental Permission (Consent is not being obtained)**
- [ ] Request to Alter Consent (Some Elements of Consent Waived)
- [ ] Request to Waive Documentation of Consent (Verbal/Oral Consent)
- [x] **Written Consent Form**
- [ ] Electronic Consent

2 * Describe the Informed Consent process in detail:

Individuals who fit the inclusion criteria for the study will be offered the opportunity to participate. Care will be exercised to assure that patients are not coerced in any way to participate. The main risk of study participation is risk of injury from the robot. This risk will be discussed with the patient as well as the potential benefit of increased knowledge about robotic therapy and possibly improved therapy. After patients have signed an informed consent, we will obtain patients' medical history and imaging information. The patients will then undergo a general medical and neurological examination and initiation of impairment testing.

3 Confirm that the consent process will explain the following:

- The activities involve research.
- The procedures to be performed.
- That participation is voluntary.
- The name and contact information for the investigator.

* ● **Yes** ○ No

4 * Describe who will obtain Informed Consent:

The study coordinator, PI, and/or other designated study team members team will perform the informed consent.

5 * If obtaining consent from a legally authorized representative (LAR), describe how you will confirm that the individual is the LAR and can provide legally effective informed consent. *(Answer "N/A" if not obtaining consent from LARs)*

N/A

6 * Describe the setting for consent:

The informed consent process with participants will be conducted in the Allied Health Building or at the VAMHCS Loch Raven facility in allocated lab space or in a study team members office where doors can be closed for privacy.

7 * Describe the provisions for assessing participant understanding:

A participant's understanding of the study will be based on his/her response to a brief questionnaire entitiled "Evaluation to Sign Informed Consent. This form questionairre will serve as a marker to assess a participant's understanding of the consent/study and promote additional discussion as needed for participant understanding.

8 * Describe the consideration for ongoing consent:

Participants are encouraged to ask questions throughout the study. Study team members also provide the interventions; therefore, participants may ask questions throughout all phases of the study related to the consent process should any arise.

ID: VIEW4E1C661D0AC00
Name: v2_Informed Consent Process

HP-00062868 View: v2_Waiver/Alteration of Consent Process

Waiver or Alteration Consent Process

You indicated that a waiver/alteration of consent is requested.

1 * Explain why the research involves no more than minimal risks to the subjects:
This request for waiver of informed consent is for recruitment purposes only, as required by the VA for studies that also obtain a waiver of HIPAA authorization for recruitment purposes. We will view information to determine eligibility but no research procedures will be conducted until such time that the participant agrees to take part in the study and signs the informed consent document. The recruitment process involves no more than minimal risk to the individual.

2 * Explain why a waiver or alteration of the consent process would not adversely affect the rights and welfare of the subjects:
This waiver request is for recruitment purposes only as required by the VA. If it is determined that the individual would be eligible to take part in the study, they will be approached and given the opportunity to agree and sign the informed consent document or they can decline participation.

3 * Informed consent is always required unless there is reason to grant a waiver or alteration of the consent process. Explain why you cannot carry out the research unless you are granted a waiver or alteration of the consent process:
This waiver request is for recruitment purposes only as required by the VA. If it is determined that the individual would be eligible to take part in the study, they will be approached and given the opportunity to agree and sign the informed consent document or they can decline participation.

4 If the research involves using identifiable private information or identifiable biospecimens, please explain why the research could not practicably be carried out without using such information or biospecimens in an identifiable format.

5 In some cases there will be additional pertinent information during the study that should be given to the participating subjects. For those subjects who have not been given informed consent because there is a waiver or alteration of the consent process, explain how the subjects will receive this additional important information. If applicable, please explain why a subject would not receive additional pertinent information.
N/A. Individuals who would be eligible to take part in the study will be given the opportunity to agree and sign the informed consent document or to decline participation.

