

Study Protocol

NCT03760016

Moderate-Intensity Exercise Versus High-Intensity Interval Training to Recover Walking Post-Stroke

Last updated March 16, 2021

Moderate-Intensity Exercise Versus High-Intensity Interval Training to Recover Walking Post-Stroke

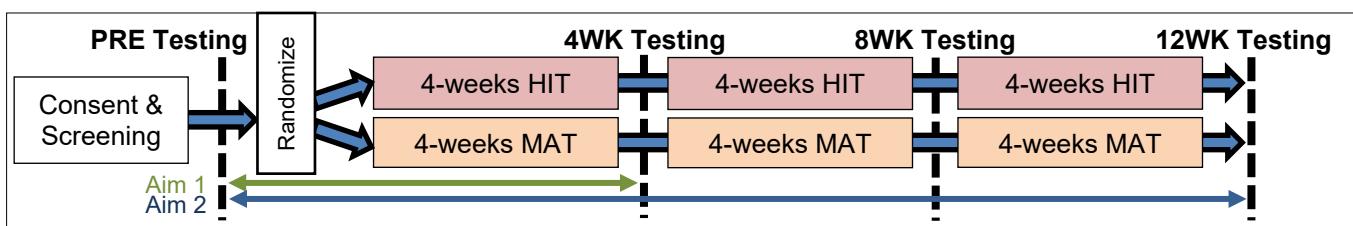
PI, Pierce Boyne PT, DPT, NCS; UD-site PI, Darcy Reisman PT, PhD; KUMC site-PI, Sandra Billinger PT, PhD

A. SPECIFIC AIMS

Fewer than 10% of stroke survivors regain adequate walking speed and endurance for normal daily functioning (e.g. grocery shopping).¹⁻⁵ This limitation in walking capacity is caused by both neurologic gait impairments from the stroke and aerobic deconditioning due to inactivity.^{6,7} Current stroke rehabilitation guidelines recommend moderate-intensity aerobic training (MAT) to address both of these issues.^{6,8} However, recent evidence from our team suggests that a clinically feasible MAT duration (4 weeks) may have only negligible effects among chronic stroke survivors (>6 months post stroke).⁹ There is growing belief that a more vigorous training intensity (>60% vs. 40-60% heart rate reserve) may be a 'critical ingredient' for greater gait and aerobic fitness improvements, with less training time.¹⁰ Yet, the optimal training intensity has been difficult to determine among stroke survivors because neurologic impairments make it challenging to reach vigorous intensity, and previous attempts using conventional exercise have fallen short of 60% heart rate reserve, even with 6 months of training.^{7,11} What is needed is a new post-stroke therapy protocol capable of reliably eliciting vigorous intensity, so that the optimal training intensity for improving walking capacity can be established.

Our transdisciplinary team, consisting of national experts in post-stroke aerobic exercise & gait rehabilitation, neurologists focused on stroke recovery, an exercise physiologist, a cardiologist and a biostatistician, has developed a novel training protocol that safely enables persons with chronic stroke to achieve vigorous intensity in the first session (a mean 76% heart rate reserve).¹² Based on the well-tested exercise science and cardiac rehabilitation strategy of high-intensity interval training (HIT), this protocol uses bursts of maximum speed walking with alternating recovery periods, to sustain higher aerobic intensities than physiologically possible with continuous exercise,¹³ and with lower perceived exertion.¹⁴ Our preliminary data demonstrate that this innovative locomotor HIT protocol can elicit >40% increases in walking capacity, gait speed and aerobic fitness in just 4 weeks. However, no previous studies have compared HIT with the current best-practice model post-stroke (MAT). Further, it is possible that the longer 12 week HIT durations tested in some heart disease studies might yield even better outcomes, approaching normal walking capacity, but this has not been tested.

The **objective of this proposal** is to determine the optimal training intensity and the minimum training duration needed to maximize immediate improvements in walking capacity in chronic stroke. We propose a single-blind 3-site RCT. Fifty persons >6 months post stroke will randomize to either 12 weeks of HIT or 12 weeks of MAT; each for 45 minutes, 3x/week. Clinical measures of walking function, aerobic fitness, daily walking activity and quality of life will be assessed at baseline (PRE) and after 4, 8 and 12 weeks of training (4WK, 8WK, 12WK).



Aim 1: Determine the optimal locomotor training *intensity* for eliciting immediate improvements in walking capacity among chronic stroke survivors. *Primary study hypothesis:* Compared with 4 weeks of MAT, 4 weeks of HIT will elicit significantly greater improvement in walking capacity, as measured by change in the 6-minute walk test from PRE to 4WK. This aim is powered for proof of concept that vigorous training intensity is a 'critical ingredient' for post-stroke locomotor recovery.

Aim 2: Determine the minimum locomotor training *duration* needed to maximize immediate improvements in walking capacity. *Hypothesis* (based on our preliminary data¹⁵): Compared with 4 & 8 weeks of HIT, 12 weeks of HIT will elicit significantly greater improvements in walking capacity and increased benefit over MAT. However, if effects peak earlier than 12WK, it would provide scientific justification to keep testing a shorter, lower-cost protocol to determine its sustained effects relative to longer training durations.

These aims will provide foundational information to guide dosing of locomotor training intensity and duration in future studies and clinical practice. Further, the expected outcomes offer the potential to transform current stroke rehabilitation and make a positive impact on the disability burden of stroke.

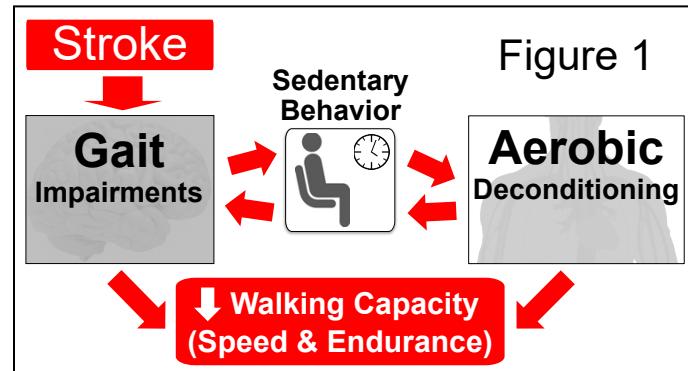
B. BACKGROUND AND SIGNIFICANCE

Stroke is a leading cause of chronic disability¹ and limited walking capacity is a major barrier to stroke recovery.⁸ Despite declining mortality rates from stroke, 795,000 people continue to experience a stroke in the United States each year, resulting in 6.6 million Americans (2.6% of adults) currently living with the chronic sequelae of stroke.¹ In addition, the chronic disability and financial burden associated with stroke are expected to continue to increase, due in part to the aging population.^{1,16} While the majority of persons in the chronic phase of stroke are able to walk without continuous physical assistance from another person,^{2,3} less than 10% have adequate walking capacity (speed and endurance) to allow normal daily functioning (e.g. work, grocery shopping).^{4,5} On average, community dwelling stroke survivors are able to walk about 0.5 m/s over short distances and 250 meters in 6 minutes,^{4,17-19} representing only ~40% of age-predicted normal gait speed and capacity (1.3 m/s and over 500 meters, respectively).²⁰⁻²² This inadequate recovery of walking is devastating because it leads to a loss of life roles, social isolation, dependency, sedentary lifestyle and increased risk for secondary cardiovascular events.^{2,4-6,8,20,23-25} Therefore, improved walking capacity is a primary goal of stroke rehabilitation.^{8,26} *Relevance:* This project targets walking capacity limitations for persons with chronic stroke.

Neurologic gait impairments and aerobic conditioning each contribute to limited walking capacity post-stroke (Figure 1).^{6,8} Approximately 50% of stroke survivors have persistent motor impairment,¹ leading to inefficient gait patterns that can double the metabolic cost of mobility.²⁷⁻²⁹ At the same time, mean aerobic capacity is reduced to about half of normal.³⁰ This deconditioning alone is enough to render walking either impossible or unsustainable,^{31,32} and to put independent living out of reach.³⁰ Thus, it is not surprising that even ambulatory, community dwelling stroke survivors

average up to 75% fewer steps/day than even the most sedentary non-disabled older adults (1400 vs. 5500).^{27,33-36}

Such physical inactivity stymies motor recovery,³³ perpetuates further deconditioning^{31,33} and contributes to a very high long-term risk for cardiac events^{23,24} and recurrent stroke,^{25,37} the leading causes of death among stroke survivors.³⁸ *Relevance:* The interventions in this proposal are designed to address both gait impairment and aerobic deconditioning, thus simultaneously targeting both of the primary contributing factors to walking capacity.



Current guidelines recommend moderate-intensity aerobic training (MAT) to improve walking capacity and other outcomes post-stroke, but this approach has known limitations.^{6,8} Compared to conventional stroke rehabilitation therapies and lower intensity training, significant benefits of MAT have been observed for aerobic fitness,³⁹⁻⁴¹ walking capacity,⁴⁰⁻⁴⁴ overall disability,⁴⁴ fatigue,⁴⁵ cardiovascular risk factors,⁴⁶⁻⁴⁹ blood flow (peripheral⁵⁰ and cerebral⁵¹), brain activation,⁵² depressive symptoms,⁵³ cognition,⁵⁴ participation⁵⁵ and quality of life.⁵⁶ However, this approach has not been adopted in most clinical stroke rehabilitation settings,⁸ because: 1) it has shown modest and inconsistent effects on gait speed,^{40,41,43} a primary stroke rehabilitation outcome,⁵⁷⁻⁵⁹ and 2) protocols involve extended training durations (typically 45 min, 3x/wk for 6 months),^{33,46,50-52,60-62} which are impossible in clinical practice due to patient adherence issues⁶³⁻⁶⁵ and reimbursement constraints.^{66,67}

There is a clear need for a more efficacious intervention to improve walking capacity post-stroke. The proposed research seeks to address this need by advancing an innovative locomotor training intervention that has the unique potential to elicit clinically meaningful improvements with a clinically feasible and resource-efficient training duration that could increase rates of exercise engagement among stroke survivors.

Locomotor high-intensity interval training (HIT) is a promising strategy for stroke rehabilitation, which uses bursts of maximum speed walking alternated with recovery periods to safely maximize training intensity.¹⁰ The scientific rationale for using locomotor HIT to target post-stroke walking capacity includes converging basic and clinical data from the fields of exercise physiology, neuroscience, cardiac rehab and stroke rehabilitation:

- Accumulating evidence in stroke and non-stroke populations suggests that **vigorous training intensity is a powerful stimulus for improving aerobic fitness**^{10,68-74} and decreasing the risk of future cardiovascular events.^{10,70-72,75} For example, in our recent meta-regression analysis of post-stroke aerobic exercise studies (n=598 participants; 15 studies), aerobic fitness improvement (vs. control) was significantly greater in studies that attempted vigorous aerobic intensity (>60% heart rate reserve [HRR]) versus moderate intensity (40-60% HRR) (VO₂-peak Δ mean difference, +2.2 mL/kg/min [95% CI: +0.6, +3.9]).⁷⁴
- **Without HIT, vigorous intensity has been difficult to achieve post-stroke.** In our recent survey of 568 physical therapists involved in stroke rehabilitation, only 0-2% of respondents across settings reported prescribing vigorous intensity exercise. The most common perceived barrier was the limited ability of stroke survivors to exercise at a training level.¹¹ Further, most previous stroke studies that have attempted to progress into vigorous aerobic intensity have either not reported the actual intensity achieved, or have fallen short of 60% HRR, even with 6 months of training.⁷ Conversely, HIT enables non-disabled adults to sustain very high aerobic intensities longer than physiologically possible with continuous exercise,¹³ and with less perceived exertion¹⁴ and better adherence.^{76,77} Therefore, the interval training strategy of HIT likely increases the feasibility and sustainability of vigorous intensity for persons with stroke.
- Stroke rehabilitation studies and principles of motor learning & neuroplasticity also suggest that **higher motor intensity results in better motor outcomes**.^{10,68,74,78-87} For example, studies by our team and others have shown that faster gait speed challenges during training (i.e. higher intensities) result in greater immediate improvements in hemiparetic gait kinematics,^{88,89} kinetics,⁹⁰ muscle activation patterns⁸⁸ and efficiency,^{61,62,84,91} while conferring greater longitudinal improvements in gait speed.^{9,81-84} HIT enables healthy adults to train at higher gait speeds than are physiologically possible with continuous exercise.¹³ Therefore, the interval training strategy of HIT likely increases the feasibility and sustainability of maximal motor intensity for persons with stroke.
- **Among healthy adults, HIT delivers significant benefits remarkably fast** (within 6 sessions over 2 weeks),⁹²⁻⁹⁴ achieving similar performance & physiologic adaptation to MAT with up to 76% less training time.^{93,95-97} If HIT is able to elicit comparable changes among stroke survivors in 4 weeks of training (twice as much), it would provide a highly clinically feasible and resource-efficient alternative to the current best-practice model (MAT), which could result in increased rates of exercise engagement among stroke survivors.
- **For persons with heart disease** (coronary artery disease,^{77,98} myocardial infarction^{77,99,100} and heart failure^{76,99,101}), **HIT has shown superior clinical, aerobic fitness**^{76,99} and **adherence**^{76,77} **outcomes compared to MAT with up to 53% less training time**^{76,77,99} and **no serious adverse events** in well over 30,000 research training hours.^{65,72,76,77,98-101} Based on these impressive safety & efficacy data, HIT is now being considered as a new standard of care for cardiac rehabilitation.^{72,102} For stroke survivors, HIT may be even more efficacious, because of its potential to maximize motor outcomes in addition to aerobic fitness.^{9,81-84} Thus, HIT efficiently targets both of the main contributing factors to walking capacity.

