STUDY PROTOCOL

STUDY TITLE: ISCHEMIC CONDITIONING IMPROVES WALKING FUNCTION POST STROKE

DATE OF DOCUMENT: 7/26/2019

Institutional Review Board
Study Protocol Form

This sheet and the entire protocol form will be maintained throughout the life of the study.

New Study Submission

Date submitted	Date approved
12/7/18	12/20/18

Amendment submissions (add rows at bottom of table as needed)

For each amendment submission complete one row of the table below.

Indicate all changes by modifying the Protocol Form and any other applicable study documents using track changes, or highlights, as a means to distinguish between previously approved information and current requested changes. Documents submitted without distinguishing between "new" vs "old" content will be returned to the PI. DO NOT DELETE PAST ACTIONS FROM THIS TABLE

Date submitted	List changes requested	Justification for the change	Date approved
3/2019	MCW Reliance Request	Matthew Durand and Jennifer Nguyen are employees of MCW. All study activities occur at MU.	4/2019
5/6/2019	Addition of study personnel.	Assist with data collection (Zhilun Zhou, Ashley Dejaco)	5/7/2019
7/3/2019	1. Addition of cardiovascular testing. 2. Addition of study personnel 3. Change in exclusion criteria 4. Addition of recruiting via MCW	1. Measuring estimated VO2 max (a sub-maximal, modified version of VO2 max testing) will allow us to better understand how ischemic conditioning improves cardiovascular function during exercise in chronic stroke. 2. Matthew Durand and Jennifer Nguyen (Dept. of PMR, MCW), Saad Alqahtani (Grad. Student MU), Toni Uhrich (Staff, MU,Health Performance Assessment core) 3. Removing the exclusion criteria of multiple strokes.	07/19/2019

Principal Investigator (PI):	**Allison Hyngstrom PT, PhD**	**PI Status:**	
Department:	**Physical Therapy**	[ ] Undergraduate [x] Faculty/Administrator	
Email Address:	**Allison.hyngstrom@marquette.edu**	[ ] Graduate [ ] Other (specify)**:**	
Faculty Advisor:			
Project Title:	**Ischemic Conditioning Improves Walking Function Post Stroke**		
Study Start Date:		**Expected End Date:**	

PI Certification

By entering my name below and submitting this document, I certify the following:

- I accept primary responsibility for the ethical conduct of this project and for safeguarding the rights and welfare of all involved human participants and/or their information.
- The information in this submission accurately reflects the proposed research.
- I will communicate any changes to this protocol by submitting an amendment request and receiving approval before implementing the change.
- I will submit a Final Report, Study Complete or Study Closed Form when this project is complete.
- I am responsible for making sure the investigators on the study team have received appropriate training in human subjects research.
- I accept responsibility for assuring adherence to applicable Federal and State research regulations and Marquette University policies applicable to this project.

I understand that this project cannot begin until I receive documentation of IRB final approval.

Allison Hyngstrom PT PhD 11/28/18

Principal Investigator Name **Date**

FOR STUDENTS, a Marquette faculty supervisor must review this completed form and enter his/her name and date of review below prior to submission. The supervisor must also be copied on the email when this document is submitted.

Faculty Supervisor: As faculty supervisor for the student investigator named above, I certify the following:

- I have reviewed the research plan and this document and I have approved the scientific and ethical aspects of the project.
- I will supervise the above listed student and ensure compliance with applicable Federal and State research regulations and Marquette University policies applicable to this project.
- I acknowledge that I am ultimately responsible for the conduct of this research project, including ensuring that all study procedures are followed as written, and that a Final Report, Study Complete or Study Closed Form is completed in a timely fashion after study completion.

I understand that this project cannot begin until an official approval letter has been received.

Faculty Supervisor Name **Date**

A. OVERVIEW

1. Indicate what level of risk you believe the study involves based on the following definition of minimal risk:

"*Minimal risk* means that the probability and magnitude of harm or 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 or tests"

[x] Minimal Risk [ ] Greater than Minimal Risk

1b. Please explain why you feel your study involves minimal risk or greater than minimal risk:
All procedures are non-invasive, have been safely and reliably been performed in the laboratory for several years, and are encountered in routine daily life or routine physical testing.

B. STUDY BACKGROUND

*Instructions: For the following questions, try to use **non-technical** language that provides a first time reader from any discipline with a clear understanding of the research, and avoid abbreviations. **Do not cut and paste text from the grant proposal, and do not refer to the grant proposal page numbers or include literature citations.** Focus your answers on the involvement and treatment of human subjects.*

2. Provide a short, non-technical summary (abstract) of the study including a summary of the scientific background and existing knowledge on the subject**:**
The purpose of this study is to examine if a safe and non-invasive intervention, called ischemic conditioning (IC), can improve gait speed, neural activation of leg muscles, and cardiovascular function when combined with traditional treadmill training in individuals with chronic stroke. Briefly, IC is a non-invasive stimulus which is triggered by using a blood pressure cuff to briefly occlude blood flow to the tissue of interest (the paretic leg) in 5-minute bouts, done a total of 5 cycles per session, making the tissue transiently ischemic. In individuals without stroke, the IC stimulus is known to increase the excitability of motor systems and improve local regulation of blood, but the positive effects of IC on motor tasks such as walking in individuals with stroke are unknown. It is proposed that IC engages the autonomic nervous system, causing the release of neurotransmitters that increase the excitability of the nervous system. IC has been safely used many special populations to improve blood flow, such as critically ill patients, individuals with chronic kidney disease, and individuals recovering from acute myocardial infarction (heart attack). We propose to investigate the effects of IC on walking speed and paretic leg function with two Specific Aims. In Aim 1, we will demonstrate the benefit of combined IC and treadmill training on walking speed post stroke. We will use a randomized, blinded, controlled design with three groups of individuals with chronic stroke (15 per group) for four weeks (12 total sessions) of training: IC+Treadmill Training, IC Sham+Treadmill Training, and IC only. Walking speed will be measured at baseline, after 6 sessions, 12 sessions, and 2 weeks post-intervention. We anticipate the largest gains in walking speed in the IC+Treadmill Training group after 12 sessions. In Aim 2, we will quantify the effects of IC and treadmill training on improvements in motor unit firing behavior and whole muscle activation. Due to enhanced neural activation of motoneuron pools, we

anticipate that IC on the paretic leg will decrease recruitment thresholds and increase motor unit firing rates during sub-maximal isometric contractions. We also anticipate increased maximal voluntary force generation. Similar to Aim 1, we expect that the largest gains in strength and task duration to occur in the stroke IC+Treadmill group after 12 sessions. In Aim 3 we will establish that ischemic conditioning and treadmill training improve endothelial function and cardiorespiratory fitness. We hypothesize that IC + Treadmill Training will result in increased flow mediated dilation in the popliteal artery of the paretic leg (improved local endothelial function) and the brachial artery of the non-paretic arm (remotely improved systemic endothelial function). Compared to the other groups, we also predict that the IC + Treadmill Training group will have the largest increase in maximal aerobic capacity as assessed by a graded exercise test to measure peak oxygen uptake (VO_2 Peak). These studies will be the first to quantify the effects of IC, a non-invasive, easy to administer, cost-effective intervention, on walking speed, motor function and cardiovascular health in chronic stroke. Future studies will investigate the molecular mechanisms of IC, the effects of IC on acute stroke populations, and the efficacy of IC compared with other walking adjuncts.