6 If you are requesting an alteration of the consent process please explain why this request is necessary for the conduct of the research study. Please identify specifically what is being altered or changed in the consent process.
N/A

ID: VIEW4E1C73B344800
Name: v2_Waiver/Alteration of Consent Process

HP-00062868

View: v2_Consent Forms - Draft

Consent and HIPAA Authorization Forms - Draft

1 Upload all of your Consent Forms for approval. Use only Microsoft Word.

Name	Created	Modified Date
62868Mod28_ICF_UMB_redline.docx(0.03)	1/1/2019 9:43 PM	2/12/2019 2:10 PM
62868Mod28_ICF_UMB_Addendum.docx(0.03)	1/1/2019 9:43 PM	2/12/2019 2:11 PM
62868Mod28_ICF_VA.docx(0.02)	1/1/2019 9:42 PM	2/12/2019 2:11 PM
62868Mod28_ICF_VA_redline.docx(0.30)	3/26/2015 4:40 PM	2/12/2019 2:11 PM
62868Mod28_ICF_UMB.docx(0.02)	1/1/2019 9:43 PM	2/12/2019 2:10 PM
VA_EEG_NIRS_Addendum(0.02)	3/8/2019 4:14 PM	3/11/2019 1:48 PM
62868Mod28_ICF_VA_Addendum.docx(0.02)	1/10/2019 10:23 AM	2/12/2019 2:11 PM
UMB_EEG_NIRS_Addendum(0.02)	3/8/2019 4:14 PM	3/11/2019 1:48 PM

IMPORTANT NOTE: the above list of consent forms (if any) are DRAFT versions. Under no circumstances should copies of these be distributed to patients/study subjects. If/when this research submission is approved by the IRB, approved consent forms will be available for download and use from the "Documents" tab of the Submission's workspace (click Exit and then look for the Documents tab - approved submissions only)

1A Archived Consent Forms:

Name	Created	Modified Date
62868Mod24_VA_UMB.docx(0.01)	1/1/2019 9:25 PM	1/1/2019 9:25 PM
62868Mod24_VA_UMB_redline.docx(0.31)	3/26/2015 4:40 PM	1/1/2019 9:25 PM
62868Mod24_VA_ICF.docx(0.01)	1/1/2019 9:24 PM	1/1/2019 9:24 PM

2 Upload any HIPAA authorization forms here:

VA HIPAA(0.08)	3/26/2015 4:24 PM	8/14/2018 1:44 PM
UMB HIPAA(0.08)	3/26/2015 4:24 PM	8/14/2018 1:42 PM

Please refer to HRPO's website for specific instructions for preparing informed consent documents and to access current templates: http://hrpo.umaryland.edu/researchers/consents.html

ID: VIEW4E1C7712D3000
Name: v2_Consent Forms - Draft

HP-00062868

View: v2_Organization Review Requirements (other than IRB)

Organization Review Requirements (other than IRB)

Answer the following questions to determine additional organizational review requirements:

1 **Department/Division Review** - All research submissions are required to undergo department/division/institutional review prior to IRB review. The following entity is listed as the required department/division/institutional review:

Neu Rehab

If this information is incorrect, please notify the HRPO office.

2 **RSC Review Criteria** - select 'Yes' if the answer is 'Yes' for any of the following questions. Review by the Radiation Safety Committee may be required.

* 2.1 Does the research involve the use of ionizing radiation? ○ Yes ● **No**

2.2 Does the research involve the sampling of radioactive human materials for subsequent use or analysis in a laboratory?

3 **IBC Review Criteria** - select 'Yes' if the answer is 'Yes' for any of the following questions. Review by the Institutional Biosafety Committee may be required.

* 3.1 Does the research involve human gene transfer? ● **Yes** ○ No
-OR-
Does the research specifically apply to human studies in which induction or enhancement of an immune response to a vector-encoded microbial immunogen is the major goal, and such an immune response has been demonstrated in model systems, and the persistence of the vector-encoded immunogen is not expected? This type of research is often referred to as recombinant vaccine trials.

3.2 Does the research involve the exposure of human subjects to pathogenic microorganisms, or the exposure of research staff to human subjects or samples known or reasonably expected to carry infectious disease(s)?

3.3 Does the research involve the sampling of materials from persons with no known infectious disease and where the only risk to study staff is occupational exposure to bloodborne pathogens as defined by the OSHA Bloodborne Pathogen Standard?

4 **Cancer Center Criteria** - Answer the following to determine if review by the Cancer Center (Hematology-Oncology) may be required.