Scientific Premise. Our primary hypothesis that vigorous training intensity (>60% vs 40-60% heart rate reserve) is a critical ingredient for improving gait and aerobic fitness post-stroke is based on converging physiologic and clinical data, mostly from small to moderate sized, single-site, single-blind, randomized controlled studies, in stroke and non-stroke populations.¹⁰ Aside from our preliminary data below, the one previous stroke study in the literature attempting to directly test this hypothesis did not use HIT or report the actual training intensity achieved, and was further limited by the use of a single-site design, low power (n=34), lack of assessor blinding, a 6-month intervention lacking clinical feasibility and a 33% attrition rate without intent-to-treat analysis.⁷³ Other stroke studies have shown promising results for “higher” intensity locomotor training, but were not designed to directly test this hypothesis because they did not include a moderate-intensity aerobic control group (MAT).^{81-84,103-109} These studies have also been limited by failing to achieve vigorous intensity (mean >60% heart rate reserve) or to describe the actual mean aerobic intensity, single-site design and, in some cases, confounding from additional co-interventions in one group (e.g. body weight support, physical assistance) or from carryover effects in longitudinal crossover designs.

We have overcome previous barriers to achieving vigorous intensity in stroke research, by *systematically*¹¹⁰ progressing a novel locomotor HIT protocol from conceptualization¹⁰ to initial protocol development,¹² to protocol refinement (adding over ground HIT), while also establishing preliminary safety^{9,12,111} & promising outcomes and confirming the feasibility of recruitment & blinded testing procedures.⁹ However, before we can justify and design a large efficacy trial, we still need an initial proof of concept that

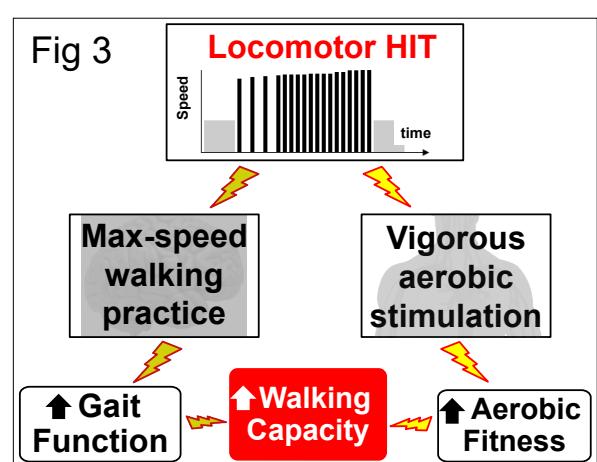
vigorous intensity is a 'critical ingredient' for locomotor training and we need to optimize the training duration dose. HIT studies in non-stroke populations have successfully used training durations ranging from 2-12 weeks,¹⁰ and our team's previous chronic stroke study with a different locomotor training intervention found continuous changes in gait function across the 12 week intervention.¹⁵ However, no previous studies in any population have compared different HIT durations or examined the time course of outcome changes.

The proposed study builds on our previous work and overcomes the limited scientific rigor of previous studies with a high-quality, moderately-sized, 3-site RCT, using our novel HIT protocol to ensure vigorous training intensity and a best-practice MAT control group. This study will determine the optimal training intensity and minimum training duration needed to maximize immediate improvements in walking capacity and other measures (gait speed, aerobic fitness, metabolic cost of gait, daily walking activity and quality of life) among chronic stroke survivors. This will be the first study designed to compare HIT and MAT in chronic stroke and the first study in any population to compare different HIT durations. Aim 1 is expected to provide proof of concept that vigorous training intensity is a 'critical ingredient' for locomotor recovery, by showing that HIT elicits significantly greater immediate improvement in walking capacity compared with MAT, using a clinically feasible 4-week training dose. Aim 2 is expected to show that longer durations of HIT elicit continued significant improvements, approaching normal walking capacity, with increasing benefit over MAT across 12 weeks of training. However, if effects peak earlier than 12 weeks, it would provide scientific justification to keep testing a shorter protocol that is more aligned with patient preferences and current reimbursement models.

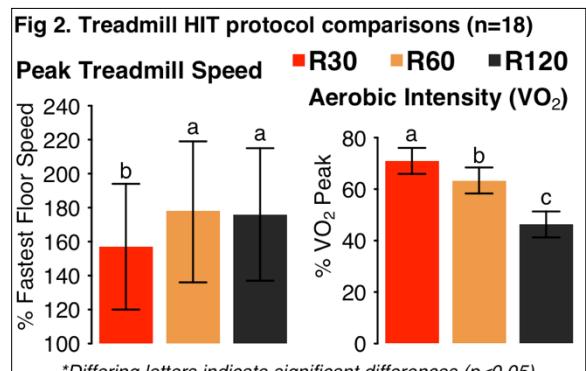
Regardless of the outcomes, our aims will provide fundamental new knowledge to inform selection of intensity and duration dosing parameters for aerobic training and gait recovery interventions post-stroke. At the same time, this study will provide all remaining needed data to justify and design a subsequent definitive trial to determine the relative efficacy of HIT and MAT for eliciting clinically meaningful and sustained improvements in walking function. Therefore, *the proposed study is significant because it is expected to constitute a critical step in a continuum of research that will lead to the clinical implementation of novel training strategies to synergistically and potently address both gait impairment and aerobic deconditioning post-stroke*. This research will likely have a major impact on the massive¹¹² disability and financial burden of stroke, because, unlike the currently recommended protocol for addressing these outcomes (MAT),^{33,46,50-52,60-62} HIT appears to provide meaningful benefits with a training duration that fits well within current clinical practice models and patient preferences.^{66,67,113} By elucidating the relative time course of changes in different outcomes, the data from this study will also inform future mechanistic and biomarker investigations in our team member's areas of expertise, including brain connectivity, neurophysiology, molecular genetics and vascular function. In addition, the data will be made publicly available after study completion to support further exploration and meta-analysis.

C. PRELIMINARY STUDIES

Our team developed a novel treadmill HIT protocol that enables persons with chronic stroke to achieve vigorous aerobic intensity (a mean 76% HRR) and fast treadmill speeds (a mean 178% of fastest floor speed) in the first session.¹² This initial HIT protocol was developed by examining the influence of recovery period duration on treadmill speed and aerobic intensity (Figure 2).¹² The shortest recovery duration used in previous studies (120 seconds)^{81,82} was suboptimal. R60 (60 second recovery) elicited the greatest immediate changes in treadmill speed while 30 second recovery elicited the highest aerobic intensity and enabled all 18 participants to achieve vigorous intensity ($\geq 60\%$ HRR/VO₂-peak).



Our treadmill HIT protocol now uses R60 for 5 min to maximize speed then transitions to R30 for 15 min to ensure vigorous aerobic stimulation, thus targeting both gait function and aerobic fitness to synergistically improve walking capacity (Fig 3).



Method: Each 20 minute HIT protocol involved 30 second bursts at maximum safe treadmill speed alternated with recovery periods of either 30, 60 or 120 seconds (R30, R60 and R120). Eighteen participants with chronic stroke performed one session of each protocol in randomized order with one week in-between

Our preliminary clinical data suggest that locomotor HIT achieves remarkable improvements in just 4 weeks. In our initial pilot randomized controlled trial with blinded outcome assessment (n=16),⁹ HIT elicited significant improvements in aerobic capacity, walking speed and the metabolic cost of walking, and some

Clinical Measure	HIT Group Change (n=11)	MAT Group Change (n=5)	data presented as mean [95% CI]
Aerobic capacity (ventilatory threshold), mL O ₂ /kg/min	+4.4 [3.1, 5.7] (+43%)	+0.6 [-1.3, 2.5] (+4%)	+3.8 [1.5, 6.1]
Fastest treadmill walking speed, m/s	+0.36 [0.25, 0.47] (+41%)	+0.07 [-0.10, 0.24] (+7%)	+0.29 [0.09, 0.49]
Fastest (floor) walking speed (10m walk test), m/s	+0.10 [0.06, 0.13] (+13%)	+0.01 [-0.04, 0.06] (+1%)	+0.08 [0.02, 0.14]
Comfortable walking speed (10m walk test), m/s	+0.10 [0.06, 0.14] (+16%)	+0.02 [-0.03, 0.08] (+3%)	+0.08 [0.01, 0.14]
Metabolic cost of walking, mL O ₂ /kg/m (lower is better)	-0.10 [-0.17, -0.03] (-25%)	-0.01 [-0.10, 0.09] (-4%)	-0.09 [-0.21, 0.03]

Method: Participants with chronic stroke were randomized 2:1 to treadmill HIT or MAT (25 min, 3x/wk, 4 weeks). A blinded rater assessed outcomes. outcome changes were significantly better than MAT even with this small sample size (Table 1).

Further, our outcomes after 4 weeks of HIT were similar to those previously reported after 6 months of MAT.⁶⁰ However, only 28% of walking speed improvements on the treadmill translated into floor (overground) walking improvements, suggesting that outcomes could be further improved with the addition of task-specific overground training. Therefore, we added over-ground HIT to our treadmill HIT protocol and performed a single-group pre-posttest study (n=4) of this revised locomotor HIT protocol (45 minutes, 3x/week for 4 weeks). Outcomes showed better translation to floor walking with dramatic, clinically meaningful improvements, including: fastest walking speed, +0.43 m/s [95% CI: 0.10, 0.76] (+43%); comfortable walking speed, +0.19 m/s [0.00, 0.38] (+24%); walking capacity (6-min walk test), +115 m [11, 219] (+41%). While the limited sample

sizes justify further study, these data support the potential for locomotor HIT to elicit greater increases in walking function and aerobic fitness than the current best-practice model (MAT), with less training time.

D. INVESTIGATOR EXPERIENCE

Pierce Boyne PT, DPT, NCS, Principal Investigator, is an Assistant Professor in the Department of Rehabilitation Sciences at the University of Cincinnati (UC) and Co-Director of the UC Neurorecovery Laboratory. He is a licensed physical therapist and a board-certified neurologic clinical specialist (American Board of Physical Therapy Specialties). He has a BS in Health Sciences with a concentration in exercise physiology and a Doctorate in Physical Therapy with a concentration in clinical research. He has also completed post-doctoral training in epidemiology and clinical/translational stroke recovery research at UC, Cincinnati Children's Hospital Medical Center and the UC Health Daniel Drake Center for Post-Acute Care, including the KL2 Research Scholar's program in the Cincinnati Center for Clinical and Translational Science and Training, funded by the NIH. In total, he has been involved with stroke recovery and rehabilitation research for 10 years, serving a variety of roles on numerous studies, including being the primary outcome testing therapist at the lead site in a national multi-site trial of post-stroke gait rehabilitation. Most relevant to this proposal, Dr. Boyne has also been the project manager and primary in-field investigator for all preliminary studies leading to this application and has led multiple previous successful collaborations with each of the external site PIs (Dr. Billinger and Dr. Reisman).

Sandra A Billinger, PT, PhD, University of Kansas Medical Center (KUMC) Site Principal Investigator, is an Associate Professor in the Department of Physical Therapy and Rehabilitation Science, University of Kansas Medical Center (KUMC). Dr. Billinger is a licensed physical therapist and holds additional certifications from the American College of Sports Medicine (Certified Exercise Specialist) and the American Physical Therapy Association (Certified Exercise Expert for the Aging Adult). Dr. Billinger started her career in cardiac rehabilitation over 15 years ago, completed a research intensive joint PT/PhD program at KUMC in 2008 and received formal clinical research training related to exercise and vascular health in stroke through a career development award (K01HD067318; 2011-2016). She has developed several exercise testing protocols for people with chronic conditions such as stroke. Dr. Billinger also has extensive experience leading and collaborating on aerobic exercise studies, especially post-stroke, including studies funded by the American Heart Association, National Institutes of Health and industrial sponsors. Dr. Billinger was also the writing group chair and lead author of the American Heart Association's Scientific Statement on physical activity and exercise for stroke survivors in 2014. In addition, she has previous experience with multi-site clinical trials, including being a site-PI for the Milestone trial, testing a pharmaceutical intervention for post-stroke gait recovery.

Darcy Reisman, PT, PhD, University of Delaware (UD) Site Principal Investigator, is an Associate Professor in the Department of Physical Therapy at the University of Delaware (UD) and is Academic Director of the Neurologic and Older Adult Clinic. With the support of NIH and Foundation funding, she has been studying movement control and recovery following stroke for over a decade. Dr. Reisman has a strong track record investigating the interaction between biomechanics and neurophysiology after stroke (K01HD050582, P20GM103446-12, R01NS055383-05, R01HD078330-01A1) in order to design targeted interventions that impact the primary impairments underlying reduced activity and participation. Dr. Reisman has also lead or been a co-investigator on numerous locomotor rehabilitation studies of chronic stroke survivors (R01NR010786-05, R21HD07142-01A1, 1R01 HD086362-01). Dr. Reisman is currently PI on R01HD078330, investigating processes of locomotor learning after stroke, and PI on R01HD086362, a multi-center clinical trial investigating the independent and combined effects of fast treadmill walking and activity monitor biofeedback among stroke survivors.

Kari Dunning PT, PhD, Co-Investigator, is a tenured Associate Professor in the Department of Rehabilitation Sciences with a secondary appointment in the Division of Epidemiology in the Department of Environmental Health at UC. She has a MS in Neuroscience, a PhD in Epidemiology and has been a physical therapist specializing in the evaluation and treatment of neurological patients for over 25 years. Dr. Dunning is Co-Founder of the UC Neurorecovery Laboratory in which the preliminary studies leading to this grant were performed. She has been conducting stroke rehabilitation research for over a decade and has been responsible for the research design, data collection, data analysis and manuscript writing for numerous studies, including being coordinating PI of a national 11-site stroke rehabilitation trial and site PI on additional

multi-site studies. Dr. Dunning is the recipient of previous research grants from the American Heart Association, the Foundation for Physical Therapy and industrial sponsors.

Daniel Carl PhD, Co-Investigator, is Assistant Professor in the Department of Rehabilitation Sciences at UC. He has a PhD in Exercise Physiology and has been conducting human subject research for over 10 years, including HIT and exercise testing as in the proposed study. Dr. Carl was also a Co-Investigator on the pilot studies leading to this proposal.