3. List the specific research aims of this project:

Aim 1: Demonstrate the benefit of IC and treadmill training on walking speed post stroke. A randomized, double-blinded, control design will be used with three groups of individuals with chronic stroke training for four weeks (12 sessions): IC + Treadmill Training, IC Sham + Treadmill Training, and IC only. Walking speed will be measured at baseline, after 6 sessions, 12 sessions, and 2 weeks post-intervention. We hypothesize the largest gains in walking speed will be in the IC + Treadmill Training group after 12 sessions. Interpretive measures of gait kinematics, kinetics, and EMG will also be assessed to understand how IC improves the quality of walking.

Aim 2: Determine the excitatory effects of IC on the activation of paretic motoneurons. Using novel high-density surface EMG arrays, we will quantify changes in paretic motor unit recruitment thresholds and firing rates. We hypothesize that IC will decrease paretic motor unit recruitment thresholds and increase peak firing rates. Interpretive measures of paretic muscle voluntary activation (assessed by electrical stimulation), maximal strength, muscle contractile properties, and changes in muscle oxygen consumption will be measured at similar time points as Aim 1. If IC enhances the excitability of motoneuron pools, we anticipate changes in voluntary activation will positively correlate with changes in walking speed more than correlations with resting twitch responses of the muscle.

Aim 3: Establish that ischemic conditioning and treadmill training improve endothelial function and cardiorespiratory fitness. We hypothesize that IC + Treadmill Training will result in increased flow mediated dilation in the popliteal artery of the paretic leg (improved local endothelial function) and the brachial artery of the non-paretic arm (remotely improved systemic endothelial function). Compared to the other groups, we also predict that the IC + Treadmill Training group will have the largest increase in maximal aerobic capacity as assessed by a graded exercise test to measure peak oxygen uptake (VO_2 Peak).

C. SUBJECTS

4. What is the requested <u>total</u> number of subjects? (*Note: this number should include subjects who later will be determined ineligible or who may be lost to attrition):*	**54**

5. Check any of the following special populations that will be targeted for enrollment in the study:

[ ] Pregnant Women/Fetuses **[ ]** Children (minors under 18) **[ ]** Prisoners

[ ] College Students* [ ] Institutional Residents [ ] Cognitively Impaired
[ ] Physically Disabled [ ] Terminally Ill [ ] Subordinates or students of the PI

[ ] Economically or educationally disadvantaged populations [x] None of These

**If using Marquette students, please consult HRP Policy 98.102 Participation of Students and Employees in Research available on the IRB website*

6. Provide the inclusion and exclusion criteria for study subjects.

Inclusion Criteria:	**Exclusion Criteria:**
Inclusion criteria include that subjects must: be at least 18 years of age, be able to give informed consent, ≥6 months post diagnosis of unilateral cortical or sub-cortical stroke, and have residual lower limb paresis.	Exclusion criteria: 1) history of chronic low back or hip pain, 2) history of substance abuse, 3) history of head trauma, 4) comorbid neurological disorder, 5) any uncontrolled medical condition, 6) pacemaker, 7) unable to follow 2 step commands 8) history of any condition where resisted leg contractions are contraindicated, 9) inability to walk for 5 minute bouts at least 80% of their comfortable over ground walking speed

D. RESEARCH ACTIVITIES

**If any of these steps will be conducted in languages other than English state this in your responses and make sure to submit both English and non-English versions of appropriate materials.*

*****If study involves the use of pre-existing data or specimens, complete this section as much as possible and make sure to also complete Appendix E*****

RECRUITMENT *REMINDER: If verbal announcements will be made please submit the script for the announcement. Also, make sure to submit copies of all recruitment flyers, advertisements, recruitment emails and other materials*	
7. Describe how and where/when subjects will be recruited for the study.	A registry maintained in the Hyngstrom Laboratory (HR 2987). Word of mouth- frequently individuals will call the laboratory or the physical therapy department interested in participating in studies who have heard about the studies through friends/etc. An online stroke subject recruitment database (MCW PRO00026783) which contains the names and medical information of stroke survivors interested in participating in stroke research.

8. State who will be doing the recruitment.	Dr. Hyngstrom PT PhD (PI), Stephany Raab MS (graduate student in Hyngstrom Lab) or Saad Alqahtani PT (graduate student in Hyngstrom Lab)
9. Are there any pre-existing relationships that may influence a research subject's decision to participate in the project? *(for example, a student being recruited by an instructor who controls his or her grade, or a healthcare provider recruiting his or her own patients)*	[ ] Yes [x] No
9b. **If Yes**- explain what steps researchers will take during the recruitment process to minimize the potential for undue pressure, influence, or coercion. *For example, having a third party consent or collect data, having researchers contact subject directly, postponing data analysis until grades have been submitted, etc…*	

SCREENING	
10. State how and when subjects will be screened for study eligibility.	Individuals will be screened by phone by Dr. Hyngstrom or study personnel (Stephany Raab MS or Saad Alqahtani PT) prior to consent process. Screening will follow a script and individuals will be questioned with respect to the exclusion/inclusion criteria(attached).
11. State if the data from ineligible subjects will be discarded and how. *If data from ineligible subjects will be kept then they are considered study subjects and should consent before the screening process*	Data from ineligible participants will be shredded immediately upon determination that they are ineligible.

CONSENT PROCESS *REMINDER: Submit copies of any consent/assent/parent permission documents that will be used*	
12. Describe the consent process- state who will be obtaining consent as well as when and where.	Either Dr. Hyngstrom or Stephanie Raab will consent the participants. Upon determination that the participants are eligible,the consent process will occur privately in the Hyngstrom Laboratory (Cramer Annex 138). Study personnel will go through the consent form and allow time for the participant to read the consent on their own and ask any questions. No testing procedures will occur until after the consent has been signed.
13. If minors will be enrolled, please describe both the minor assent and parent permission process.	N/A

14. Will subjects be signing a consent form?	**[x]** Yes **[ ]** No – please complete Appendix A, Section 1 to request a waiver of documentation of consent
15. Will any of the required elements of consent be altered or removed (this is common in studies involving deception) or is there a request to waive consent altogether?	**[ ]** Yes—please complete Appendix A, Section 2 to request a waiver or alteration of consent **[x]** No