* Does the protocol involve in any way studies related to the prevention, treatment, diagnosis, or imaging of neoplastic diseases? ○ Yes ● **No**

5 **General Clinical Research Center Review Criteria** - the GCRC offers free and/or cost shared resources for patient-oriented research. Click Here for more information.

Answer the following to determine if review by the GCRC may be required.

* Will the General Clinical Research Center (GCRC) facility or resources be used to conduct this activity? ○ Yes ● **No**

6 **VA Review Criteria** - Answer the following questions to determine if review by the VAMHCS R&D Committee may be required.

* 6.1 - Will the research be conducted by VA Investigators including PIs, Co-PIs, and Site Investigators on VA time (serving on compensated, WOC, or IPA appointments)? ● **Yes** ○ No

* 6.2 - Will the research utilize VA resources (e.g., equipment, funds, medical records, databases, tissues, etc.)? ● **Yes** ○ No

* 6.3 - Will the research be conducted on VA property, including space leased to and used by VA? ● **Yes** ○ No

PLEASE NOTE that the research may be funded by VA, by other sponsors, or may be unfunded.

ID: VIEW4E1AF91AB2400
Name: v2_Organization Review Requirements (other than IRB)

HP-00062868 View: v2_Institutional Biosafety Committee Review Required

Institutional Biosafety Committee Review Required

1 **NOTE**: based on your answers to questions on a previous page (see below) review by the Institutional Biosafety Committee (IBC) is required. This will involve extra steps on your (study team) part. Clicking the Continue button will result in the system creating a blank IBC Submission form for you. You will be required to fill out and submit this IBC form before you will be able to submit the Protocol form. The IBC Submission workspace and form can be reached by clicking the appropriate button on the left hand side of the Protocol submission's workspace (web page) after exiting the Protocol form.

2 **Question** - answered on IBC RSC review requirements page:

3.1 Does the research involve human gene transfer? - OR - Does the research specifically apply to human studies in which induction or enhancement of an immune response to a vector-encoded microbial immunogen is the major goal, and such an immune response has been demonstrated in model systems, and the persistence of the vector-encoded immunogen is not expected? This type of research is often referred to as recombinant vaccine trials.
3.2 Does the research involve: a) the exposure of human subjects to pathogenic microorganisms, or b) the potential exposure of UMB research staff to infectious materials through the sampling or processing of materials from patients with known infectious disease or from environmental surfaces?
3.3 Does the research involve the sampling of materials from persons with no known infectious disease and where the only risk to study staff is occupational exposure to bloodborne pathogens as defined by the OSHA Bloodborne Pathogen Standard?

Yes

If the answer to this question is wrong, an IBC submission is not required, use the Jump To menu or your browser's <

3 * **Confirm** - you have read the above information and understand that in addition to the IRB Protocol form, you will fill out and submit the IBC Submission form :

● **Yes** ○ No

ID: VIEW4E1AF91ED4C00
Name: v2_Institutional Biosafety Committee Review Required

HP-00062868 View: v2_Use of Non-Veterans

VA-Specific Criteria

1 * What is the relevance of this research to the mission of VA and the Veteran population that it serves*?

The long-range goal of the proposed work is to meet the Veterans Health Administration Office of Research and Development Strategic Plan 2009-2014 listed objective 2.6 and transform the field of rehabilitation by developing evidence and procedures that selectively incorporate robot-assisted training into the routine management of stroke related upper extremity hemiparesis. Prevalence in our veteran population is expected to rise since 64% of the population is aged 55 or older. 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. We expect that the results from this study will provide objective evidence for choosing the Robot + TTT rehabilitation technique in the long time period following sub-acute recovery. It will also bring potential insights for the science of predicting outcomes and optimally matching therapeutic techniques in this period. While use of robotic training is key part of the treatment in this trial, it should be generalize to any intensive therapy oriented toward the impaired upper extremity, for example the intensive comparison therapy used in the VA Cooperative Study. There will also be further insight gained into the issue of minimal clinically significant change in a range of outcome scales in the chronic period, when compensatory movement strategies become the most important part of rehabilitation.