Brett Kissela MD, MS, Co-Investigator, is Albert Barnes Voorheis Professor and Chair in the Department of Neurology and Rehabilitation Medicine at UC and Co-Founder of the UC Neurorecovery Laboratory in which the preliminary studies leading to this grant were performed. Dr. Kissela is a vascular neurologist with expertise on stroke trials, stroke recovery, rehabilitation and neuroplasticity. He has been involved with HIT research from conceptualization through the pilot studies that led to this proposal.

Oluwole Awosika MD, Co-Investigator, is Assistant Professor in the Department of Neurology and Rehabilitation Medicine at UC and Co-Director of the UC Neurorecovery Laboratory. He is a board-certified adult neurologist with over eight years' experience with analyzing and correlating clinical radiographs involving stroke patients. He also has a strong background in basic neuroscience, neurophysiology and neuroplasticity research, neurorehabilitation training, and a post-doctoral fellowship in motor learning, neurophysiology, and neuromodulation with Dr. Leonardo Cohen at NINDS.

Myron Gerson MD, Co-Investigator, is Professor Emeritus of Cardiology and Internal Medicine at UC and Director of the Cardiovascular Stress Laboratory at UC Medical Center. Dr. Gerson is a cardiologist with expertise in exercise testing, cardiovascular safety and cardiometabolic health. He was also a Co-Investigator on the pilot studies leading to this proposal.

E. EXPERIMENTAL DESIGN AND METHODS

E.1. Methods and Procedures

Study design

We propose a 3-site, 2-arm randomized controlled trial with blinded outcome assessment, stratified blocked randomization and an active control group (MAT) based on current best practice recommendations (Fig 4). Fifty persons with residual gait impairment >6 months post stroke will be recruited, consented, screened and randomized to either locomotor HIT or locomotor MAT. Treatment sessions will be time-matched between groups at 45 minutes, 3x/week for 12 weeks. Walking function, aerobic fitness and quality of life will be assessed by blinded raters at baseline (**PRE**) and after 4, 8 and 12 weeks of training (**4WK [primary endpoint], 8WK, 12WK**). Outcome measures will include: walking capacity (6-Minute Walk Test, *primary outcome measure*), gait speed (10-Meter Walk Test), aerobic fitness (ventilatory threshold & $VO_{2\text{ peak}}$), metabolic cost of gait, daily walking activity and quality of life (Stroke Impact Scale).

Recruitment

As in previous studies, recruitment will utilize a multimodal approach, including: 1) Continuous outreach to regional therapists and physicians; 2) Outreach to stroke support groups; 3)

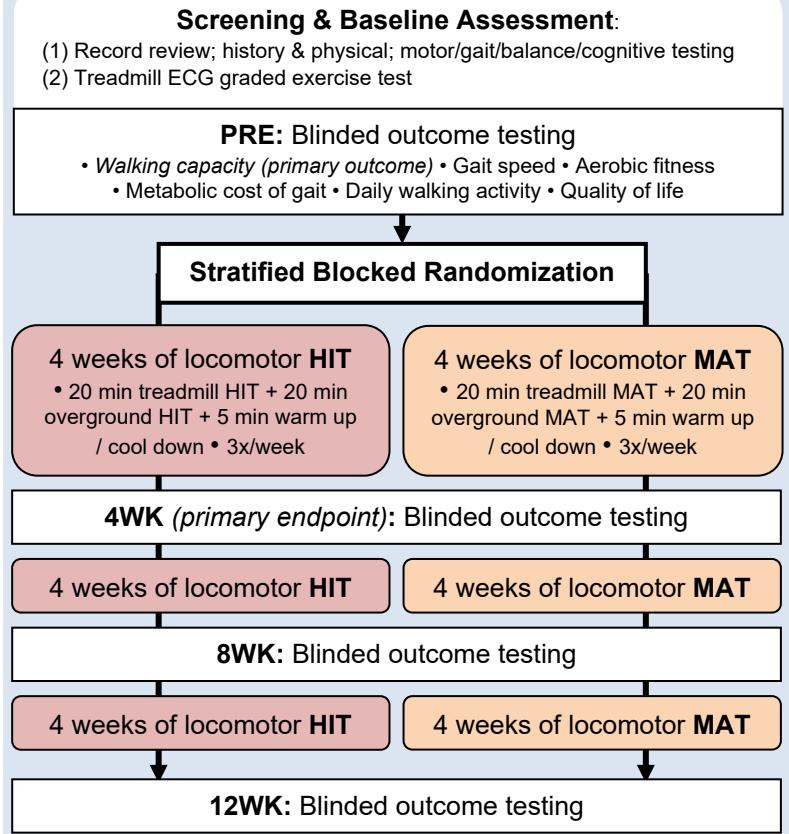
Advertisements in newspapers, magazines, social media, physician offices and therapy clinics; 4) Existing databases of local stroke survivors interested in participating in research; 5) Screening medical records for potentially eligible participants. This initial identification of potential participants via medical records will only be used by study staff at UC or KUMC. UD study staff will not recruit using medical records.

Clinician referrals can be done in two ways: 1) the clinicians may provide the study team contact information to the potential participant; 2) if the potential participant verbally approves, the clinician can give the study team their name and contact information. Screening medical records for potentially eligible participants (by UC or KUMC study staff) will involve searching for cases of stroke and assessing other eligibility criteria in the electronic medical records system and databases of local hospitals and clinics, as in our previous UC IRB approved studies (e.g. 2013-7676, 2016-1916). We are requesting a HIPAA waiver for this purpose, as in our previous studies. For any potential participants who are identified solely by medical record review, we will only initiate a call to the participant if they have had a clinical encounter with one of the study investigators. Otherwise, we will initiate contact by mailing the participant an IRB approved flier (with the envelope addressed to "Current Resident") or by emailing an IRB approved flier to the email address(es) listed in their medical records (with the email address blind carbon copied).

For persons interested in participating, we will further explain the study, confirm initial eligibility and perform informed consent. After a research staff member explains the purpose of study and the consent, potential participants will be given the option to wait at least 24 hours to decide if they want to participate. During this consenting process, the potential participant will be provided a copy of the consent form. Standardized questions will be asked to ensure that the potential participant understands the study before consenting. HIPAA authorization will also be obtained as part of the consent process.

Figure 4. Study design

Informed consent



Spanish-speaking participants may be enrolled in the trial, if a site reports that Spanish-speaking individuals have expressed interest in participating. In this case, an approved Spanish-language version of the site's informed consent document will be used during the informed consent process. The consent process will be conducted as described in the previous paragraph. However, an official medical interpreter will be present during the consent process to interpret from English to Spanish and Spanish to English. A Spanish-speaking team member or medical interpreter will also be available during the study visits.

Eligibility criteria (Table 3) are based on our research experience, previous studies,^{33,50,51,54,69,76,77,81,82,98-101,141} and exercise guidelines^{6,142} and will maximize safety while balancing internal & external validity.¹⁴³

Table 3. Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
<p>1) Age 40-80 years</p> <p>2) Single stroke for which participant sought treatment, experienced 6 months to 5 years prior to study entry</p> <p>3) Walking speed <1.0 m/s on the 10 meter walk test^{21,57}</p> <p>4) Able to walk 10m over ground with assistive devices as needed and no continuous physical assistance from another person (guarding and intermittent assistance for loss of balance allowed)³³</p> <p>5) Able to walk 3 minutes on the treadmill at $\geq 0.13\text{m/s}$ (0.3 mph) (treadmill screening test)^{142,144}</p> <p>6) Stable cardiovascular condition (AHA class B,¹⁴² allowing for aerobic capacity <6 METs)</p> <p>7) Able to communicate with investigators, follow a 2-step command and correctly answer consent comprehension questions</p>	<p>1) Exercise testing uninterpretable for ischemia or arrhythmia (e.g. resting ECG abnormality that makes an exercise ECG uninterpretable for ischemia,¹⁴² and no other recent (within the past year) clinical testing to rule out these conditions).</p> <p>2) Evidence of significant arrhythmia or myocardial ischemia on treadmill ECG graded exercise test¹⁴² in the absence of recent (within the past year) more definitive clinical testing (e.g. stress nuclear imaging) with a negative result.</p> <p>3) Hospitalization for cardiac or pulmonary disease within past 3 months</p> <p>4) Implanted pacemaker or defibrillator</p> <p>5) Significant ataxia or neglect (score of 2 on NIH stroke scale item 7 or 11)¹⁴⁵</p> <p>6) Severe lower limb spasticity (Ashworth >2)¹⁴⁶</p> <p>7) Recent history (<3 months) of illicit drug or alcohol abuse or significant mental illness</p> <p>8) Major post-stroke depression (Patient Health Questionnaire [PHQ-9] ≥ 10)¹⁴⁷ in the absence of depression management by a health care provider</p> <p>9) Currently participating in physical therapy or another interventional study</p> <p>10) Recent botulinum toxin injection to the paretic lower limb (<3 months) or planning to have botulinum toxin injections</p> <p>11) Foot drop or lower limb joint instability without adequate stabilizing device, as assessed by a study staff physical therapist</p> <p>12) Clinically significant neurologic disorder other than stroke or unable to walk outside the home prior to stroke</p> <p>13) Other significant medical condition likely to limit improvement or jeopardize safety, (e.g. joint contracture, gait limited by pain), as assessed by a study staff physical therapist</p> <p>14) Pregnancy</p> <p>15) Previous exposure to fast treadmill walking (>3 cumulative hours) during clinical or research therapy in the past year</p>

Screening and Baseline Assessment

After informed consent, participants will undergo screening and baseline assessment to confirm eligibility and to obtain baseline characteristics and potential cofactors. This testing may include: a medical record review (possibly including clinical radiography¹⁵⁹), a history & physical assessment (including pre-stroke functional status, stroke severity,¹⁴⁵ motor impairment,^{155,156} gait^{57,144} and balance^{154,157,158} testing), cognitive testing,¹⁵⁴ depression screening,¹⁴⁷ a treadmill screening test¹⁴⁴ and a stroke-specific treadmill ECG graded exercise stress test.¹⁴⁸ Female participants will also be asked about the possibility of pregnancy and will agree (as part of the informed consent process) to notify research staff if they have any reason to think they might be pregnant during the study. In this case, study activities would continue only after a urine pregnancy test is done and found to be negative.

Stress testing will be performed according to published guidelines^{127,137-139} by trained, experienced exercise testing laboratory staff at each of the sites. Assistance will be provided as needed from a licensed physical therapist or physical therapist assistant on the study team. Participants will wear a harness secured to an overhead support system for safety in case of loss of balance. ECG and vitals will be monitored. Participants will perform a maximal effort, graded treadmill exercise test to volitional fatigue. Treadmill speed will begin below the participant's fastest safe speed from the treadmill screening test. Increases in speed and/or grade will be used to gradually increase the workload until peak exercise capacity is reached. Test termination criteria will include participant request to stop at volitional fatigue, severe gait instability, or according to published guidelines.^{127,137-139}

Participants will be verbally notified about the results of their stress test. If they are disqualified from further participation in the study based on the results, they will also be given the option to have the results sent to their physician.

Blinded Outcome Testing

Outcome testing will be administered by licensed physical therapists or physical therapist assistants who are blinded to group randomization. Testing will occur before intervention (PRE) and after approximately 4, 8 and 12 weeks of training (4WK [*primary endpoint*], 8WK, 12WK). Each testing session will last approximately 2 hours and may include the following measures:

- Walking capacity testing (*6-minute walk test, primary outcome measure*) involves walking back and forth around two cones, using assistive devices, orthotics, guarding and rest breaks as needed.¹⁴⁸ The distance that the participant is able to walk in six minutes is recorded.
- Walking speed testing (*10-meter walk test*) will be performed with a stopwatch and/or a commercially available electronic walkway.^{146,147} Participants will walk down a hallway and/or electronic walkway, using assistive devices, orthotics and guarding as needed. Each test may be performed twice at comfortable speed and twice as fast as possible.
- Aerobic capacity testing involves respiratory gas measurement (VO₂ and VCO₂) by having the participant breathe through a facemask during an exercise test. This testing will use the same exercise protocol as the stress test above and may be performed simultaneously with the stress test. Peak aerobic capacity is defined as the highest VO₂ measurement achieved during the test. After finishing this test and a rest period, participants may complete a verification phase to help determine whether maximum physiologic capacity (a true VO₂-max) was reached.¹⁵¹ During this verification phase, the participant would be asked to walk as fast as possible for approximately 3 minutes. The treadmill screening test may be repeated at each testing time point to inform speed selection for aerobic capacity testing.
- The metabolic cost of gait is measured by the oxygen consumption rate (VO₂) during gait, with adjustment for walking speed and resting VO₂.⁷⁹ The metabolic cost of gait will be assessed with treadmill walking at approximately the average speed recorded during the 6-minute walk test.
- Daily walking activity assessment involves wearing an activity monitor continuously during waking hours for ≥ 3 days and possibly recording sleep/wake times.¹⁵²⁻¹⁵⁵ The monitor will be worn on the non-paretic leg.
- The Stroke and Aphasia Quality of Life Scale,^{157,158} Stroke Impact Scale,¹³⁸ EQ-5D and Patient Health Questionnaire¹⁴⁷ are reliable and valid self-report quantitative surveys that include questions about quality of life. One or more of these questionnaires will be used.
- The Global Rating of Change (GROC)¹⁵⁹ is a questionnaire that assesses overall impressions of change in health status from the perspective of the participant. The GROC is a 15 point ordinal scale with -7 indicating "a very great deal worse," 0 indicating "no change," and +7 indicating "a very great deal better". The GROC is not applicable at baseline testing because it measures change only.

Heart rate data may also be recorded during the above testing. If there are any issues with data capture (e.g. equipment malfunction), it is possible that participants could be asked to repeat individual tests as long as it would still be possible to obtain quality data without increasing risk to the participant.

Randomization

Participants will be enrolled after PRE testing and randomized to either HIT or MAT. Randomization will be stratified by site and by baseline walking speed (<0.4 , ≥ 0.4 m/s), to help ensure that groups are balanced within sites and on this critical prognostic factor.^{149,150} Within each stratum, we will randomize in *block sizes of 2 or 4*. Block size will be *randomly permuted* to prevent personnel from being able to predict the last randomization within a block.