STUDY PROCEDURES	
16. Describe any interventions or activities the subjects will be asked to perform.	**Experimental Protocols** The following clinical, motor and blood flow testing protocols will be performed at baseline and after ischemic conditioning sessions 6 and 12, and 2 weeks post intervention. **Gait Assessments and Clinical Testing:** Clinical testing and measurements of gait velocity, as described below, will be performed prior to motor testing. Following gait and clinical testing, participants will then undergo motor and blood flow testing. **Motor Testing:** The knee extensors and plantar flexors will be tested separately, and the order will be counterbalanced. 1)Maximal Voluntary Contraction Protocol: Maximal voluntary contractions will be the first procedure performed by each subject. Individuals will be assisted in to a seated position in a Biodex Dynamometer. The baseline maximal voluntary contraction task will involve an increase in force from zero to maximum over 2-3 s. Subjects will be able to observe the exerted force on a monitor and will be verbally encouraged to achieve maximal force. Subjects will rest for 60s between trials. Trials will be repeated until peak forces from two of the three trials are within 5% of each other (usually 3-4 trials). The peak force generated will be used as the maximal voluntary contractions. 2)Voluntary activation, Muscle Contractile Properties: Voluntary activation measurements will be made concurrent with maximal voluntary contraction measurements. During the 2nd and 3rd maximal voluntary contractions, the quadriceps or gastrocnemius muscle will be electrically stimulated (Digitimer North America, FL). Electrodes will be placed over the quadriceps muscle. The stimulation intensity will be set to supramaximal levels (10% above resting maximal twitch) for both stimulations. Individuals will be stimulated during a maximal effort (superimposed twitch) and then at rest(resting twitch). This measurement will be done before and after ischemic conditioning. The ratio of the superimposed twitch

torque (SIT) and the resting twitch (RT) will be used to quantify voluntary activation will with the following: 100* [1-(SIT/RT)][24]. The superimposed twitch will be used as a measure of voluntary activation. A decrease in the superimposed twitch amplitude across ischemic conditioning session time points will indicate an increase in voluntary activation. Following the 2nd and 3rd maximal voluntary contractions, resting twitch responses of the muscle will be elicited. Changes in the rate of relaxation of the twitch response will indicate an effect of ischemic conditioning on muscle contractile properties.

3)Sub-maximal Ramp Contractions: To measure motor unit firing behavior, subjects will perform 2 isometric knee extensor and plantar flexor contractions ramping from 0% to 50% maximal effort.

4)Sub-maximal Fatiguing Contraction: Using visual feedback and receiving verbal feedback, individuals will maintain a 30% maximal voluntary contraction until they can no longer maintain with a ± 5% error window.

5)Hyperemic Blood Flow in Response to Muscle Contractions: Measurements may be performed and would be made using a General Electric Vivid i ultrasound equipped with a 13.0 MHz probe designed for vascular imaging. Superficial femoral artery diameter and blood flow will be measured at the same site 4-5 cm distal to the bifurcation of the common femoral artery as previously described.[1-4] Resting blood flow, and the hyperemic response to muscle contractions will be measured before and immediately after each contraction and after muscle fatigue and averaged over 3 cardiac cycles.[5] Blood flow will be quantified using the software on the Vivid i ultrasound.

Maximal voluntary contraction, voluntary activation, and ramp contractions measures will then be repeated on the non-paretic leg during the same session after at least 30 mins of rest to understand ay systemic effects. Order of paretic and non-paretic leg testing will be counterbalanced.

ISCHEMIC CONDITIONING Intervention: Subjects will undergo a total of 12 sessions (3/week for 4 weeks) of ischemic conditioning (cuff inflation to 225 mmHg) or ischemic conditioning Sham (cuff inflation to 10 mmHg). The participant will be positioned in supine on a therapy table. A rapid inflation cuff (Hokanson, Bellevue WA) will be placed around the proximal thigh of the paretic leg. The cuff will be inflated to 225 mmHg for 5 minutes, then released for a 5-minute recovery period. 5 cycles of inflation/recovery will be performed (total of 50 mins). For the separate group receiving

	the sham ischemic conditioning, this will consist of the same physical set-up, but the cuff will only be inflated to 10 mmHg. Participants will be blinded to the sham or typical ischemic conditioning protocol. During the first and last ischemic conditioning sessions, oxygen saturation of the tibialis anterior muscle of the test leg will be measured using the near infrared spectroscopy during the occlusion protocol to monitor the tissue response to occlusion (Fig. 6). Near infrared spectroscopy measurements will be made from the tibialis anterior during occlusion because the occlusion of the thigh would cause a mechanical artifact in a quadriceps measurement. **Treadmill Training Protocol:** The participants will perform 3 treadmill training sessions/week for a 4 week period (12 sessions total). During each session, treadmill training will immediately follow ischemic conditioning or ischemic conditioning Sham. To ensure safety, all subjects will be assisted into a fall arrest harness and instructed to use handgrips during walking. Subjects will walk on a treadmill for six, 5-minute intervals. Walking speed will be continuously adjusted to maintain heart rate between 50% and 60% of age-adjusted maximal heart rate to minimize the confounder of intensity.[8] Participants will be asked to log daily physical activity. **Flow mediated dilation of the Popliteal (Paretic) and Brachial (non-paretic) Artery:** **Only performed at baseline, after 12 sessions, and 2 weeks post-intervention** Study participants will be required to fast for 8 hours, but medications will not be withheld and if necessary may be taken with food. After 15 minutes rest, the participant's leg will be slightly elevated or their arm will be extended and a pneumatic cuff will be placed around the calf, 5-7 cm distal to the popliteal fossa, or the forearm, immediately distal to the antecubital fossa. Baseline artery diameter and blood flow velocity will be measured. After baseline images have been captured using Vascular Imager (Medical Imaging Applications), the cuff will be inflated to 225 mmHg for five minutes to occlude blood flow to the lower leg or arm. Immediately after cuff release, artery diameter will be continuously captured for 3 minutes (EKG gated) post cuff release and measured off-line using Brachial Analyzer (Medical Imaging Applications). A greater flow mediated dilation response would be consistent with improved endothelial cell function. Study personnel will perform all flow mediated dilation and hyperemic blood flow measurements and analysis. Study personnel will be blinded to the treatment condition. **VO2 Max Test**: **Only performed at baseline, after 12 sessions, and 2 weeks post-intervention** Under the