2 * Describe who will be enrolled in this study:

- ○ Non-veterans will be enrolled in this study
- ○ Only veterans will be enrolled in this study
- ● **Veterans and Non-veterans will be enrolled in this study**

2.1 * If non-veterans will be enrolled in this study, provide a description of non-veterans who will be enrolled (For example: community members, family members/caretakers of Veterans, clinicians/caregivers to Veterans, etc.):

Non-veterans will be drawn from the community, including those who have had rehabilitation at area facilities, family members of veterans seen in the Neurology ambulatory services of the, veterans' caregivers, etc.

2.2 If non-veterans will be enrolled in this study, provide a substantive justification** for the enrollment of non-veterans in this research:

There are insufficient numbers of Veterans who meet all inclusion criteria and are able to travel to the Baltimore area to participate in this study. For stroke subjects, their stroke must be their main health deficit (e.g. no TBI or orthopaedic problems). Stroke research is, however, very relevant to present and former military personnel and should be pursued. By including non-veterans, this will allow for a larger subject pool which will increase the strength of the study statistically speaking.

2.3 * If this is a VA-funded study, was the use of non-veterans discussed within your merit award proposal?

- ● **Yes**
- ○ No
- ○ N/A

*

http://www.va.gov/about_va/mission.asp

VA Mission Statement
To fulfill President Lincoln's promise “To care for him who shall have borne the battle, and for his widow, and his orphan” by serving and honoring the men and women who are America’s Veterans.

VA Core Values
VA’s five core values underscore the obligations inherent in VA’s mission: Integrity, Commitment, Advocacy, Respect, and Excellence. The core values define “who we are,” our culture, and how we care for Veterans and eligible beneficiaries. Our values are more than just words – they affect outcomes in our daily interactions with Veterans and eligible beneficiaries and with each other. Taking the first letter of each word—Integrity, Commitment, Advocacy, Respect, Excellence—creates a powerful acronym, “I CARE,” that reminds each VA employee of the importance of their role in this Department. These core values come together as five promises we make as individuals and as an organization to those we serve.
Integrity: Act with high moral principle. Adhere to the highest professional standards. Maintain the trust and confidence of all with whom I engage.
Commitment: Work diligently to serve Veterans and other beneficiaries. Be driven by an earnest belief in VA’s mission. Fulfill my individual responsibilities and organizational responsibilities.
Advocacy: Be truly Veteran-centric by identifying, fully considering, and appropriately advancing the interests of Veterans and other beneficiaries.
Respect: Treat all those I serve and with whom I work with dignity and respect. Show respect to earn it.
Excellence: Strive for the highest quality and continuous improvement. Be thoughtful and decisive in leadership, accountable for my actions, willing to admit mistakes, and rigorous in correcting them.

**
a. Non-Veterans may be entered into a VA-approved research study that involves VA outpatient or VA hospital treatment (38 CFR 17.45, 17.92), but only when there are insufficient Veteran patients suitable for the study. The investigator must justify including non-Veterans and the IRB must review the justification and provide specific approval for recruitment of non-Veterans.
b. Non-Veterans may be recruited for studies that will generally benefit Veterans and their well-being but would not include Veterans as subjects. Examples include surveys of VA providers, studies involving Veterans’ family members, or studies including active duty military personnel. Although active duty military personnel are not considered Veterans, they should be included in VA studies whenever appropriate.
---

e. Non-Veterans may not be entered into VA studies simply because a non-Veteran population is easily accessible to the investigator.

[VHA Handbook 1200.05 §24]

ID: VIEW4E1C7A737E800
Name: v2_Use of Non-Veterans

HP-00062868 View: v2_VA Prohibited Research

VA Prohibited Research

1 * Is the research planned emergency research in subjects from whom consent can not be prospectively obtained?
○ Yes ● **No**

2 * Does the study involve children **AND** is greater than minimal risk?
○ Yes ● **No**

3 * Will recruitment phone calls involve asking veterans for their Social Security numbers?
○ Yes ● **No**

ID: VIEW4E1C8AF03A400
Name: v2_VA Prohibited Research

HP-00062868

View: v2_Additional VA

Additional VA

1 * For data that is combined, which site is the "Data Coordinating Center"?
UMB

2 If VA data will be combined with non-VA data, describe when and how this will occur and where the combined data will be stored.
After collection of data at VA sites, data will be brought to UMB, processed, and stored. Physical data is transported in locked cases and stored in locked offices or laboratories and in locked cabinets. Electronic data will be stored on FIPS140-2 and HIPAA/HITECH compliant electronic storage that is accessible only by authorized research staff via password protection or multi-factor authentication.