Training Intervention Protocols

Common features between protocols. Participants in both groups will be asked to perform 36 training sessions over approximately 12 weeks, with repeated outcome testing after each [12 session / 4 week] block. Target training frequency will be 3 sessions per week. Both groups will train for approximately 45 minutes per session, v.5, 16Mar2021

using orthotic & assistive devices and handrail balance support on the treadmill as needed.¹⁴⁴ Each session will include a 3 minute warm up, 10 min overground training with guarding from a physical therapist, 20 min treadmill training wearing a harness for fall protection, another 10 min overground training and a 2 min cool down. Target heart rates (HRs) will be based on the peak HR from exercise testing, to account for β -blocker medications.¹⁴⁴

Locomotor high-intensity interval training (HIT). This protocol was developed and refined in our preliminary studies. It involves repeated bursts of walking at speeds up to the participant's fastest safe speed, alternated with recovery periods of slower walking or rest. During overground HIT, burst speed is increased using visual feedback about the distance covered during each burst and encouragement to increase distance. During treadmill HIT, speed is systematically progressed throughout each session based on participant performance criteria and heart rate response.^{9,81,82} Target average HR for each session is approximately 85% HR_{peak} (~70% HR reserve [HRR]).

Locomotor moderate-intensity aerobic training (MAT). Similar to our pilot randomized controlled trial,⁹ this protocol will follow the widely reported training regimen of Macko et al,^{33,46,50,51,60-62,144,215,216} used as the basis for current post-stroke exercise guidelines.^{6,8} The only adjustment for this study will be the addition of overground MAT¹⁰⁹ to match the training modes and duration of locomotor HIT. During both treadmill and overground MAT, speed will be continuously adjusted to maintain an initial target HR of 40 \pm 5% heart rate reserve (HRR), progressing by 5% HRR every 2 weeks up to 60% HRR, as tolerated.¹⁴⁴

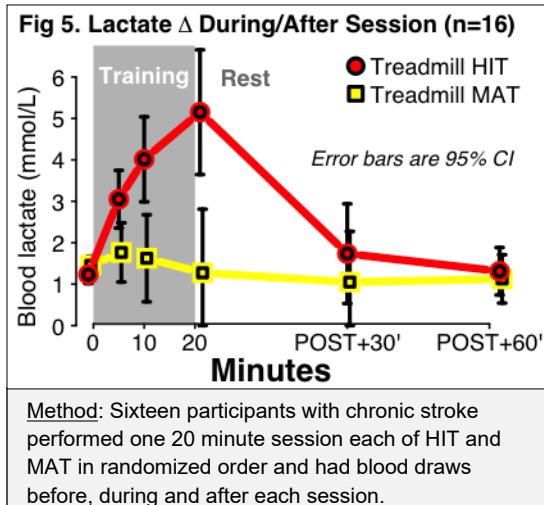
Intervention fidelity measures

Integrity of the training protocol may be assessed by the following measures:

- Adherence will be measured by the number of training sessions attended
- Aerobic intensity will be measured by training heart rates. Heart rate data may be collected by a heart rate transmitter worn around the chest (e.g. Polar H7), an ECG, a pulse oximeter and/or manual palpation. Heart rate data may be processed using an iPod (or similar) application (e.g. FitDigits iCardio).
- Anaerobic intensity may be measured by *blood lactate concentration* after the treadmill training portion of one or more sessions, using a finger stick and a point-of-care blood lactate analyzer. Blood lactate accumulation is a key feature of vigorous training intensity that provides a mechanistic basis for expected benefits over moderate intensity. Our preliminary data confirmed that among persons with chronic stroke, the anaerobic threshold still occurs almost exactly at the 60% HR reserve transition point between moderate and vigorous intensity.¹³⁶ Further, we demonstrated that our treadmill HIT protocol elicits a consistent and robust lactate response in this population, which is significantly greater than the null effect elicited by MAT ($p<0.001$; Fig 5). In animal and healthy adult studies, increased blood lactate has been shown to drive skeletal muscle mitochondrial adaptations that increase aerobic capacity,¹⁶⁶ to upregulate neurotrophins that facilitate brain plasticity¹⁶⁷ and to predict greater motor learning when paired with skill practice.¹⁶⁸
- Neuromotor intensity may be measured by *treadmill and over ground training speeds* each session.
- Repetition of practice may be measured by *step counts* during each session, using an activity monitor on the non-paretic leg.^{27,34,35,169,170}

Concurrent outside interventions

To test for other between-group differences during the intervention period that could explain differences in outcomes, we may also assess the following measures:



- Concurrent walking practice may be measured by *step counts outside of training sessions*. Participants would be asked to take an activity monitor home to wear during waking hours throughout study participation.¹⁷¹
- Concurrent therapy may be measured by *any changes in medications* and the *number of sessions of outside therapy (e.g. speech & occupational therapy)*.¹⁵⁶

E.2. Data Analysis and Data Monitoring

General approach

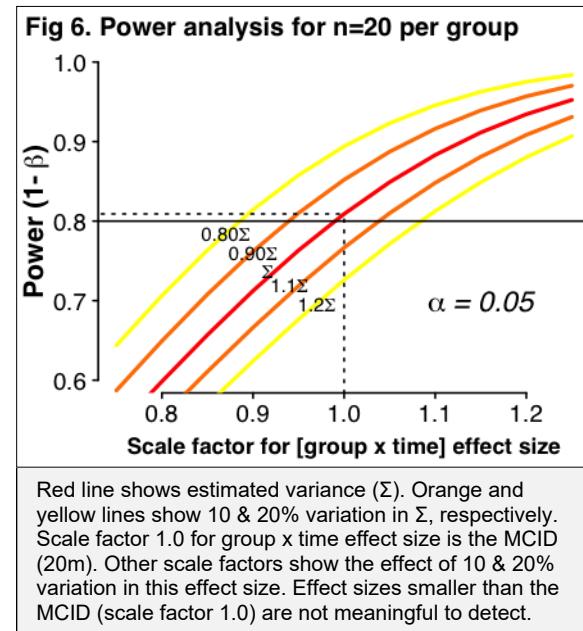
The REDCap® web-based system²¹⁷ will be used for data entry and data monitoring. All baseline variables and data on intervention fidelity and concurrent outside interventions will be compared between groups with t-tests and X². The primary analysis will follow *intent-to-treat* methods and any missing data will be handled with the method of maximum likelihood, assuming that patterns of missingness do not violate the missing at random assumption.²¹⁸

The primary general linear model for both Aims will include fixed effects for intercept, group (HIT, MAT), time (PRE, 4WK, 8WK, 12WK), [group X time], site (UC, KUMC, UD), [site x time], baseline gait speed category (<0.4, ≥0.4 m/s) and [baseline gait speed category x time] (to account for the stratification factors)^{218,222} with an *unstructured covariance matrix* (to account for the repeated nature of the data without making assumptions about covariance patterns).²¹⁸ Time will be modeled as a categorical factor (i.e. analysis of response profiles²¹⁸), since there is no available information about the expected pattern in the HIT mean response over time.

Sample Size

This study is powered to detect the minimal clinically important difference (MCID) of 20 meters in walking capacity (6-minute walk test) change²²⁰ between groups.

GLIMMPS²²¹ was used to estimate the sample size needed to detect a significant [group x time] effect at each time point, using the model above with a two-sided α of 0.05. The 6-minute walk test change estimate for the MAT group (+15 m / 4 wks) was taken from our 4-week pilot study⁹ and resulted in a 12WK change estimate (+45 m) somewhat larger than previously observed (+25 m).⁶⁰ In contrast, the HIT group estimate (MAT group change plus MCID = +35 m / 4 wks) was notably lower than observed in our most recent 4-week pilot study (+115 m in 4 wks), indicating that the true effect size may be much larger and easier to detect than the MCID. Variance & covariance parameters for each time point were estimated by pooling data across our two previous 4-week studies (n=20), using the mean variance for each time point and the highest suggested exponential decay rate (0.5)²²¹ for the repeated measures correlations involving 8WK and 12WK. These calculations indicated a target sample size of 40 (20/group) for ≥80% power (Fig 6). *To conservatively account for attrition, we plan to enroll at least 50 and up to 75 participants.*



Hypothesis Testing

Aim 1: Determine the optimal locomotor training *intensity* for eliciting immediate improvements in walking capacity among chronic stroke survivors

Hypothesis 1a (H_{1a}): Compared with MAT, HIT will elicit significantly greater improvement in walking capacity (6-minute walk distance) from PRE to 4WK (*primary study hypothesis*)

Hypothesis 1b (H_{1b}): Compared with MAT, HIT will elicit significantly greater improvement in secondary outcomes from PRE to 4WK

H_{1a} will be tested by the significance of the [group x time] contrast from Baseline to POST-4wk for the 6-minute walk test at $\alpha=0.05$. For H_{1b}, secondary outcomes will be tested separately using the same model as H_{1a} to identify the most sensitive measures to carry forward into future studies.¹¹⁰ The Benjamini-Hochberg procedure²²³ will be used to control the false discovery rate (FDR) for the secondary outcomes.

Aim 2: Determine the minimum locomotor training duration needed to maximize immediate effects

Hypothesis 2a (H_{2a}): Within the HIT group, *walking capacity* (6 minute walk test distance) and *secondary outcomes* will significantly increase from 4WK to 8WK and from 8WK to 12WK

Hypothesis 2b (H_{2b}): Compared to MAT, HIT will elicit significantly greater improvements in *walking capacity* and *secondary outcomes* from PRE to 8WK and from PRE to 12WK

H_{2a} will be tested by the significance of the respective time contrasts within the HIT group. **H_{2b}** will be tested by the significance of the respective [group x time] contrasts. Secondary outcomes will have FDR control.²²³

Data and Safety Monitoring Plan

An adverse event (AE) is an undesired medical occurrence in a participant who is undergoing study procedures and does not necessarily have a causal relationship with the treatment or study procedures. This includes any adverse clinical change that occurs at any time following consent. A serious AE (SAE) is any adverse experience occurring during study participation that results in any of the following outcomes: death; a life threatening situation; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability/incapacity.^{209,210} The data and safety monitoring plan for this study will include participant monitoring for AEs and other problems, review of AEs and other problems by the study team and IRB, and an independent data safety monitoring board (DSMB).

Participant safety monitoring

Based on safety data from our preliminary studies^{9,12} and the extensive previous HIT research among persons with heart disease,^{65,72,76,77,98-101} and MAT research among persons post-stroke,³³ we expect a similar rate of non-serious adverse events (AEs) between HIT and MAT (e.g. temporary exercise-related soreness and fatigue), without any study-related serious AEs. As in our previous studies, we will systematically monitor for AEs. Each study visit, participant voluntary reporting of AEs will be encouraged and AEs of interest will be specifically queried, including: falls, injuries, faintness, pain and fatigue. During training, safety monitoring will include HR, blood pressure, and continuous observation for other signs or symptoms of cardiorespiratory insufficiency, worsening neurologic impairments or orthopedic injury, using accepted stopping criteria.^{142,208} AEs will be followed until resolution and categorized according to type and severity (grade 1-5),^{209,210} causal relationship with the intervention (yes/possibly/no) and whether anticipated (listed in the protocol / informed consent form or expected in the target population).

Reporting and review of AEs and other problems involving risk

All observed or volunteered AEs and other problems involving risk to research participants or others that occur throughout the study will be recorded and reported to the IRB according to UC IRB protocol, as well as reported to the DSMB (see further information about the DSMB below).. As such, all *unanticipated* AEs and other problems involving risk will be reported to the IRB and DSMB within 10 days of study staff knowledge of the event. AEs or other problems resulting in temporary or permanent interruption of the study activities by the PI to avoid potential harm to participants will be reported to the IRB and DSMB immediately (within 48 hours). Other AEs or study problems will be reported to the IRB at the time of continuing review and to the DSMB at least annually. AEs will be discussed between site PIs during regular conference calls. Withdrawal from the study and modifications to study procedures as a result of an AE or because of therapeutic measures taken to treat an AE will be at the discretion of the site PIs, in consultation with the study physicians as appropriate.

Data safety monitoring board (DSMB)

The DSMB will consist of at least 3 members separate from the study team, including at least one physician and at least one biostatistician, with collective experience in the management of patients with stroke, exercise and clinical trials. A quorum will require at least 2 members, including the chair. Persons with a significant conflict of interest (financial, institutional or scientific) will not be permitted to be DSMB members. The DSMB will meet at least (approximately) annually. A summary report will be sent to the DSMB prior to each meeting, including safety and clinical outcome data. DSMB meetings will include open sessions where the DSMB may discuss any issues with the study team and closed sessions where the DSMB alone decides on its recommendations. The DSMB will assess the risks and benefits of study participation for all participants and will provide a written report of their analyses and recommendation as to whether the study should continue, whether modifications to the study are needed or if the study should be terminated. These reports will be sent to the investigators and the IRB.

Safety Data Analysis

In the unexpected event of one or more SAEs, the SAE rate will be compared between groups to confirm that there is no significant difference in major safety risk between HIT and MAT. This analysis will use a logistic regression model with SAE (yes/no) as the dependent variable and fixed effects for group, site and baseline gait speed category. If there are SAE(s) in one group only, a continuity correction (0.5 SAEs added to each group) will still allow the odds ratio to be calculated.⁹ Secondary safety outcomes (different grades/categories of AEs) will be tested using the same model, with [# AEs / # training sessions] as the dependent variable.⁹

E.3. Data Storage and Confidentiality

Risk of any breach to participant privacy or confidentiality will be minimized by: 1) maintaining all physical participant files in locked filing cabinets; 2) minimizing use of participant identifiers on data collection forms, electronic files and the secure REDCap web-database; 3) not storing any participant identifiers on peripheral devices used for data processing (e.g. electronic walkway for gait testing, iPod application used for heart rate data); 4) only allowing de-identified data exports from REDCap and ensuring that the final dataset does not include any identifiers or other variables that could lead to deductive disclosure of individual participant identities before submitting it to a public research data archive (e.g. NIH/NICHD data and specimen hub [DASH]); 5) uploading files that need centralized review (e.g. clinical brain imaging data and metabolic cart data files from exercise testing) to a secure server designed for research data (REDCap or a UC research data server); 6) only allowing study personnel and laboratory staff (e.g. Cardiac Stress Laboratory) to access the data and giving only as much access as necessary to perform study roles and ensure participant safety; and 7) destroying the link between participant identifiers and participant ID number after the final data analysis is completed.