	supervision of Toni Uhrich, MS (Director of the Human Performance Assessment Core at Marquette University), subjects will begin an exercise test pedaling at a workload of 10 Watts on a recumbent bicycle. Pedaling resistance will be increased by 15 watts every 2 minutes until (1) subjects report they are fatigued and do not feel they can continue, (2) the participant's VO2 peak plateaued or decreased despite continuation of exercise, (3) the participant was unable to maintain a steady cadence, or (4) at the discretion of the study team based on the American College of Sports Medicine Guidelines for Exercise Testing (see attached ACSM Exercise Guidelines). Heart rate and pulse oximetry will be measured throughout the test, as will exhaled air using a metabolic cart. Subjects will also be asked to rate their perceived level of effort using the Borg Scale of perceived exertion (a scale of 6-20 commonly used for graded exercise tests). The subjects are free to stop the test at any time they choose.
17. Describe what data will be collected from subjects and how. Include descriptions of any equipment that will be used.	Note: Data will be collected for motor testing aims on the same test session days(pre intervention, and after 6 sessions, 12 session and 2 weeks post intervention). VO2 Max testing and flow mediated dilation testing will occur on testing sessions separate from the motor test sessions at baseline, after 12 sessions, and 2 weeks post intervention. **Aim 1** Gait Speed: Self-selected walking speed will be quantified using the valid and reliable Ten Meter Walk Test[9]. Self-selected walking speed is a primary determinant in daily ambulatory activity[10,11]. Bipolar Surface EMG Measurements: Bipolar surface EMG recordings may be used to interpret changes in strength in response to ischemic conditioning and treadmill training. Wireless bipolar surface EMG may be measured using Ag/AgCl electrodes placed on the following muscles: rectus femoris, vastus medialis, medial hamstrings, tibialis anterior and medial gastrocnemius. EMG signals will be amplified (x 1,000-10,000) and bandpass filtered (10-500 Hz) (Delsys Trigno; Natick, MA). Signals will be sampled at 1 kHz using a data acquisition card (National Instruments Corp.). Clinical Measurements of Leg and Walking Function: The following clinical metrics will be interpretive measures to understand how ischemic conditioning affects motor impairments that contribute to movement dysfunction post stroke: Functional Gait Assessment (dynamic walking balance)[12], the 6 minute walk test (walking endurance)[13], Lower Extremity Fugl-Meyer (coordination)[14], manual muscle tests (strength), the Ashworth Scale (spasticity)[15], and maximal walking speed. At baseline and at the 2 week follow up, participants will be asked to complete the Physical Activity Questionnaire (PAQ) index[16] which estimates activity levels

and approximates the calorie expenditure above basal metabolic rate. We have used the PAQ in previous studies[17,18].

Near infrared Spectroscopy (NIRS) Measurements of Leg Muscle Oxygen Saturation: A 4-channel INVOS™ (Somantics, Troy, MI) cerebral/somatic oximeter may be used to continually measure regional oxygen saturation of the vastus lateralis and tibialis anterior muscles of the test leg (Fig. 6) *during the* ischemic conditioning *protocol*. NIRS measurements will be made during the first and last sessions of ischemic conditioning and maximal voluntary contraction testing (Aim 2). Based on previous near infrared spectroscopy studies[19-23] the rate of oxygen de-saturation of the muscle groups during muscle contraction will be calculated, as well as the time to peak re-saturation and time to return to baseline.

Aim 2

Surface EMG Motor Unit Measurements and Decomposition: Surface motor unit potentials will be recorded from the vastus lateralis and gastrocnemius muscles using a non-invasive, multi-channel linear array of 64 EMG electrodes (OT Bioelectronnica, Torino, Italy). The 64 channel linear array will be placed between the innervation zone and tendon and oriented with muscle fiber direction using hypoallergenic paste (similar to EEG Cap) and tape. We propose that ischemic conditioning will enhance motoneuron excitability and responsiveness to descending commands through the release of brainstem neuromodulators. As our preliminary data support, ischemic conditioning decreases the force recruitment thresholds.

Knee Extension and Plantarflexion Torque: A Biodex dynamometer (Biodex Medical Systems, New York) will be used to measure isometric knee extension and may be used to measure plantar flexion torques during MVCs (strength) and during a sub-maximal contraction fatiguing protocol (task endurance). For knee extension trials, subjects will be positioned with the hip and knee at 90 degrees. For plantar flexion trials, the knee will be adjusted to 20 degrees of flexion. Custom-written LabVIEW (National Instruments Corp., Austin, TX) programs will be used to acquire all data. Torque signals will be low-pass filtered and sampled at 1000 HZ using a data acquisition card (National Instruments Corp.) and PC. The MVC will be defined as the peak torque generated during a given 2-3 s effort. Knee extension and plantarflexion torques provide an objective, high resolution measurement of motor output.

Voluntary Activation (see Fig. 1 for example): Voluntary activation (neural drive to the muscle) may be assessed by stimulating the muscle with a brief stimulus (superimposed twitch) while the subject performs during a maximal voluntary contraction (MVC). Immediately after the MVC (within 5 s) a

	twitch contraction will be performed at rest (resting twitch). The stimulation intensity will be set to supramaximal levels (10% above resting maximal twitch) for both stimulations. This will be done before and after ischemic conditioning. The ratio of the superimposed twitch torque (SIT) and the resting twitch (RT) will be used to quantify voluntary activation will with the following: 100* [1-(SIT/RT)][24]. Reductions in voluntary activation are due to failure in pathways upstream of the neuromuscular junction[24,25]. We expect voluntary activation will increase in the paretic leg after ischemic conditioning treatment. Perceived Exertion: We will be monitoring the individuals subjective perception of exertion which may differ from their cardiovascular response to exercise. Individuals will rate their exertion using the 6-20 Borg Rate of Perceived Exertion Scale. Heart Rate: Heart rate will be continuously monitored using a 4 lead EKG. EKG and blood pressure electrodes (Finapres Nova, purchased 2016) to make non-invasive measurements of heart rate and blood pressure. In addition, to using heart rate data to monitor the response to exercise, variability in heart rate will be analyzed off line to examine the effects of ischemic conditioning on the relative contributions of sympathetic/parasympathetic drive to control of heart rate. Hyperemic Blood Flow in Response to Muscle Contractions: Measurements may be performed and would be made using a General Electric Vivid i ultrasound equipped with a 13.0 MHz probe designed for vascular imaging. Superficial femoral artery diameter and blood flow will be measured at the same site 4-5 cm distal to the bifurcation of the common femoral artery as previously described.[1-4] Resting blood flow, and the hyperemic response to muscle contractions will be measured before and immediately after each contraction and after muscle fatigue and averaged over 3 cardiac cycles.[5] Blood flow will be quantified using the software on the Vivid i ultrasound. **Aim 3** Percent FMD: Artery diameter will be recorded continuously onto a laptop using Vascular Imager and percent FMD will be calculated offline using Brachial Analyzer software. VO2 Peak: Exercise capacity and VO2 peak will be measured using a metabolic cart and standard procedures.
18. State who will be collecting the data, where data collection will occur and any steps taken to maintain subjects' privacy during data collection.	Study personnel, Stephanie Raab and/or Saad Alqahtani will be collecting the data. Data will be collected in the Falk Laboratory, Cramer Annex room 138A. Although the Falk Laboratory is a shared space, only on study session is allowed at any given time. Thus, only study personnel from this protocol will be in the laboratory during a study session.

	All documents used during the studies will be de-identified and stored in a locked cabinet in Dr. Hyngstrom dedicated lab space adjacent to the Falk laboratory, Cramer Annex 138.
19. Describe the length of study visits and total number of study visits. Include any follow-up data collection time points and what data will be collected at these follow-ups.	Participation will include at least four test sessions (pre, after 6 and 12 IC sessions and 2 weeks post IC). Participation will include at least 12 training sessions. Because of the time dependency of the effects of IC, there may be some variability in the number of test/training sessions if make up sessions need to be performed in case of illness, etc. Aim 3 testing procedures will occur in separate test sessions at baseline, after 12 sessions, and two-weeks post intervention.