3 If the VAMHCS is the Local Coordinating Center holding the "combined data", how is the data collected? (This answer may overlap with Research Related Procedures. If so, please refer to that section.)
N/A

4 If the VAMHCS is the Local Coordinating Center holding the "combined data", how is the data received and combined with the UM data?
N/A

5 If the UM is the Coordinating Center holding the "combined data", will you only use the combined data set while not on VA time or will you obtain approval from VA ORD/Regional Counsel to do this as an "off-site" VA Research activity.
The laboratory space at UMB is considered designated VA research space by a memorandum of understanding, so it is not considered an "off-site" research activity.

ID: VIEW8D5931EAC5B1E6E
Name: v2_Additional VA

HP-00062868 View: v2_VA Review Required

VA Maryland Health Care System Review Required

1

Note: Based on the answers provided in your submission, this protocol qualifies as a VA study. Therefore, VAMHCS Research &Development (R&D) Committee approval (in addition to IRB approval) is required prior to engaging in any research activities. **Importantly, you must submit the protocol to the VAMHCS Research Service within 60 days of IRB approval.**

**Details related to the VA submission and approval processes are best obtained by calling or visiting the Baltimore VA Research Office (Fred Ivey @ 410-605-7000 x6582). Despite not being able to submit at VA until after IRB approval is obtained, we strongly encourage immediate consultation with the VA R&D service, allowing time for early familiarization with VA requirements and VA Service clearance for your proposed work.

VA Research Service **Forms** can be accessed using the following link:

https://www.maryland.va.gov/research/human/human_subject_forms.asp

**In addition to the post-IRB VA approval process referenced above, there are also VA-specific items that must be addressed before IRB review. Failure to address the two VA components listed below will prevent your protocol from even receiving a full IRB review.

1. **VA information security and privacy Officer (ISO-PO) Approval:** This must happen before the IRB will move your protocol to full-board review. The ISO-PO approval process is initiated by submitting an ISO-PO checklist (accessible through the VA Forms link above) to the Baltimore VA Research Service. Personnel from the VA Research Office will then work to get the required approval signatures, ensuring that the signed ISO-PO checklist is uploaded as a public comment to your protocol's History Log. Again, your protocol CANNOT move forward to full IRB review without a fully signed ISO-PO checklist in the History Log, so getting that item submitted to the VA Research Service as quickly as possible should be a top priority.

2. **Specification of Research Activity Locations:** VA policy mandates that locations of all research activities (including data coordination, data analysis, and data storage) be clearly specified within appropriate sections of the CICERO protocol and the VA Informed Consent Document. Please ensure that locations of all research activities are clearly specified throughout these documents before submitting the protocol to IRB. This is particularly important for "VA Collaborative Studies" (i.e. those studies involving research activities that occur at both VA and non-VA sites). However, all studies, be they collaborative or not, should make clear delineation of research activity locations and data locations an emphasis.

2 **Questions answered on 'Organizational Review Requirements' page**:

The research will be conducted by VA Investigators including PIs, Co-PIs, and Site Investigators on VA time (serving on compensated, WOC, or IPA appointments):	**Yes**
The research will utilize VA resources (e.g. equipment, funds, medical records, databases, tissues, etc.):	**Yes**
The research will be conducted on VA property, including space leased to and used by VA:	**Yes**

Questions answered on 'VA Prohibited Research' page:

The research is planned emergency research in subjects from whom consent can not be prospectively obtained:	**No**
The study involves fetuses:	**No**
The study involves in vitro fertilization:	**No**
The research involves work with embryonic stem cells:	**No**
The study involves children AND is greater than minimal risk:	**No**
Recruitment phone calls involve asking veterans for their Social Security numbers:	**No**

If the answers to these questions are wrong, use the Jump To menu to return to the 'Organization Review Requirements' page to change your answers.