E.4. Setting

Most study activities will be performed in rehabilitation/exercise research laboratories at each site. Stress testing will be conducted in either clinical or appropriately equipped research exercise testing laboratories.

E.5. Laboratory Methods and Facilities

None

E.6. Estimated Period of Time to Complete the Study

We estimate that each participant will be involved in the study for approximately 5 months and that the overall study will take approximately 5 years to complete.

F. HUMAN SUBJECTS

F.1. Sample Size

Approximately 17 participants (up to 30) will be enrolled in this study at each site (UC, UD, KUMC). Approximately 50 total participants (up to 75) will be enrolled in the study.

F.2. Eligibility Criteria

Table 3. Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none">1) Age 40-80 years2) Single stroke for which participant sought treatment experienced 6 months to 5 years prior to study entry3) Walking speed <1.0 m/s on the 10 meter walk test^{21,57}4) Able to walk 10m over ground with assistive devices as needed and no continuous physical assistance from another person (guarding and intermittent assistance for loss of balance allowed)³³5) Able to walk 3 minutes on the treadmill at ≥ 0.13m/s (0.3 mph) (treadmill screening test)^{142,144}6) Stable cardiovascular condition (AHA class B,¹⁴² allowing for aerobic capacity <6 METs)7) Able to communicate with investigators, follow a 2-step command and correctly answer consent comprehension questions	<ul style="list-style-type: none">1) Exercise testing uninterpretable for ischemia or arrhythmia (e.g. resting ECG abnormality that makes an exercise ECG uninterpretable for ischemia or arrhythmia,¹⁴² and no other recent (within the past year) clinical testing available to rule out these conditions)2) Evidence of significant arrhythmia or myocardial ischemia on treadmill ECG graded exercise test¹⁴² in the absence of recent (within the past year) more definitive clinical testing (e.g. stress nuclear imaging) with a negative result.3) Hospitalization for cardiac or pulmonary disease within past 3 months4) Implanted pacemaker or defibrillator5) Significant ataxia or neglect (score of 2 on NIH stroke scale item 7 or 11)¹⁴⁵6) Severe lower limb spasticity (Ashworth >2)¹⁴⁶7) Recent history (<3 months) of illicit drug or alcohol abuse or significant mental illness8) Major post-stroke depression (Patient Health Questionnaire [PHQ-9] ≥ 10)¹⁴⁷ in the absence of depression management by a health care provider9) Currently participating in physical therapy or another interventional study10) Recent botulinum toxin injection to the paretic lower limb (<3 months) or planning to have botulinum toxin injections11) Foot drop or lower limb joint instability without adequate stabilizing device, as assessed by a study staff physical therapist12) Clinically significant neurologic disorder other than stroke or unable to walk outside the home prior to stroke13) Other significant medical condition that would limit improvement or jeopardize safety (e.g. joint contracture, gait limited by pain), as assessed by a study staff physical therapist14) Pregnancy15) Previous exposure to fast treadmill walking (>3 cumulative hours) during clinical or research therapy in the past year

F.3. Gender, Age Range, Racial/Ethnic Distribution and Vulnerability

The target age range is 40-80 years old. This age range is consistent with the majority of the post-stroke population and will provide sufficient homogeneity to maximize study internal validity. We will not recruit based on gender, race or ethnicity, nor will we exclude anyone on these bases. Based on our previous clinical and research experience and stroke incidence rates, we expect approximately 50% of participants to be Caucasian, approximately 30% to be African American and approximately 45% to be female.²²⁵⁻²²⁷ No vulnerable populations will be included in this study. Because some stroke survivors may be considered vulnerable due to cognitive impairments, we will ask a series of comprehension questions after reviewing the informed consent form that participants must answer correctly to be enrolled, as in our previous studies.

F.4. Recruitment Sources and Plans

As in previous studies, recruitment will utilize a multimodal approach, including: 1) Continuous outreach to regional therapists and physicians; 2) Outreach to stroke support groups; 3) Advertisements in newspapers, magazines, social media, physician offices and therapy clinics; 4) Existing databases of local stroke survivors interested in participating in research; 5) Screening medical records for potentially eligible participants. This initial identification of potential participants via medical records will only be used by UC or KUMC study staff. UD study staff will not recruit using medical records.

Clinician referrals can be done in two ways: 1) the clinicians may provide the study team contact information to the potential participant; 2) if the potential participant verbally approves, the clinician can give the study team their name and contact information. Screening medical records for potentially eligible participants (by UC or KUMC study staff) will involve searching for cases of stroke and assessing other eligibility criteria in the

electronic medical records system and databases of local hospitals and clinics, as in our previous UC IRB approved studies (e.g. 2013-7676, 2016-1916). We are requesting a HIPAA waiver for this purpose, as in our previous studies. For any potential participants who are identified solely by medical record review, we will only initiate a call to the participant if they have had a clinical encounter with one of the study investigators. Otherwise, we will initiate contact by mailing the participant an IRB approved flier (with the envelope addressed to "Current Resident") or by emailing an IRB approved flier to the email address(es) listed in their medical records (with the email address blind carbon copied).

For persons interested in participating, we will further explain the study, confirm initial eligibility and perform informed consent. After a research staff member explains the purpose of study and the consent, potential participants will be given the option to wait at least 24 hours to decide if they want to participate. During this consenting process, the potential participant will be provided a copy of the consent form. Standardized questions will be asked to ensure that the potential participant understands the study before consenting. HIPAA authorization will also be obtained as part of the consent process. Incorporated into the consent document is the option to agree to or refuse to participate in video recording or photographs of research activities that may be used for educational or training purposes apart from the collection of research data.

G. RISK/BENEFIT ASSESSMENT

G.1. Potential Risks

As with any exercise, there is risk of discomfort, soreness and fatigue associated with participation as well as a very low risk of musculoskeletal injury, skin abrasion and cardiovascular events.¹⁴² There is also very low potential risk of falling during clinical outcome testing and training. There may also be a risk of faintness, especially if the participant is dehydrated or does not eat on the day of exercise. Finger stick blood sampling for lactate measurement may cause a small amount of pain. Mild bruising or scarring is possible, but atypical. The risk of local infection is very low.

These risks will be minimized by: 1) recruiting a study sample with stable cardiovascular condition and normal cardiovascular responses to an exercise test (among other criteria);⁶ 2) using a screening and exercise testing protocol with a strong safety track record across >500 recorded exercise tests and well over 15,000 recorded treadmill aerobic exercise sessions among persons with stroke;^{33,144} 3) using HIT protocols that were developed and optimized by our research team in previous studies^{9,12} and in collaboration with a cardiologist. These protocols were also based on previous HIT studies among persons with heart disease that demonstrated no serious adverse events in well over 30,000 recorded exercise hours;¹⁰ 4) securing participants during all treadmill walking using a harness connected to an overhead support system for safety in case of loss of balance; 5) using appropriate guarding during overground walking and balance testing, which will be performed by physical therapists and physical therapist assistants; 6) instructing participants to stay hydrated and to eat within 3 hours prior to arriving for each exercise testing or training session; 7) providing water or a snack if the participant reports insufficient intake; 8) asking participants with insulin-dependent diabetes to take a blood glucose reading prior to exercise using their own testing supplies, providing a snack if blood glucose is low, and postponing study activities if blood glucose remains out of range (generally <95 or >250 mg/dL); and 9) ensuring that personnel performing finger stick blood sampling for lactate testing are trained in antiseptic technique and only collect the minimal needed amount of blood (approximately one drop).

We have completed 4 IRB-approved studies to date involving similar or identical screening, testing and training procedures, involving a total of over 50 participants. These studies have included extensive monitoring for adverse events (AEs), including participant interviews before and after each session and continuous observation of participants and electrocardiograms throughout each session. No serious AEs related to locomotor HIT have occurred. Normal exercise-related soreness and fatigue are the most commonly reported AEs, especially after the initial training sessions. These symptoms do not typically interfere with normal functioning or last longer than a day. In our pilot RCT, AE rates were similar between HIT and MAT (Table 7).⁹

Table 7. Adverse Events (AEs) in Pilot RCT

Data reported as no. of participants with AE (total no. of AEs) [AE incidence rate per 100 sessions]

	HIT (n=13, sessions=141)	MAT (n=5, sessions=60)	HIT/MAT AE odds ratio (95% CI)
Any AE	9 (21) [14.9]	4 (8) [13.3]	1.14 (0.47-2.73)
Related to intervention	6 (13) [9.2]	1 (4) [6.7]	1.42 (0.44-4.55)
-Grade 1 (mild)	5 (10) [7.1]	1 (3) [5.0]	1.45 (0.38-5.47)
-Grade 2 (moderate)	2 (3) [2.1]	1 (1) [1.7]	1.28 (0.13-12.59)
-Grade 3-5 (severe-death)	0 (0) [0.0]	0 (0) [0.0]	N/A
-Cardiac disorder	0 (0) [0.0]	0 (0) [0.0]	N/A
-Joint/muscle pain	5 (8) [5.7]	1 (4) [6.7]	0.84 (0.24-2.91)
-Fatigue	3 (3) [2.1]	0 (0) [0.0]	3.03 (0.15-59.56)*
-Nausea	0 (0) [0.0]	0 (0) [0.0]	N/A
-Lightheadedness	1 (2) [1.4]	0 (0) [0.0]	2.15 (0.10-45.43)*
-Other nervous system	0 (0) [0.0]	0 (0) [0.0]	N/A
-Fall	0 (0) [0.0]	0 (0) [0.0]	N/A
-Other injury	0 (0) [0.0]	0 (0) [0.0]	N/A
Unrelated to intervention	6 (8) [5.7]	3 (4) [6.7]	0.84 (0.24-2.91)
-Grade 1 (mild)	5 (7) [5.0]	2 (2) [3.3]	1.51 (0.31-7.51)
-Grade 2 (moderate)	1 (1) [0.7]	2 (2) [3.3]	0.21 (0.02-2.33)
-Grade 3-5 (severe-death)	0 (0) [0.0]	0 (0) [0.0]	N/A
-Atrial fibrillation	1 (2) [1.4]	0 (0) [0.0]	2.15 (0.10-45.43)*
-Other cardiac disorder	0 (0) [0.0]	0 (0) [0.0]	N/A
-Joint/muscle pain	2 (2) [1.4]	1 (2) [3.3]	0.42 (0.06-3.03)
-Fatigue	1 (1) [0.7]	0 (0) [0.0]	1.28 (0.05-31.86)*
-Nausea	0 (0) [0.0]	0 (0) [0.0]	N/A
-Lightheadedness	1 (1) [0.7]	0 (0) [0.0]	1.28 (0.05-31.86)*
-Other nervous system	0 (0) [0.0]	0 (0) [0.0]	N/A
-Fall	1 (1) [0.7]	2 (2) [3.3]	0.21 (0.02-2.33)
-Other injury	1 (1) [0.7]	0 (0) [0.0]	1.28 (0.05-31.86)*

AE odds ratios are from logistic regression modeling of no. of AEs / no. of sessions per participant. CI, confidence interval. *Continuity corrected by adding 0.5 AEs to each group so that AE odds ratios could be calculated. HIT, high-intensity interval training; MAT, moderate-intensity aerobic training

Emergency Response Planning. Although we expect that the study will be safe, we are also well prepared for any unlikely events. AEs will be promptly reported to the IRB and DSMB (see Data and Safety Monitoring Plan above) and referrals for follow up care will be made according to the severity and type of event. Should an emergency medical situation occur during study activities, emergency medical care would be provided and the participant would be transported to the nearest emergency room.

G.2. Potential Benefits

All eligible participants will receive graded exercise testing, clinical testing and up to 36 locomotor training sessions at no cost. Both training protocols being used in this study have some evidence of efficacy for improving walking speed, walking capacity, the metabolic cost of walking and aerobic capacity. While these benefits are not guaranteed for individual participants, we believe that the potential benefits outweigh the potential risks, especially since these outcomes have been previously associated with increased quality of life in this population. Our qualitative experience also indicates that persons with stroke generally find the risks to be acceptable and the results to be beneficial. In the case of abnormal findings on graded exercise tests, it is also possible that these tests could result in early detection of cardiovascular conditions.

Importance of the Knowledge to be Gained

This study will provide fundamental new knowledge to inform selection of intensity and duration dosing parameters for aerobic training and gait recovery interventions post-stroke. At the same time, this study will provide all remaining needed data to justify and design a subsequent definitive trial to determine the relative efficacy of HIT and MAT for eliciting *clinically meaningful and sustained improvements* in walking function. Therefore, *the proposed study is significant because it is expected to constitute a critical step in a continuum of research that will lead to the clinical implementation of novel training strategies to synergistically and potently address both gait impairment and aerobic deconditioning post-stroke*. This would likely have a major impact on the massive¹¹² disability and financial burden of stroke, because, unlike the currently recommended protocol for addressing these outcomes (MAT),^{33,46,50-52,60-62} HIT appears to provide significant benefits with a training duration that fits well within current clinical practice models.^{66,67,113} By elucidating the relative time course of changes in different outcomes, the data from this study will also inform future mechanistic and biomarker investigations in our team member's areas of expertise, including brain connectivity, neurophysiology, molecular genetics and vascular function. In addition, the de-identified data will be made publicly available after study completion to support further exploration and meta-analysis. We believe that the minimized risks to participants are reasonable based on the potential positive implications of this project.

G.2. Alternatives to Participation

This study will recruit participants with chronic stroke discharged from all forms of therapy. Therefore, the alternative to study participation is not to participate.

H. PAYMENT

Participants will be paid \$75 at each outcome testing visit (PRE, 4WK, 8WK, 12WK; up to \$300 total).