20. Will data be collected or analyzed using an internet-based application such as Qualtrics, Survey Monkey, RedCap or Dedoose? **[ ]** Yes **[x]** No

a. If yes, please state the program(s) that will be used and the security features:

b. Will subject identifiers such as email address, name, IP address, etc… be associated with the data at any point?

[x] No- State the specific steps taken to anonymize data:
At time of consent, participants will be given a unique code
[ ] Yes- List the identifiers that will be recorded and the justification for doing so i.e, sending reminders, linking to other data, etc…:

21. Will any social media platforms (Twitter/Facebook/Instagram, etc…) be used for recruitment, communication with subjects or data collection?

[x] No [ ] Yes- please explain which platforms, how they will be used and provide the text for review:

22. Does this study have a data safety monitoring plan? A data safety monitoring plan is a common requirement in federally funded studies that collect clinical data.
[x] No **[ ]** Yes, Please describe or attach plan:

E. RISKS AND BENEFITS

BENEFITS	
23. List any anticipated direct benefits to the subject from participation in the research. *If none, state this here and, if applicable, in the consent form.*	Individuals in all groups may benefit. Individuals in two of the groups will receive four week of treadmill training which may result in increased over ground walking speed and endurance. Supported by recent evidence in our laboratory, individuals receiving IC alone may also have increased over ground walking speed.
24. State any benefits to society from this research study.	Results from the study could help the development of rehabilitation therapies that improve walking and quality of life in individuals with chronic stroke.
RISKS	

25. Describe any reasonably anticipated risks, harms or discomforts from all study procedures. **Make sure to consider risks involved with recruitment and screening as well as risks associated with interventions and data collection.* **Include physical risks as well as psychological, social, legal and other related risks*	1. Adverse cardiovascular response to exercise: According to the American Heart association, reoccurrence of stroke during exercise is extremely rare, but is a possible risk[26]. 2. Muscle Fatigue: We will be measuring the effect of fatigue on patterns of muscle activation. Subjects may experience transient feelings of tiredness or weakness due to fatigue in their leg musculature. 3. Exercise Induced Muscle Soreness: Because we will be asking participants to maximally contract muscles in legs, some soreness in the muscles may appear after the muscle testing. 4. Skin Irritation: Participants may experience some mild skin irritation from the surface EMG or NIRS electrodes. 5. Discomfort from Electrical Stimulation: Subjects may experience some discomfort from the electrical stimulation to their leg. 6. Discomfort Due to Cuff Inflation: Subjects may experience some discomfort during the brief periods of cuff inflation of the ischemic conditioning protocol. The cuff will be inflated to super systolic level. The sensation is similar to what is experienced when standard blood pressure measurements are made. The difference will be how long the cuff is inflated. Here the cuff will be inflated for 5 minutes at a time. 7. Light Headedness. There is a risk the subject may become fatigued or light headed due to the 8-hour fasting period prior to the FMD study (Aim 3).
MINIMIZING RISKS	
26. Explain what steps are being taken to minimize the risks described above.	1. Adverse cardiovascular response to exercise: As recommended by the American Heart Association, the guidelines used most often for monitoring a person with stroke's response to exercise are consistent with patients post myocardial infarction[26]. Per the American Heart Association's guidelines, if prior to any testing or familiarization procedures, resting blood pressure is greater than 180 mm Hg systolic or 110 mmHg diastolic or resting pulse is greater than 110 beats per minute, subjects will not be allowed to participate in any procedures that day. If during the course of the testing a subject's blood pressure is greater than 240 mmHg systolic or 115 mmHg diastolic their session will be terminated. Because some subjects may be taking medication that affects heart contractility or rate, study personnel will ask subjects to report their perceived exertion (Borg scale[27,28]). If subjects report a number equal to or higher than 16 we will terminate testing for that

	day. This scale is sensitive to strain on the cardiovascular system in chronic stroke that may not be reflected in changes in blood pressure, heart rate, and respiration rate. All study personnel will be certified in CPR and AED training. If a cardiovascular emergency should occur during any of the study sessions, study personnel would immediately call Public Safety as they are the campus first responders. As physical therapists, we are trained to recognize the signs and symptoms of a cardiovascular emergency. As the designated first responders, Public Safety would coordinate with emergency services (call 911) and provide immediate first aid including the use of an AED if needed. Public Safety is able to respond to our location within minutes and EMT response is under 5 minutes. This protocol was jointly established between the Department of Physical Therapy and Public Safety in 2010. 2. Muscle Fatigue*:* To prevent any prolonged feeling of neuromuscular muscular fatigue (i.e. more than 15-20 minutes) the fatigue protocol will only be performed one time and the subject will be allowed to recover before leaving. Study personnel will monitor blood pressure, pulse and heart rate before, during, and after the fatigue task. 3. Muscle Soreness: This soreness will be slight, will in no way impede normal daily activity and if present will be expected to subside within a few days. Participants will be instructed to notify their physician as well as Dr. Hyngstrom if muscle soreness persists beyond a few days. 4. Skin Irritation: This irritation involves redness of the skin and usually subsides within a few hours. In the last7 years of testing using the electrodes, no individuals have reported skin irritation following the study. 5. Discomfort from Electrical Stimulation: Participants will be instructed to tell study personnel present during testing if they are experiencing any discomfort and the level of stimulation will be adjusted to a comfortable level. 6. Discomfort from Cuff Inflation: Participants will be instructed to tell study personnel present during testing if they are experiencing discomfort and the level of inflation will be adjusted to a comfortable level. To date, we have tested over 40 participants (stroke and control) using the cuff inflation protocol and all participants have tolerated well (none withdrew themselves or requested to stop protocol).

	7. Light Headedness: An 8-hour fast is common when conducting FMD and blood flow studies. Most subjects will be arriving in the morning; therefore, fasting for 8 hours during the nighttime hours should not have a substantial effect on the subjects. The subjects will be given a snack and something to drink when they are complete with the study.
RISK/BENEFIT RATIO	
27. Describe how the risks to subjects are reasonable compared to the benefits to the subjects or society in general.	Due to the non-invasive and routine nature of proposed study procedures and the potential for an increase in walking function, the benefits outweigh the potential risks.