3 * **Confirm** - You have read the above information and understand that in addition to this IRB application form (CICERO), you are required to send a submission to the VAMHCS R&D Committee **within 60 days of receiving IRB approval**.

● **Yes** ○ No

ID: VIEW4E1C8F0D7B000
Name: v2_VA Review Required

HP-00062868 View: v2_Summary of Required Reviews (other than IRB)

Summary of Required Reviews (other than IRB)

1 **Additional Committee Reviews** - Based on your responses to the previous questions, you have identified the following additional reviews. To complete or view these additional committees' forms, click on the links below or exit this application and click on the appropriate button on left side of this submission's webpage.

Name of Related Submission		
IBC: SRT4 (HP-00062868_14)	Workspace	SmartForm

2 **Required Department and Specialty Reviews** - Based on the PI's organization (department, division, etc.) affiliation and answers to previous questions (use of Cancer Center, etc.), the organizations listed below are required to review this application. These reviews are conducted online and no additional forms or steps by the study team are required.

Name of Organization	**Review Status**
Neu Rehab	Complete

ID: VIEW4E1C8D9AE4000
Name: v2_Summary of Required Reviews (other than IRB)

HP-00062868 View: v2_Additional Documents

Additional Documents

1

Upload all additional documents here:

Name	Created	Modified Date
62868_ISO_PO_Mod24.pdf(0.05)	3/26/2015 4:26 PM	8/16/2018 5:40 PM
Subject Forms - Instructions for Lab Appointment(0.01)	2/6/2018 11:46 AM	2/6/2018 11:46 AM
Subject Forms - Research Study Appointments(0.01)	2/6/2018 11:46 AM	2/6/2018 11:46 AM
SOP - Saliva Sample Instructions(0.01)	2/6/2018 11:44 AM	2/6/2018 11:44 AM
Equipment - ArmeoPower Technical Data(0.01)	5/18/2017 10:53 AM	5/18/2017 10:53 AM
Equipment - ArmeoPower User Manual(0.01)	5/18/2017 10:52 AM	5/18/2017 10:52 AM
citiCompletionReport6085605_Kaplan.pdf(0.01)	3/13/2017 5:23 PM	3/13/2017 5:23 PM
HIPAA125_Kaplan.pdf(0.01)	3/13/2017 5:23 PM	3/13/2017 5:23 PM
HIPAA201_Kaplan.pdf(0.01)	3/13/2017 5:23 PM	3/13/2017 5:23 PM
Consent - Evaluation to Sign Consent(0.01)	3/31/2016 12:11 PM	3/31/2016 12:11 PM
Equipment - Magstim TMS Information(0.01)	4/22/2015 4:16 PM	4/22/2015 4:16 PM
Equipment - MagStim FDA letter(0.01)	4/22/2015 4:15 PM	4/22/2015 4:15 PM
Equipment - MagStim Manual(0.01)	4/22/2015 4:15 PM	4/22/2015 4:15 PM
Equipment - IMT Robot User Manual(0.01)	4/22/2015 4:14 PM	4/22/2015 4:14 PM
Equipment - IMT Robot Plan and Letter(0.01)	4/22/2015 4:14 PM	4/22/2015 4:14 PM
Equipment - IMT Robot Information(0.01)	4/22/2015 4:13 PM	4/22/2015 4:13 PM
VA - PI Tool for Collaborative Studies(0.02)	3/26/2015 4:25 PM	3/27/2015 11:09 AM
VA - Research Protocol Safety Survey(0.01)	3/26/2015 4:26 PM	3/26/2015 4:26 PM

ID: VIEW4E0962513A000
Name: v2_Additional Documents

HP-00062868 View: v2_Final Page of Application

Final Page of Application

You have reached the final page of this application. It is recommended that you click on the "Hide/Show Errors" link on the upper or lower breadcrumb row of this page. The "Hide/Show Errors" will do a search of your application, and highlight areas that are required or need to be completed prior to submitting.