I. SUBJECT COSTS

All study testing and treatment will be provided at no cost. Parking will also be provided at no cost.

J. CONSENT FORM

See separate documents

K. MOCK STUDY PARTICIPANTS FOR PERSONNEL TRAINING

Each site has over 8 years of experience in successfully completing stroke rehabilitation research.^{135,139,140} As in previous studies, personnel will be trained for study roles using lecture, audiovisual supports, demonstration and/or experiential learning with hands-on practice. For demonstration, hands-on practice and creating audiovisual supports, persons with and without stroke will be recruited at each site and asked to play the role of mock study participant to assist with personnel training. These mock participants will be asked to perform one or more of the study activities described in this protocol on one or more visits. Prior to performing these activities, mock participants will also be asked to:

- Provide written informed consent and HIPAA authorization following procedures outlined above, using a separate consent form specifically designed for mock participants
- Provide demographic information for IRB continuing review
- Undergo any study screening procedures described above that are needed for the safety of the activity being performed
 - Prior to any maximal effort exercise testing, mock participants will have the following screening:
 - Medical history
 - Gait observation
 - Treadmill acclimation
 - Prior to any exercise training, mock participants will have the following screening:
 - Medical history
 - Gait observation
 - Treadmill acclimation
 - Exercise stress test with electrocardiographic monitoring. This requirement will be waived if the mock participant:
 - Has had a similar or more definitive test (e.g. pharmacologic stress, nuclear imaging) done within the past 3 years with negative results, OR
 - Is classified as “Low-Risk” for vigorous exercise according to American College of Sports Medicine (ACSM) criteria:¹⁴²
 - Apparently healthy men <45 years old and women <55 years old, with no known cardiovascular, pulmonary or metabolic disease who are asymptomatic and have <2 cardiovascular risk factors
 - Persons with cerebrovascular disease are not considered low-risk
 - Cardiovascular risk factors include:
 - Smoker, or quit smoking in past 6 months
 - Blood pressure >140/90 or take blood pressure medication
 - Blood cholesterol >200 mg/dL or LDL >130 mg/dL
 - Pre-diabetes or fasting blood glucose \geq 100 mg/dL
 - Family history of heart attack or heart surgery before age 55 (father or brother) or age 65 (mother or sister)
 - Body mass index >30
 - Physically inactive (<30 minutes moderate-intensity exercise, 3d/wk)

Other areas where the protocol differs for mock participants are described below.

Sample Size

Up to 10 mock participants will be enrolled in this study at each site (up to 30 total).

Eligibility Criteria

Mock participants will be screened with the same eligibility criteria as actual study participants, with the following exceptions: 1) mock participants may or may not have had a stroke; 2) mock participant age range will be 18-80 years; and 3) some eligibility criteria may not be assessed if they are not relevant to the safety of the activity to be performed.

Data Storage and Confidentiality

Mock participant data and confidentiality will be maintained using the same procedures used for actual study participants, except that mock participant data will be kept separate from actual study data (e.g. separate REDCap database for personnel training) and will not be used for any purpose other than personnel training and education.

Setting

Setting will be the same for mock and actual participants, except that exercise testing for mock participants at UC and KUMC may be done in a rehabilitation research laboratory rather than a cardiac stress laboratory if the mock participant meets the ACSM Low-Risk criteria or has had a negative cardiac stress test within the past 3 years.

Estimated Period of Time to Complete the Study

Mock participants will be involved in the study for just one visit or up to 5 months. If the same mock participant is willing to participate again after 5 months have passed, we would redo the consent process at that time.

Payment

Mock participants will not be paid for participation.

K. LITERATURE CITED

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB; American Heart Association Statistics Committee; Stroke Statistics Subcommittee. Heart disease and stroke statistics-2016 update: A report from the American Heart Association. *Circulation*. 2016;133(4):e38-e360.
2. Mayo NE, Wood-Dauphinee S, Cote R, Durcan L, Carlton J. Activity, participation, and quality of life 6 months poststroke. *Arch Phys Med Rehabil*. 2002;83(8):1035-1042.
3. Jorgensen HS, Nakayama H, Raaschou HO, Vive-Larsen J, Stoier M, Olsen TS. Outcome and time course of recovery in stroke. Part II: Time course of recovery. The Copenhagen Stroke Study. *Arch Phys Med Rehabil*. 1995;76(5):406-412.
4. Ada L, Dean CM, Lindley R, Lloyd G. Improving community ambulation after stroke: The AMBULATE trial. *BMC Neurol*. 2009;9:8-2377-9-8.
5. Hill K, Ellis P, Bernhardt J, Maggs P, Hull S. Balance and mobility outcomes for stroke patients: A comprehensive review. *Aust J Physiother*. 1997;43:173-80.
6. Billinger SA, Arena R, Bernhardt J, Eng JJ, Franklin BA, Johnson CM, MacKay-Lyons M, Macko RF, Mead GE, Roth EJ, Shaughnessy M, Tang A; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Lifestyle and Cardiometabolic Health; Council on Epidemiology and Prevention; Council on Clinical Cardiology. Physical activity and exercise recommendations for stroke survivors: A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(8):2532-53.
7. Billinger SA, Boyne P, Coughenour E, Dunning K, Mattlage A. Does aerobic exercise and the FITT principle fit into stroke recovery? *Curr Neurol Neurosci Rep*. 2015;15(2):519-014-0519-8.
8. Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, Deruyter F, Eng JJ, Fisher B, Harvey RL, Lang CE, MacKay-Lyons M, Ottenbacher KJ, Pugh S, Reeves MJ, Richards LG, Stiers W, Zorowitz RD; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research. Guidelines for adult stroke rehabilitation and recovery: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2016;47(6):e98-e169.
9. Boyne P, Dunning K, Carl D, Gerson M, Khoury J, Rockwell B, Keeton G, Westover J, Williams A, McCarthy M, Kissela B. High-intensity interval training and moderate-intensity continuous training in ambulatory chronic stroke: A feasibility study. *Phys Ther*. 2016;96(10):1533-1544.
10. Boyne P, Dunning K, Carl D, Gerson M, Khoury J, Kissela B. High-intensity interval training in stroke rehabilitation. *Top Stroke Rehabil*. 2013;20(4):317-330.
11. Boyne P, Billinger S, MacKay-Lyons M, Barney B, Khoury J, Dunning K. Aerobic exercise prescription in stroke rehabilitation: A web-based survey of United States physical therapists. *J Neurol Phys Ther*. in press.
12. Boyne P, Dunning K, Carl D, Gerson M, Khoury J, Kissela B. Within-session responses to high-intensity interval training in chronic stroke. *Med Sci Sports Exerc*. 2015;47(3):476-84.
13. Dupont G, Blondel N, Lensed G, Berthoin S. Critical velocity and time spent at a high level of VO₂ for short intermittent runs at supramaximal velocities. *Can J Appl Physiol*. 2002;27(2):103-115.
14. Guiraud T, Nigam A, Juneau M, Meyer P, Gayda M, Bosquet L. Acute responses to high-intensity intermittent exercise in CHD patients. *Med Sci Sports Exerc*. 2011;43(2):211-217.
15. Reisman D, Kesar T, Perumal R, Roos M, Rudolph K, Higginson J, Helm E, Binder-Macleod S. Time course of functional and biomechanical improvements during a gait training intervention in persons with chronic stroke. *J Neurol Phys Ther*. 2013;37(4):159-165.

16. Broderick JP, William M. Feinberg lecture: Stroke therapy in the year 2025: Burden, breakthroughs, and barriers to progress. *Stroke*. 2004;35(1):205-211.

17. Dean CM, Richards CL, Malouin F. Walking speed over 10 metres overestimates locomotor capacity after stroke. *Clin Rehabil*. 2001;15(4):415-421.

18. Dean CM, Richards CL, Malouin F. Task-related circuit training improves performance of locomotor tasks in chronic stroke: A randomized, controlled pilot trial. *Arch Phys Med Rehabil*. 2000;81(4):409-417.

19. Ada L, Dean CM, Hall JM, Bampton J, Crompton S. A treadmill and overground walking program improves walking in persons residing in the community after stroke: A placebo-controlled, randomized trial. *Arch Phys Med Rehabil*. 2003;84(10):1486-1491.

20. Mayo NE, Wood-Dauphinee S, Ahmed S, Gordon C, Higgins J, McEwen S, Salbach N. Disablement following stroke. *Disabil Rehabil*. 1999;21(5-6):258-268.

21. Bohannon RW, Williams Andrews A. Normal walking speed: A descriptive meta-analysis. *Physiotherapy*. 2011;97(3):182-189.

22. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. *Am J Respir Crit Care Med*. 1998;158(5 Pt 1):1384-1387.

23. Lackland DT, Elkind MS, D'Agostino R Sr, Dhamoon MS, Goff DC Jr, Higashida RT, McClure LA, Mitchell PH, Sacco RL, Sila CA, Smith SC Jr, Tanne D, Tirschwell DL, Touzé E, Wechsler LR; American Heart Association Stroke Council; Council on Epidemiology and Prevention; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Quality of Care and Outcomes Research. Inclusion of stroke in cardiovascular risk prediction instruments: A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2012;43(7):1998-2027.

24. Adams RJ, Chimowitz MI, Alpert JS, et al. Coronary risk evaluation in patients with transient ischemic attack and ischemic stroke: A scientific statement for healthcare professionals from the Stroke Council and the Council on Clinical Cardiology of the American Heart Association/American Stroke Association. *Circulation*. 2003;108(10):1278-1290.

25. Furie KL, Kasner SE, Adams RJ, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42(1):227-276.

26. Bohannon RW, Horton MG, Wikholm JB. Importance of four variables of walking to patients with stroke. *Int J Rehabil Res*. 1991;14(3):246-250.

27. Michael KM, Allen JK, Macko RF. Reduced ambulatory activity after stroke: The role of balance, gait, and cardiovascular fitness. *Arch Phys Med Rehabil*. 2005;86(8):1552-1556.

28. Corcoran PJ, Jebsen RH, Brengelmann GL, Simons BC. Effects of plastic and metal leg braces on speed and energy cost of hemiparetic ambulation. *Arch Phys Med Rehabil*. 1970;51:69-77.

29. Gersten JW, Orr W. External work of walking in hemiparetic patients. *Scand J Rehab Med*. 1971;3:85-88.

30. Smith AC, Saunders DH, Mead G. Cardiorespiratory fitness after stroke: A systematic review. *Int J Stroke*. 2012;7(6):499-510.

31. Billinger SA, Coughenour E, Mackay-Lyons MJ, Ivey FM. Reduced cardiorespiratory fitness after stroke: Biological consequences and exercise-induced adaptations. *Stroke Res Treat*. 2012;2012:959120.

32. Ivey FM, Hafer-Macko CE, Macko RF. Exercise rehabilitation after stroke. *NeuroRX*. 2006;3(4):439-450.

33. Ivey FM, Hafer-Macko CE, Macko RF. Task-oriented treadmill exercise training in chronic hemiparetic stroke. *J Rehabil Res Dev*. 2008;45(2):249-259.

34. Shaughnessy M, Michael KM, Sorkin JD, Macko RF. Steps after stroke: Capturing ambulatory recovery. *Stroke*. 2005;36(6):1305-1307.

35. Haeuber E, Shaughnessy M, Forrester LW, Coleman KL, Macko RF. Accelerometer monitoring of home- and community-based ambulatory activity after stroke. *Arch Phys Med Rehabil.* 2004;85(12):1997-2001.

36. Tudor-Locke C, Bassett DR, Jr. How many steps/day are enough? preliminary pedometer indices for public health. *Sports Med.* 2004;34(1):1-8.

37. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics--2012 update: A report from the American Heart Association. *Circulation.* 2012;125(1):e2-e220.

38. Gordon NF, Gulanick M, Costa F, et al. Physical activity and exercise recommendations for stroke survivors: An American Heart Association scientific statement from the Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention; the Council on Cardiovascular Nursing; the Council on Nutrition, Physical Activity, and Metabolism; and the Stroke Council. *Circulation.* 2004;109(16):2031-2041.

39. Marsden DL, Dunn A, Callister R, Levi CR, Spratt NJ. Characteristics of exercise training interventions to improve cardiorespiratory fitness after stroke: A systematic review with meta-analysis. *Neurorehabil Neural Repair.* 2013;27(9):775-788.

40. Pang MY, Charlesworth SA, Lau RW, Chung RC. Using aerobic exercise to improve health outcomes and quality of life in stroke: Evidence-based exercise prescription recommendations. *Cerebrovasc Dis.* 2013;35(1):7-22.

41. Stoller O, de Bruin ED, Knols RH, Hunt KJ. Effects of cardiovascular exercise early after stroke: Systematic review and meta-analysis. *BMC Neurol.* 2012;12:45-2377-12-45.

42. Kendall BJ, Gothe NP. Effect of aerobic exercise interventions on mobility among stroke patients: A systematic review. *Am J Phys Med Rehabil.* 2016;95(3):214-24.

43. Mehta S, Pereira S, Janzen S, Mays R, Viana R, Lobo L, Teasell RW. Cardiovascular conditioning for comfortable gait speed and total distance walked during the chronic stage of stroke: A meta-analysis. *Top Stroke Rehabil.* 2012;19(6):463-470.

44. Saunders DH, Sanderson M, Brazzelli M, Greig CA, Mead GE. Physical fitness training for stroke patients. *Cochrane Database Syst Rev.* 2013;10:CD003316.

45. Zedlitz AM, Rietveld TC, Geurts AC, Fasotti L. Cognitive and graded activity training can alleviate persistent fatigue after stroke: A randomized, controlled trial. *Stroke.* 2012;43(4):1046-1051.

46. Ivey FM, Ryan AS, Hafer-Macko CE, Goldberg AP, Macko RF. Treadmill aerobic training improves glucose tolerance and indices of insulin sensitivity in disabled stroke survivors: A preliminary report. *Stroke.* 2007;38(10):2752-2758.