DECEPTION:	
28. Does the study involve deception (providing false information) or incomplete disclosure (withholding information about study purposes or activities)?	**[ ]** Yes **[x]** No
If yes, answer the following	
a. What information will be withheld from the subject?	N/A
b. Why is deception or incomplete disclosure necessary?	N/A
c. Describe how and when subjects will be debriefed. *REMINDER: Submit a copy of your debriefing sheet or script*	N/A

INCENTIVES	
29. Will an incentive be offered to subjects?	**[x]** Yes **[ ]** No
a. **If yes**, please describe the incentive including dollar amounts and/or monetary value.	$450.00 total if individuals participate in all four test sessions and twelve treatment sessions. If subjects choose to participate in Aim 3, which requires 3 additional visits, they will receive $50 per visit and be paid a grand total of $600.
30. State when subjects will receive the incentive. Describe any pro-rating based on amount of study completed.	Participants will receive 50.00 in cash at the end of the familiarization session and each test sessions. Participants will receive 100 dollars in cash after 6 treatment sessions and additional $100 in cash after completing the twelfth treatment session. Subjects will receive $50 after each session in Aim 3.
31. Will extra-credit be offered to students as an incentive?	**[ ]** Yes **[x]** No
a. **If yes**, please state the amount of extra credit being offered	

b. **If yes,** state the non-research alternative for extra credit that students will be offered. *REMINDER: This alternative must be equivalent in duration and effort to the study activities and should be included in consent forms and recruitment materials*	

F. DATA HANDLING

Direct Identifiers
32. If you will be collecting any direct identifiers such as name, date of birth, address or telephone number, with the research data, please state what identifiers will be collected, why it is necessary and how the data containing identifiers will be secured.
Name, date of birth, email address and telephone number will be collected to contact if needed. Age is needed to be used as part of sample description in manuscripts. *Subjects will be identified by an alphanumerical code.* A spreadsheet will be kept that links the participants name to their study code on a password protected computer in Dr. Hyngstrom's office (Cramer 346).

Data Security			
33. Complete the following table to provide details on the procedures in place to maintain the confidentiality and security of the study data.			
Data type	**Who will have access? Where will they be stored? What security measures are in place?**	**When and how will they be deidentified?**	**When and how will they be destroyed?**
Signed consent forms	Signed consent forms will be kept in locked cabinet in Schroeder Complex 346 (Dr. Hyngstrom's office). Only Dr. Hyngstrom will have access to the documents.		After 10 years, paper records will be shredded and all computer files will be deleted. No data will be used for future research purposes.
Hard copy data (questionnaires, etc…)	Data sheets will be kept in a locked cabinet in Dr. Hyngstrom's laboratory (Cramer Annex 138). Only study personnel will have access to the documents.	*At time of consent. Subjects will be identified by an alphanumerical code.* A spreadsheet will be kept that links the participants name to their study code on a password	After 10 years, paper records will be shredded and all computer files will be deleted.

		protected computer in Dr. Hyngstrom's office (Cramer 346).	
Electronic datasets	Data sets will be kept on password protected computers in Dr. Hyngstrom's laboratory and Dr. Hyngstrom's office, and on the laptops of study personnel. All data sets will have de-identified data.	*At time of consent. Subjects will be identified by an alphanumerical code.* A spreadsheet will be kept that links the participants name to their study code on a password protected computer in Dr. Hyngstrom's office (Cramer 346).	After 10 years, computer files will be deleted.
Key linking names to study IDs (if data are coded)	A spreadsheet will be kept that links the participants name to their study code on a password protected computer in Dr. Hyngstrom's office (Cramer 255c).		After 10 years, computer files will be deleted.
Audio or video recordings	n/a		
Other (*add rows as needed for your study*)	n/a		

34. Indicate if data will be stored at any time (even temporarily) on electronic portable devices such as laptops, digital recorders, or flash drives.

[x] Identifiable data WILL NOT be stored on portable devices
[ ] Identifiable data WILL be stored on portable devices (NOTE: PHI and sensitive data stored in this manner must be encrypted)

a. Rationale for storage of personal/private identifiable data on these devices**: N/A**

b. State the security measures in place and where devices will be stored**: N/A**

35. Will study data be shared outside of the study team or with non-local team members? [ ] Yes [x] No

a. If yes, describe with whom, for what purposes, and how the sharing will take place and the security measures in place to protect data during transfer**:**

36. Will data or specimens (identifieable or deidentified) be stored for future use? [x] Yes [ ] No

If yes, please describe and make sure to include in consent form**:**
Name and contact information (phone number and email address) will be stored to contact participants to participate in future studies.

37. Breaking confidentiality: Will any information, such as abuse of a child or elder, be collected that is subject to mandated reporting requirements? Or, will any data be collected that would require study staff to report results to medical professionals to ensure the safety of the subject? [ ] Yes [x] No
If yes, please describe the circumstances under which this could happen below and make sure to notify subjects of this in the consent form**:N/A**

G: DISSEMINATION AND OTHER STUDY INFORMATION

38. Describe your plans for disseminating the results of the study (include educational products such as dissertations/masters theses as well as academic products such as publications or presentations). Make sure to state if identifiers will be used in any research products and if data will be presented in the aggregate or individual level. If direct quotes will be used, please state this and include in the consent form:
Results may be disseminated in the following forms: manuscripts, oral presentations, poster presentations, dissertations, and future grant applications.

39. Have you registered your project with the Office of Research and Sponsored Programs (ORSP)? [ ] Yes [ ] No

If Yes, Please list your Marquette ORSP Institutional Proposal # (XXXXXXXX), which can be found in Kuali: ***00032902***

40. Is this project funded by NIH, HHS, Dept of Education, NSF or any other federal agency?
[x] No** [ ] Yes* If so, which agency? **:**

**If your project is federally funded, you must also submit a copy of the proposal to the IRB.*
***If your project receives funding in the future you are required to notify the IRB of this via an amendment process*

Does the investigator or key personnel have a potential financial conflict of interest in this study that should be disclosed?
[ ] Yes [x] No If Yes, Please explain*:*

H: STUDY PERSONNEL

Provide the names, titles and affiliations of **all** investigators (include PI, faculty advisor, co-PIs, and investigators from outside institutions) in the table below. Please add lines as needed

To minimize future amendment submissions, non-key personnel roles such as student or graduate student "research assistant" do not require those individuals to be individually named. Consider entering "research Assistants" in the name field and "n/a" in the contact email field.

Name	Institution	Status (Faculty, Grad., Undergrad., etc.)	Contact e-mail
Allison Hyngstrom	MU	Faculty	Allison.hyngstrom@marquette.edu
Saad Alqahtani	MU	Grad student	Saad.alqahtani@marquette.edu
Stephanie Raab	MU	Grad student	Stephanie.raab@marquette.edu
Brian.schmit@marquette.edu	MU	Faculty	Brian.schmit@marquett.edu
Matthew Durand	MCW	Faculty	Mdurand@mcw.edu
Jennifer Nguyen	MCW	Staff	Jnguyen@mcw.edu
Zhilun Zhou	MU	Grad student	Zhilun.zhou@marquette.edu
Ashley Dejaco	MU	Undergrad student	Ashley.dehaco@marquette.edu
Toni Uhrich	MU	Staff	Toni.uhrich@marquette.edu

***Human subjects training is required for all human subject investigators. See http://www.marquette.edu/orc/irb/training-education.shtml for more information on this requirement.**

I.