By submitting this application, you are electronically routing the protocol for departmental scientific review and all other necessary reviews. According to information you have provided, this application will be routed to the following Departments for review prior to being forwarded to the IRB for review. These reviews are conducted online and no additional forms or steps by the study team are required.

Name of Organization	**Review Status**
Neu Rehab	Complete

Required Safety Committee Reviews - In addition to the IRB, the following committees must review this submission. Each additional committee has a separate online form that the study team will be required to fill out. All committee applications (IRB plus those listed here) must be completed properly before the 'package' of applications can be submitted. The team may complete these additional forms in any order or at any time prior to submission of the IRB Application. To complete or view these additional committees' forms, click on the links below or exit this application and click on the appropriate button on left side of this submission's Workspace.

Name of Related Submission		
IBC: SRT4 (HP-00062868_14)	Workspace	SmartForm

You may check the progress of your application at any time by returning to the Workspace of this submission. A detailed history, including notes, dates, and times of events, is provided to you for this purpose.

If a reviewer returns the application to you, you must address their concerns and resubmit the protocol for review to all designated departments. After all departments have reviewed the application, it will automatically be sent to the IRB for review. Changes made to the submission after its approval must be submitted as modifications.

Investigator Attestation
By submitting this application, I, the Principal Investigator (PI), certify that the information provided in this application is complete and correct. Research will be conducted according to the submission as described, only by the approved principal investigator and study team members.

In addition, I agree to the responsibilities of a PI, including:

- Obtaining informed consent (if applicable) from all subjects as outlined in the submission.
- Reporting new information to the IRB per the requirements of the Investigator Manual.
- If Required, obtaining renewal of the protocol prior to the expiration of the approval period or halt all study activities upon study expiration.
- Accepting ultimate responsibility for the protection of the rights and welfare of human subjects, conduct of the study and the ethical performance of the project.
- Ensuring performance of all research activities by qualified personnel according to the IRB approved submission.
- Ensuring that research personnel have or will receive appropriate training.
- Ensuring no changes will be made in the research until approved by the IRB (except when necessary to eliminate apparent immediate hazards to subjects).

Click the "Finish" button and then click "Submit Application" in the submission Workspace.

ID: VIEW4E1B10C500000
Name: v2_Final Page of Application

HP-00062868 View: IRB - Add a Team Member

Add a Team Member

1 * Select Team Member:
Linda Horn

2 Research Role:
Research Team Member

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
○ Yes ● **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
○ Yes ● **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
○ Yes ● **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Dr. Horn is a physical therapist with experience in other clinical trials at the local study site.

HP-00062868 View: IRB - Add a Team Member

Add a Team Member

1 * Select Team Member:
Jill Whitall

2 Research Role:
Research Team Member

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
● **Yes** ○ No

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
○ Yes ● **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
○ Yes ● **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Professor in Physical Rehabilitation Science at UMB & part-time Professor of Neuromotor Rehabilitation at University of Southampton. Doctoral training in motor development and learning applied to stroke rehabilitation for over 20 years. Expertise primarily in the outcomes and intervention areas and sensorimotor coordination.

HP-00062868 View: IRB - Add a Team Member

Add a Team Member

1 * Select Team Member:
Susan Conroy

2 Research Role:
Sub-Investigator

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
● **Yes** ○ No

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
● **Yes** ○ No

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
○ Yes ● **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Dr. Conroy has been a co-investigator and/or research team member for multiple VA rehabilitation studies. She is an experienced physical therapist and has 10 years experience in robot-assisted upper extremity stroke studies at VAMHCS.

HP-00062868 View: IRB - Add a Team Member

Add a Team Member

1 * Select Team Member:
Huichun Xu

2 Research Role:
Research Team Member

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
● **Yes** ○ No

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
● **Yes** ○ No

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
○ Yes ● **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Dr. Xu is an M.D., Ph.D. degree holder who has progressed from post-doctoral training with Dr. Braxton Mitchell to an Instructor position in the Department of Medicine. He has extensive experience in transcriptome screening in human studies of stroke. He has been mentored by Pepper Center investigators and has knowledge of the local sites. Furthermore, his involvement is limited to interpretation of molecular biology assays.