47. Rimmer JH, Rauworth AE, Wang EC, Nicola TL, Hill B. A preliminary study to examine the effects of aerobic and therapeutic (nonaerobic) exercise on cardiorespiratory fitness and coronary risk reduction in stroke survivors. *Arch Phys Med Rehabil.* 2009;90(3):407-412.

48. Takatori K, Matsumoto D, Okada Y, Nakamura J, Shomoto K. Effect of intensive rehabilitation on physical function and arterial function in community-dwelling chronic stroke survivors. *Top Stroke Rehabil.* 2012;19(5):377-383.

49. Billinger SA, Mattlage AE, Ashenden AL, Lentz AA, Harter G, Rippee MA. Aerobic exercise in subacute stroke improves cardiovascular health and physical performance. *J Neurol Phys Ther.* 2012;36(4):159-165.

50. Ivey FM, Hafer-Macko CE, Ryan AS, Macko RF. Impaired leg vasodilatory function after stroke: Adaptations with treadmill exercise training. *Stroke.* 2010;41(12):2913-2917.

51. Ivey FM, Ryan AS, Hafer-Macko CE, Macko RF. Improved cerebral vasomotor reactivity after exercise training in hemiparetic stroke survivors. *Stroke.* 2011;42(7):1994-2000.

52. Luft AR, Macko RF, Forrester LW, Villagra F, Ivey F, Sorkin JD, Whitall J, McCombe-Waller S, Katzel L, Goldberg AP, Hanley DF. Treadmill exercise activates subcortical neural networks and improves walking after stroke: a randomized controlled trial. *Stroke.* 2008;39(12):3341-50.

53. Eng JJ, Reime B. Exercise for depressive symptoms in stroke patients: A systematic review and meta-analysis. *Clin Rehabil*. 2014;28(8):731-739.

54. Quaney BM, Boyd LA, McDowd JM, Zahner LH, He J, Mayo MS, Macko RF. Aerobic exercise improves cognition and motor function poststroke. *Neurorehabil Neural Repair*. 2009;23(9):879-885.

55. Stuart M, Benvenuti F, Macko R, Taviani A, Segenni L, Mayer F, Sorkin JD, Stanhope SJ, Macellari V, Weinrich M. Community-based adaptive physical activity program for chronic stroke: feasibility, safety, and efficacy of the Empoli model. *Neurorehabil Neural Repair*. 2009;23(7):726-734.

56. Chen MD, Rimmer JH. Effects of exercise on quality of life in stroke survivors: A meta-analysis. *Stroke*. 2011;42(3):832-837.

57. Tilson JK, Sullivan KJ, Cen SY, Rose DK, Koradia CH, Azen SP, Duncan PW; Locomotor Experience Applied Post Stroke (LEAPS) Investigative Team. Meaningful gait speed improvement during the first 60 days poststroke: Minimal clinically important difference. *Phys Ther*. 2010;90(2):196-208.

58. Schmid A, Duncan PW, Studenski S, Lai SM, Richards L, Perera S, Wu SS. Improvements in speed-based gait classifications are meaningful. *Stroke*. 2007;38(7):2096-2100.

59. Perry J, Garrett M, Gronley JK, Mulroy SJ. Classification of walking handicap in the stroke population. *Stroke*. 1995;26(6):982-989.

60. Macko RF, Ivey FM, Forrester LW, Hanley D, Sorkin JD, Katzel LI, Silver KH, Goldberg AP. Treadmill exercise rehabilitation improves ambulatory function and cardiovascular fitness in patients with chronic stroke: A randomized, controlled trial. *Stroke*. 2005;36(10):2206-2211.

61. Macko RF, DeSouza CA, Tretter LD, Silver KH, Smith GV, Anderson PA, Tomoyasu N, Gorman P, Dengel DR. Treadmill aerobic exercise training reduces the energy expenditure and cardiovascular demands of hemiparetic gait in chronic stroke patients. A preliminary report. *Stroke*. 1997;28(2):326-330.

62. Macko RF, Smith GV, Dobrovolny CL, Sorkin JD, Goldberg AP, Silver KH. Treadmill training improves fitness reserve in chronic stroke patients. *Arch Phys Med Rehabil*. 2001;82(7):879-884.

63. Tiedemann A, Sherrington C, Dean CM, Rissel C, Lord SR, Kirkham C, O'Rourke SD. Predictors of adherence to a structured exercise program and physical activity participation in community dwellers after stroke. *Stroke Res Treat*. 2012;2012:136525.

64. Jurkiewicz MT, Marzolini S, Oh P. Adherence to a home-based exercise program for individuals after stroke. *Top Stroke Rehabil*. 2011;18(3):277-284.

65. Moholdt T, Aamot IL, Granøien I, Gjerde L, Myklebust G, Walderhaug L, Hole T, Graven T, Stølen T, Mølmen-Hansen HE, Støylen A, Skogvoll E, Slørdahl SA, Wisloff U. Long-term follow-up after cardiac rehabilitation: A randomized study of usual care exercise training versus aerobic interval training after myocardial infarction. *Int J Cardiol*. 2011;152(3):388-390.

66. Duncan P, Studenski S, Richards L, Gollub S, Lai SM, Reker D, Perera S, Yates J, Koch V, Rigler S, Johnson D. Randomized clinical trial of therapeutic exercise in subacute stroke. *Stroke*. 2003;34(9):2173-2180.

67. Kwakkel G. Impact of intensity of practice after stroke: Issues for consideration. *Disabil Rehabil*. 2006;28(13-14):823-830.

68. Lam JM, Globas C, Cerny J, Hertler B, Uludag K, Forrester LW, Macko RF, Hanley DF, Becker C, Luft AR. Predictors of response to treadmill exercise in stroke survivors. *Neurorehabil Neural Repair*. 2010;24(6):567-574.

69. Globas C, Becker C, Cerny J, Lam JM, Lindemann U, Forrester LW, Macko RF, Luft AR. Chronic stroke survivors benefit from high-intensity aerobic treadmill exercise: A randomized control trial. *Neurorehabil Neural Repair*. 2012;26(1):85-95.

70. Rankin AJ, Rankin AC, Macintyre P, Hillis WS. Walk or run? is high-intensity exercise more effective than moderate-intensity exercise at reducing cardiovascular risk? *Scott Med J*. 2012;57(2):99-102.

71. Wisloff U, Ellingsen O, Kemi OJ. High-intensity interval training to maximize cardiac benefits of exercise training? *Exerc Sport Sci Rev*. 2009;37(3):139-146.

72. Guiraud T, Nigam A, Gremiaux V, Meyer P, Juneau M, Bosquet L. High-intensity interval training in cardiac rehabilitation. *Sports Med*. 2012;42(7):587-605.

73. Ivey FM, Stookey AD, Hafer-Macko CE, Ryan AS, Macko RF. Higher treadmill training intensity to address functional aerobic impairment after stroke. *J Stroke Cerebrovasc Dis*. 2015;24(11):2539-2546.

74. Boyne P, Welge J, Kissela B, Dunning K. Factors influencing the efficacy of aerobic exercise for improving fitness and walking capacity after stroke: A meta-analysis with meta-regression. *Arch Phys Med Rehabil*. 2016 Oct 12. pii: S0003-9993(16)31143-1. doi: 10.1016/j.apmr.2016.08.484. [Epub ahead of print] Pubmed PMID: 27744025.

75. Ciolac EG. High-intensity interval training and hypertension: Maximizing the benefits of exercise? *Am J Cardiovasc Dis*. 2012;2(2):102-110.

76. Fu TC, Wang CH, Lin PS, Hsu CC, Cherng WJ, Huang SC, Liu MH, Chiang CL, Wang JS. Aerobic interval training improves oxygen uptake efficiency by enhancing cerebral and muscular hemodynamics in patients with heart failure. *Int J Cardiol*. 2013;167(1):41-50.

77. Rognmo O, Hetland E, Helgerud J, Hoff J, Slordahl SA. High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease. *Eur J Cardiovasc Prev Rehabil*. 2004;11(3):216-222.

78. Hornby TG, Straube DS, Kinnaird CR, Holleran CL, Echauz AJ, Rodriguez KS, Wagner EJ, Narducci EA. Importance of specificity, amount, and intensity of locomotor training to improve ambulatory function in patients poststroke. *Top Stroke Rehabil*. 2011;18(4):293-307.

79. Outermans JC, van Peppen RP, Wittink H, Takken T, Kwakkel G. Effects of a high-intensity task-oriented training on gait performance early after stroke: A pilot study. *Clin Rehabil*. 2010;24(11):979-987.

80. Rose D, Paris T, Crews E, Wu SS, Sun A, Behrman AL, Duncan P. Feasibility and effectiveness of circuit training in acute stroke rehabilitation. *Neurorehabil Neural Repair*. 2011;25(2):140-148.

81. Pohl M, Mehrholz J, Ritschel C, Ruckriem S. Speed-dependent treadmill training in ambulatory hemiparetic stroke patients: A randomized controlled trial. *Stroke*. 2002;33(2):553-558.

82. Lau KW, Mak MK. Speed-dependent treadmill training is effective to improve gait and balance performance in patients with sub-acute stroke. *J Rehabil Med*. 2011;43(8):709-713.

83. Sullivan KJ, Knowlton BJ, Dobkin BH. Step training with body weight support: Effect of treadmill speed and practice paradigms on poststroke locomotor recovery. *Arch Phys Med Rehabil*. 2002;83(5):683-691.

84. Moore JL, Roth EJ, Killian C, Hornby TG. Locomotor training improves daily stepping activity and gait efficiency in individuals poststroke who have reached a "plateau" in recovery. *Stroke*. 2010;41(1):129-135.

85. Kwakkel G, Wagenaar RC, Twisk JW, Lankhorst GJ, Koetsier JC. Intensity of leg and arm training after primary middle-cerebral-artery stroke: A randomised trial. *Lancet*. 1999;354(9174):191-196.

86. Lisman J, Spruston N. Postsynaptic depolarization requirements for LTP and LTD: A critique of spike timing-dependent plasticity. *Nat Neurosci*. 2005;8(7):839-841.

87. Peinemann A, Reimer B, Löer C, Quartarone A, Münchau A, Conrad B, Siebner HR. Long-lasting increase in corticospinal excitability after 1800 pulses of subthreshold 5 hz repetitive TMS to the primary motor cortex. *Clin Neurophysiol*. 2004;115(7):1519-1526.

88. Lamontagne A, Fung J. Faster is better: Implications for speed-intensive gait training after stroke. *Stroke*. 2004;35(11):2543-2548.

89. Tyrell CM, Roos MA, Rudolph KS, Reisman DS. Influence of systematic increases in treadmill walking speed on gait kinematics after stroke. *Phys Ther*. 2011;91(3):392-403.

90. Hsiao H, Awad LN, Palmer JA, Higginson JS, Binder-Macleod SA. Contribution of paretic and nonparetic limb peak propulsive forces to changes in walking speed in individuals poststroke. *Neurorehabil Neural Repair*. 2016;30(8):743-52.

91. Reisman DS, Rudolph KS, Farquhar WB. Influence of speed on walking economy poststroke. *Neurorehabil Neural Repair*. 2009;23(6):529-534.

92. Burgomaster KA, Hughes SC, Heigenhauser GJ, Bradwell SN, Gibala MJ. Six sessions of sprint interval training increases muscle oxidative potential and cycle endurance capacity in humans. *J Appl Physiol*. 2005;98(6):1985-1990.

93. Gibala MJ, Little JP, van Essen M, Wilkin GP, Burgomaster KA, Safdar A, Raha S, Tarnopolsky MA. Short-term sprint interval versus traditional endurance training: Similar initial adaptations in human skeletal muscle and exercise performance. *J Physiol*. 2006;575(Pt 3):901-911.

94. Hood MS, Little JP, Tarnopolsky MA, Myslik F, Gibala MJ. Low-volume interval training improves muscle oxidative capacity in sedentary adults. *Med Sci Sports Exerc*. 2011;43(10):1849-1856.

95. Bartlett JD, Hwa Joo C, Jeong TS, Louhelainen J, Cochran AJ, Gibala MJ, Gregson W, Close GL, Drust B, Morton JP. Matched work high-intensity interval and continuous running induce similar increases in PGC-1alpha mRNA, AMPK, p38, and p53 phosphorylation in human skeletal muscle. *J Appl Physiol*. 2012;112(7):1135-1143.

96. Burgomaster KA, Howarth KR, Phillips SM, Rakobowchuk M, Macdonald MJ, McGee SL, Gibala MJ. Similar metabolic adaptations during exercise after low volume sprint interval and traditional endurance training in humans. *J Physiol*. 2008;586(1):151-160.

97. Rakobowchuk M, Tanguay S, Burgomaster KA, Howarth KR, Gibala MJ, MacDonald MJ. Sprint interval and traditional endurance training induce similar improvements in peripheral arterial stiffness and flow-mediated dilation in healthy humans. *Am J Physiol Regul Integr Comp Physiol*. 2008;295(1):R236-42.

98. Moholdt TT, Amundsen BH, Rustad LA, Wahba A, Løvø KT, Gullikstad LR, Bye A, Skogvoll E, Wisløff U, Slørdahl SA. Aerobic interval training versus continuous moderate exercise after coronary artery bypass surgery: A randomized study of cardiovascular effects and quality of life. *Am Heart J*. 2009;158(6):1031-1037.

99. Wisløff U, Støylen A, Loennechen JP, Bruvold M, Rognmo Ø, Haram PM, Tjønna AE, Helgerud J, Slørdahl SA, Lee SJ, Videm V, Bye A, Smith GL, Najjar SM, Ellingsen Ø, Skjaerpe T. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: A randomized study. *Circulation*. 2007;115(24):3086-3094.

100. Moholdt T, Aamot IL, Granøien I, Gjerde L, Myklebust G, Walderhaug L, Brattbakk L, Hole T, Graven T, Stølen TO, Amundsen BH, Mølmen-Hansen HE, Støylen A, Wisløff U, Slørdahl SA. Aerobic interval training increases peak oxygen uptake more than usual care exercise training in myocardial infarction patients: A randomized controlled study. *Clin Rehabil*. 2012;26(1):33-44.