Is this study…		Submission directions	Resources
...accessing or using protected health information (PHI) from a HIPAA-covered entity?	[ ] Yes [x] No	→ Also complete **Appendix B** and provide any supporting documentation such as a draft authorization form or a request to waive authorization	HIPAA Privacy Rule HIPAA and Research Covered Entities on MU Campus
…using student educational records/data including GPA, course documents, etc…?	[ ] Yes [x] No	→ Also complete **Appendix C**	FERPA regulations MU FERPA policies
…collecting data through electrical powered equipment that comes in contact with subjects (excluding computers and battery –operated devices)?	[x] Yes [ ] No	→ Make sure to describe the device in **Section II.D**, complete **Appendix D** and submit a copy of the purchase receipt or last safety testing record	MU's Electrical Safety Testing Policy
… testing the safety and/or efficacy of a new medical device or drug?	[ ] Yes [x] No	→ FDA regulations may apply- please contact the ORC to discuss click here to email the ORC)	Also see MU's device safety in research website
… using secondary data or biospecimens collected outside of this research study?	[ ] Yes [x] No	→ Also complete **Appendix E**	

Submission Instructions: Email this completed form and any supporting documents including consent forms, information sheets, surveys, interview questions, etc. as attachments to orc@mu.edu with the following subject line:

New Study Submission for [first and last name of PI] or
Amendment Submission for [first and last name of PI], HR-[XXXX]

- In the body of e-mail, include the title of the study and an itemized list of attachments.
- The email address of the sender must be the Principal Investigator's Marquette email.
- If the PI is a **student**, the faculty advisor **must** be cc'd.

Once submitted, the IRB will e-mail back a response of receipt. If you do not receive an e-mail confirmation of submission within 3-5 days of submission, please contact the IRB by phone (288-7570) or email (orc@mu.edu) to verify receipt.

Appendix A: Consent

*****COMPLETE ONLY IF REQUESTING TO WAIVE, ALTER, OR WAIVE DOCUMENTATION OF CONSENT*****

Section 1. WAIVER OF DOCUMENTATION OF CONSENT (not requiring subject to sign the consent form)

Complete either Option A, B or C questions

OPTION A		OPTION B		OPTION C
Would the signed consent document be the only record linking the subject to the study? [ ] Yes [ ] No		Does the research pose no more than minimal risk? [ ] Yes [ ] No		Is it NOT the cultural norm for subjects to sign these type of documents? [ ] Yes [ ] No
Is breach of confidentiality the principal risk to the subjects? [ ] Yes [ ] No	OR	Does the research include any activities that would require signed consent in a non-research context? [ ] Yes [ ] No	OR	Is an alternate mechanism of documenting consent being included in the protocol? [ ] Yes [ ] No

Provide a justification/explanation for the responses above:

Section 2. WAIVER OR ALTERATION OF CONSENT

Are you requesting:

[ ] Waiver of consent
[ ] Alteration or removal of required elements of consent- State what will be altered or removed**:**

Respond to the following questions:

1. Does the research pose more than minimal risk to the participants?	
2. Will the waiver adversely affect participants' rights and welfare?	
3. Why would it be impracticable to carry out the research without the waiver or alteration?	
4. When appropriate, how will pertinent information be returned to or shared with participants?	
5. Explain why the study cannot be conducted using de-identified datasets (if appropriate).	
6. Is this study approved by governmental officials, designed to evaluate public service programs and is impracticable to be carried out without the waiver?	

Appendix B: HIPAA

*****COMPLETE ONLY IF REQUESTING TO USE PROTECTED HEALTH INFORMATION IN THE STUDY*****

Protected Health Information (PHI) = Health information + identifiers

Will the project require the use or disclosure of PHI?
] YES [x] NO (If NO, you do not need to fill out the rest of this appendix).

If the answer is YES, indicate the source of protected health information:

Marquette University Sources		Non-Marquette University Sources	
[ ]	School of Dentistry	[ ]	Hospital medical records (in- and /or outpatient)
[ ]	College of Health Sciences	[ ]	Health professional/Clinic records
[ ]	College of Nursing	[ ]	Health professional/Office records
[ ]	Dental Hygiene	[ ]	Laboratory, pathology and/or radiology results
[ ]	Speech Pathology and Audiology	[ ]	Biological samples
[ ]	Counseling and Educational Psychology	[ ]	Interviews/questionnaires
[ ]	Clinical Psychology	[ ]	Mental health records
[ ]	MU Medical Center	[ ]	Billing records
[ ]	Intercollegiate Athletics	[ ]	Data previously collected for research purposes
[ ]	Other (describe):	[ ]	Decedent information
		[ ]	Other (describe):

A. Nature of Request:
[ ] Authorization (Also submit draft authorization form)
[ ] Waiver of authorization (Also submit completed request to waive authorization)
[ ] Limited data set agreement

B. Details

1. Identify all individuals who will have access to data and PHI:

2. Describe the PHI that will be gathered, used or disclosed as part of this research project:
Age, date of stroke, type of stroke, and reported medical history including current medications. These data are important for describing participant characteristics and assisting with the interpretation of the results.

3. Describe the identifiers that will be gathered, used or disclosed as part of this research project:

4. Explain why the research cannot practicably be conducted without requested PHI:

C. Data Security: explain safeguards and how data will be stored.

1. Electronic (check all that apply)
[ ] Secure network [ ] Password access
[ ] Coded, with master list kept as a hard copy or on a secure network, separate from PHI/data
[ ] Other (explain):

2. Hard copy (check all that apply)
[ ] Locked suite [ ] Locked filing cabinet [ ] Locked office
[ ] Data de-identified with master list secured and kept separately
[ ] Other (explain):

D. Sharing of PHI
1. Will the PHI be removed from the entity that owns the PHI?

[ ] YES [ ]NO

2. Will the PHI be shared/used by others than P.I. and research staff?
[ ] NO [ ] YES (mark all that apply below)

[ ] Statistician [ ] Colleagues
[ ] Other research laboratories [ ] Publications
[ ] Data & Safety monitoring committees
[ ] Sponsor [ ] Consultants
[ ] Participants (Subjects)
[ ] Other(s) – explain _____

a. If data will be shared, which of the following apply?

[ ] With identifiers [ ] Without identifiers [ ] With a linkage code
[ ] As a Limited Data Set (Requires data use agreement)

E. Retention of PHI

1. How long will the information be retained?
[ ] End of study [ ] A set date (provide date):
[ ] When data analysis is complete
[ ] Other (explain):

2. How will the information be destroyed?
a. Electronic (explain):

b. Hard copy (explain):

3. Is there a justification for retaining the identifiers?

[ ] YES [ ] NO

If YES, what is the justification?
[ ] Health reasons (explain):
[ ] Scientific (explain):
[ ] Legal (explain):
[ ] Other (explain):

4. Will the stored PHI be reused or disclosed to any other person or entity except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of PHI would be permitted?

[ ] NO [ ] YES- explain:

Appendix C: FERPA

*****COMPLETE ONLY IF USING STUDENT EDUCATIONAL DATA FOR RESEARCH PURPOSES*****

1. Are you accessing individual student educational data including course documents, GPA, registry information, or grades?

[ ] YES [ ] NO

2. List the specific student educational data you are accessing:

3. Will you be recording student identifiers (name, MU ID#, etc…) with the educational data?

[ ] YES [ ] NO

4. How will you gain access to the educational data (i.e., will the registrar be providing it to you, will you be pulling it from your own students' records, etc…)?

5. Is any use of individual-level, identifiable student data clearly stated in a consent form that students will be signing?

[ ] YES [ ] NO

Please contact the registrar's office with any questions about FERPA permissions and requirements
http://www.marquette.edu/mucentral/registrar/

Appendix D: Electrical Safety Testing

*****COMPLETE ONLY IF ELECTRICAL EQUIPMENT WILL COME IN CONTACT WITH SUBJECTS*****

*Note- this policy does not apply to devices that are battery-operated or computers used for data collection

Office of Research Compliance policy #98.106 requires that electrical equipment that comes in contact with research subjects is required to pass electrical safety testing every three years starting from the date of purchase. If this study uses electrical equipment, please list it below, describe what it is and provide the most recent testing date or date of purchase. Note that custom modified devices must undergo testing prior to use in human subjects research.

Name of device	Description	Date of testing or date of purchase (indicate which)
GE Vivid I ultrasound		12/2018
Delysis wireless EMG	Measures muscle activity	2018, battery operated
OT AMplifier	Measures muscle activity	12/2018
Biodex	Measures strength of different muscle groups	12/2018
Bertec Treadmill	Treadmill with embedded force sensors	Uses 220 power supply
Near Infrared Spectroscopy Machine	Infrared light used to noninvasively measure oxygen saturation to the muscle	12/2018

Appendix E- Pre-existing data or specimens

*****COMPLETE ONLY IF USING PRE-EXISTING DATA OR SPECIMENS FOR RESEARCH PURPOSES*****

1. Answer the following:

	Yes	No	n/a
a. Will the data or specimens include identifying information?			
b. Does the data include ONLY information protected under HIPAA?			
c. Will you be attempting to re-identify or contact subjects?			

2. Describe the data or specimens that will be used in this study. Include where they are coming from, how/why they were originally collected, and list the specific data fields (if applicable).

3. What is the total number of existing records or specimens that will be used in this study?

4. Describe the plan to obtain consent for use of the data/specimens in this study or complete Appendix A to request a waiver of consent. If the data or specimens were collected in a previous study, please state if subjects were made aware that their specimens or data would be stored and used in future studies.

5. How will data or specimens be transported to research team and what security measures are in place during transit?

6. Make sure you have described data storage and security in Section V of the protocol form or describe it here:

1. de Groot PC, Poelkens F, Kooijman M, Hopman MT. Preserved flow-mediated dilation in the inactive legs of spinal cord-injured individuals. *Am J Physiol Heart Circ Physiol.* 2004;287(1):H374-380.
2. Donato AJ, Uberoi A, Wray DW, Nishiyama S, Lawrenson L, Richardson RS. Differential effects of aging on limb blood flow in humans. *Am J Physiol Heart Circ Physiol.* 2006;290(1):H272-278.
3. Nishiyama SK, Walter Wray D, Berkstresser K, Ramaswamy M, Richardson RS. Limb-specific differences in flow-mediated dilation: the role of shear rate. *J Appl Physiol.* 2007;103(3):843-851.
4. Thijssen DH, Dawson EA, Black MA, Hopman MT, Cable NT, Green DJ. Heterogeneity in conduit artery function in humans: impact of arterial size. *Am J Physiol Heart Circ Physiol.* 2008;295(5):H1927-1934.
5. Durand MJ, Murphy SA, Schaefer KK, et al. Impaired Hyperemic Response to Exercise Post Stroke. *PLoS One.* 2015;10(12):e0144023.
6. Buchanan CE, Kadlec AO, Hoch AZ, Gutterman DD, Durand MJ. Hypertension during Weight Lifting Reduces Flow-Mediated Dilation in Nonathletes. *Med Sci Sports Exerc.* 2017;49(4):669-675.
7. Durand MJ, Dharmashankar K, Bian JT, et al. Acute exertion elicits a H2O2-dependent vasodilator mechanism in the microvasculature of exercise-trained but not sedentary adults. *Hypertension.* 2015;65(1):140-145.
8. Hornby TG, Holleran CL, Hennessy PW, et al. Variable Intensive Early Walking Poststroke (VIEWS): A Randomized Controlled Trial. *Neurorehabil Neural Repair.* 2015.
9. Mudge S, Stott NS. Timed walking tests correlate with daily step activity in persons with stroke. *Arch Phys Med Rehabil.* 2009;90(2):296-301.
10. Middleton A, Fulk GD, Beets MW, Herter TM, Fritz SL. Self-Selected Walking Speed is Predictive of Daily Ambulatory Activity in Older Adults. *J Aging Phys Act.* 2016;24(2):214-222.
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12. Lin JH, Hsu MJ, Hsu HW, Wu HC, Hsieh CL. Psychometric comparisons of 3 functional ambulation measures for patients with stroke. *Stroke.* 2010;41(9):2021-2025.
13. Bushnell C, Bettger JP, Cockroft KM, et al. Chronic Stroke Outcome Measures for Motor Function Intervention Trials: Expert Panel Recommendations. *Circ Cardiovasc Qual Outcomes.* 2015;8(6 Suppl 3):S163-169.
14. de Oliveira R, Cacho EW, Borges G. Post-stroke motor and functional evaluations: a clinical correlation using Fugl-Meyer assessment scale, Berg balance scale and Barthel index. *Arq Neuropsiquiatr.* 2006;64(3B):731-735.
15. Brashear A, Zafonte R, Corcoran M, et al. Inter- and intrarater reliability of the Ashworth Scale and the Disability Assessment Scale in patients with upper-limb poststroke spasticity. *Arch Phys Med Rehabil.* 2002;83(10):1349-1354.
16. Kriska A, Bennett P. An epidemiological perspective of the relationship between physical activity and NIDDM: from activity assessment to intervention. *Diabetes Metab Rev.* 1992;8:355-372.
17. Hyngstrom AS, Kuhnen HR, Kirking KM, Hunter SK. Functional implications of impaired control of submaximal hip flexion following stroke. *Muscle Nerve.* 2013.
18. Hunter SK, Yoon T, Farinella J, Griffith EE, Ng AV. Time to task failure and muscle activation vary with load type for a submaximal fatiguing contraction with the lower leg. *J Appl Physiol.* 2008;105(2):463-472.
19. Sébastien L, Mathieu G, Vincent G, Martin J, Jean-Claude CT, Anil N. Reproducibility of near-infrared spectroscopy parameters measured during brachial artery occlusion and reactive hyperemia in healthy men. *Journal of biomedical optics.* 2012;17(7):77010.
20. Vasiliki G, Stavros D, Georgios T, Maria A-N, Serafeim N. Utilizing the vascular occlusion technique with NIRS technology. *International Journal of Industrial Ergonomics.* 2010;40(2):218-222.
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25. Taylor JL, Gandevia SC. Transcranial magnetic stimulation and human muscle fatigue. *Muscle Nerve.* 2001;24(1):18-29.
26. Thompson PD, Franklin BA, Balady GJ, et al. Exercise and acute cardiovascular events placing the risks into perspective: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism and the Council on Clinical Cardiology. *Circulation.* 2007;115(17):2358-2368.
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