101. Freyssin C, Verkindt C, Prieur F, Benaich P, Maunier S, Blanc P. Cardiac rehabilitation in chronic heart failure: Effect of an 8-week, high-intensity interval training versus continuous training. *Arch Phys Med Rehabil*. 2012;93(8):1359-64.

102. Arena R, Myers J, Forman DE, Lavie CJ, Guazzi M. Should high-intensity-aerobic interval training become the clinical standard in heart failure? *Heart Fail Rev*. 2013;18(1):95-105.

103. Holleran CL, Straube DD, Kinnaird CR, Leddy AL, Hornby TG. Feasibility and potential efficacy of high-intensity stepping training in variable contexts in subacute and chronic stroke. *Neurorehabil Neural Repair*. 2014;28(7):643-651.

104. Holleran CL, Rodriguez KS, Echauz A, Leech KA, Hornby TG. Potential contributions of training intensity on locomotor performance in individuals with chronic stroke. *J Neurol Phys Ther*. 2015;39(2):95-102.

105. Askim T, Dahl AE, Aamot IL, Hokstad A, Helbostad J, Indredavik B. High-intensity aerobic interval training for patients 3-9 months after stroke. A feasibility study. *Physiother Res Int*. 2014;19(3):129-39.

106. Gjellesvik TI, Brurok B, Hoff J, Torhaug T, Helgerud J. Effect of high aerobic intensity interval treadmill walking in people with chronic stroke: A pilot study with one year follow-up. *Top Stroke Rehabil.* 2012;19(4):353-360.

107. Mackay-Lyons M. Aerobic treadmill training effectively enhances cardiovascular fitness and gait function for older persons with chronic stroke. *J Physiother.* 2012;58(4):271-9553(12)70131-5.

108. Eich HJ, Mach H, Werner C, Hesse S. Aerobic treadmill plus bobath walking training improves walking in subacute stroke: A randomized controlled trial. *Clin Rehabil.* 2004;18(6):640-651.

109. Gordon CD, Wilks R, McCaw-Binns A. Effect of aerobic exercise (walking) training on functional status and health-related quality of life in chronic stroke survivors: A randomized controlled trial. *Stroke.* 2013;44(4):1179-1181.

110. Dobkin BH. Progressive staging of pilot studies to improve phase III trials for motor interventions. *Neurorehabil Neural Repair.* 2009;23(3):197-206.

111. Carl D, Boyne P, Rockwell B, Gerson M, Khoury J, Kissela B, Dunning K. Preliminary safety analysis of high-intensity interval training (HIT) in persons with chronic stroke. *Applied physiology, nutrition, and metabolism.* in press.

112. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER 3rd, Moy CS, Muntnar P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2015 update: A report from the American Heart Association. *Circulation.* 2015;131(4):e29-322.

113. Duncan PW, Sullivan KJ, Behrman AL, Azen SP, Wu SS, Nadeau SE, Dobkin BH, Rose DK, Tilson JK, Cen S, Hayden SK; LEAPS Investigative Team. Body-weight-supported treadmill rehabilitation after stroke. *N Engl J Med.* 2011;364(21):2026-2036.

114. Dunning K, O'Dell M, Kluding P, Wu S, Feld J, Ginosian J, McBride K. The functional ambulation: Standard treatment versus electrical stimulation therapy (FASTEST) trial for stroke: study design and protocol. *Open Access J Clin Trials.* 2013;5:39-49.

115. Kluding PM, Dunning K, O'Dell MW, Wu SS, Ginosian J, Feld J, McBride K. Foot drop stimulation versus ankle foot orthosis after stroke: 30-week outcomes. *Stroke.* 2013;44(6):1660-1669.

116. MacKay-Lyons MJ, Makrides L. Cardiovascular stress during a contemporary stroke rehabilitation program: Is the intensity adequate to induce a training effect? *Arch Phys Med Rehabil.* 2002;83(10):1378-1383.

117. Kuys S, Brauer S, Ada L. Routine physiotherapy does not induce a cardiorespiratory training effect post-stroke, regardless of walking ability. *Physiother Res Int.* 2006;11(4):219-227.

118. Duncan PW, Sullivan KJ, Behrman AL, Azen SP, Wu SS, Nadeau SE, Dobkin BH, Rose DK, Tilson JK; LEAPS Investigative Team. Protocol for the locomotor experience applied post-stroke (LEAPS) trial: A randomized controlled trial. *BMC Neurol.* 2007;7:39.

119. Johnson L, Burridge JH, Demain SH. Internal and external focus of attention during gait re-education: An observational study of physical therapist practice in stroke rehabilitation. *Phys Ther.* 2013;93(7):957-966.

120. Dobkin BH, Duncan PW. Should body weight-supported treadmill training and robotic-assistive steppers for locomotor training trot back to the starting gate? *Neurorehabil Neural Repair.* 2012;26(4):308-317.

121. Lewek MD, Cruz TH, Moore JL, Roth HR, Dhaher YY, Hornby TG. Allowing intralimb kinematic variability during locomotor training poststroke improves kinematic consistency: A subgroup analysis from a randomized clinical trial. *Phys Ther.* 2009;89(8):829-839.

122. Hornby TG, Campbell DD, Kahn JH, Demott T, Moore JL, Roth HR. Enhanced gait-related improvements after therapist- versus robotic-assisted locomotor training in subjects with chronic stroke: A randomized controlled study. *Stroke*. 2008;39(6):1786-1792.

123. Reisman DS, McLean H, Keller J, Danks KA, Bastian AJ. Repeated split-belt treadmill training improves poststroke step length asymmetry. *Neurorehabil Neural Repair*. 2013;27(5):460-468.

124. Boyd L, Weinstein C. Explicit information interferes with implicit motor learning of both continuous and discrete movement tasks after stroke. *J Neurol Phys Ther*. 2006;30(2):46-59.

125. Orrell AJ, Eves FF, Masters RS. Motor learning of a dynamic balancing task after stroke: Implicit implications for stroke rehabilitation. *Phys Ther*. 2006;86(3):369-380.

126. Wulf G, Landers M, Lewthwaite R, Tollner T. External focus instructions reduce postural instability in individuals with Parkinson Disease. *Phys Ther*. 2009;89(2):162-168.

127. Fasoli SE, Trombly CA, Tickle-Degnen L, Verfaellie MH. Effect of instructions on functional reach in persons with and without cerebrovascular accident. *Am J Occup Ther*. 2002;56(4):380-390.

128. McNevin NH, Wulf G, Carlson C. Effects of attentional focus, self-control, and dyad training on motor learning: Implications for physical rehabilitation. *Phys Ther*. 2000;80(4):373-385.

129. Hyndman D, Ashburn A, Yardley L, Stack E. Interference between balance, gait and cognitive task performance among people with stroke living in the community. *Disabil Rehabil*. 2006;28(13-14):849-856.

130. Boyne P, Reisman D, Brian M, Barney B, Franke A, Carl D, Khoury J, Dunning K. Ventilatory threshold may be a more specific measure of aerobic capacity than peak oxygen consumption rate in persons with stroke. *Top Stroke Rehabil*. 2016 Jul 25:1-9. [Epub ahead of print] Pubmed PMID: 27454553.

131. Awad LN, Reisman DS, Pohlig RT, Binder-Macleod SA. Reducing the cost of transport and increasing walking distance after stroke: A randomized controlled trial on fast locomotor training combined with functional electrical stimulation. *Neurorehabil Neural Repair*. 2016;30(7):661-670.

132. Danks KA, Pohlig R, Reisman DS. Combining fast-walking training and a step activity monitoring program to improve daily walking activity after stroke: A preliminary study. *Arch Phys Med Rehabil*. 2016;97(9):S185-93.

133. Mattlage AE, Ashenden AL, Lentz AA, Rippee MA, Billinger SA. Submaximal and peak cardiorespiratory response after moderate-high intensity exercise training in subacute stroke. *Cardiopulm Phys Ther J*. 2013;24(3):14-20.

134. Billinger SA, Taylor JM, Quaney BM. Cardiopulmonary response to exercise testing in people with chronic stroke: A retrospective study. *Stroke Res Treat*. 2012;2012:987637.

135. Billinger SA, Tseng BY, Kluding PM. Modified total-body recumbent stepper exercise test for assessing peak oxygen consumption in people with chronic stroke. *Phys Ther*. 2008;88(10):1188-1195.

136. Boyne P, Buhr S, Rockwell B, Khoury J, Carl D, Gerson M, Kissela B, Dunning K. Predicting heart rate at the ventilatory threshold for aerobic exercise prescription in persons with chronic stroke. *J Neurol Phys Ther*. 2015;39(4):233-240.

137. Mattlage AE, Rippee MA, Abraham MG, Sandt J, Billinger SA. Estimated prestroke peak VO₂ is related to circulating IGF-1 levels during acute stroke. *Neurorehabil Neural Repair*. 2017;31(1):65-71.

138. Mattlage AE, Rippee MA, Sandt J, Billinger SA. Decrease in insulin-like growth factor-1 and insulin-like growth factor-1 ratio in the first week of stroke is related to positive outcomes. *J Stroke Cerebrovasc Dis*. 2016;25(7):1800-1806.

139. Dunning K, Levine P, Schmitt L, Israel S, Fulk G. An ankle to computer virtual reality system for improving gait and function in a person 9 months poststroke. *Top Stroke Rehabil*. 2008;15(6):602-610.

140. Reisman DS, Wityk R, Silver K, Bastian AJ. Locomotor adaptation on a split-belt treadmill can improve walking symmetry post-stroke. *Brain*. 2007;130(7):1861-1872.

141. Gillen JB, Little JP, Punthakee Z, Tarnopolsky MA, Riddell MC, Gibala MJ. Acute high-intensity interval exercise reduces the postprandial glucose response and prevalence of hyperglycaemia in patients with type 2 diabetes. *Diabetes Obes Metab*. 2012;14(6):575-577.

142. American College of Sports Medicine (ACSM). *ACSM's guidelines for exercise testing and prescription*. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2014.

143. Thorpe KE, Zwarenstein M, Oxman AD, Treweek S, Furberg CD, Altman DG, Tunis S, Bergel E, Harvey I, Magid DJ, Chalkidou K. A pragmatic-explanatory continuum indicator summary (PRECIS): A tool to help trial designers. *J Clin Epidemiol*. 2009;62(5):464-475.

144. Macko RF, Ivey FM, Forrester LW. Task-oriented aerobic exercise in chronic hemiparetic stroke: Training protocols and treatment effects. *Topics in Stroke Rehabilitation*. 2005;12(1):45-57.

145. Brott T, Adams HP Jr, Olinger CP, Marler JR, Barsan WG, Biller J, Spilker J, Holleran R, Eberle R, Hertzberg V. Measurements of acute cerebral infarction: A clinical examination scale. *Stroke*. 1989;20(7):864-870.

146. Ashworth B. Preliminary trial of carisoprodol in multiple sclerosis. *Practitioner*. 1964;192:540-542.

147. Williams LS, Brizendine EJ, Plue L, Bakas T, Tu W, Hendrie H, Kroenke K. Performance of the PHQ-9 as a screening tool for depression after stroke. *Stroke*. 2005;36(3):635-638.

148. Macko RF, Katzel LI, Yataco A, Tretter LD, DeSouza CA, Dengel DR, Smith GV, Silver KH. Low-velocity graded treadmill stress testing in hemiparetic stroke patients. *Stroke*. 1997;28(5):988-992.

149. Ada L, Dean CM, Lindley R. Randomized trial of treadmill training to improve walking in community-dwelling people after stroke: The AMBULATE trial. *Int J Stroke*. 2013;8(6):436-444.

150. Dean CM, Ada L, Lindley RI. Treadmill training provides greater benefit to the subgroup of community-dwelling people after stroke who walk faster than 0.4m/s: A randomised trial. *J Physiother*. 2014;60(2):97-101.

151. Dean CM, Rissel C, Sherrington C, Sharkey M, Cumming RG, Lord SR, Barker RN, Kirkham C, O'Rourke S. Exercise to enhance mobility and prevent falls after stroke: The community stroke club randomized trial. *Neurorehabil Neural Repair*. 2012;26(9):1046-1057.

152. Dean CM, Rissel C, Sherrington C, Sharkey M, Cumming RG, Lord SR, Barker RN, Kirkham C, O'Rourke SD. Exercise intervention to prevent falls, enhance mobility and increase physical activity in community dwellers after stroke: A randomised controlled trial. Sydney: *NSW Ministry of Health*. 2011. Available at: <<http://www.health.nsw.gov.au/research/Publications/2006-exercise-for-falls.pdf>>

153. Middleton A, Fritz SL, Lusardi M. Walking speed: The functional vital sign. *J Aging Phys Act*. 2015;23(2):314-322.

154. Dobkin BH, Nadeau SE, Behrman AL, Wu SS, Rose DK, Bowden M, Studenski S, Lu X, Duncan PW. Prediction of responders for outcome measures of locomotor experience applied post stroke trial. *J Rehabil Res Dev*. 2014;51(1):39-50.

155. Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. I. A method for evaluation of physical performance. *Scand J Rehab Med*. 1975;7:13-31.

156. Burke E, Dobkin BH, Noser EA, Enney LA, Cramer SC. Predictors and biomarkers of treatment gains in a clinical stroke trial targeting the lower extremity. *Stroke*. 2014;45(8):2379-2384.

157. Berg K, Wood-Dauphinee S, Williams JI, Gayton D. Measuring balance in the elderly: Preliminary development of an instrument. *Physiother Can*. 1989;41:304-311.

158. Blum L, Korner-Bitensky N. Usefulness of the Berg Balance Scale in stroke rehabilitation: A systematic review. *Phys Ther*. 2008;88(5):559-566.

159. Nadeau SE, Dobkin B, Wu SS, Pei Q, Duncan PW, LEAPS Investigative Team. The effects of stroke type, locus, and extent on long-term outcome of gait rehabilitation: The LEAPS experience. *Neurorehabil Neural Repair*. 2016;30(7):615-25.

160. Jones PS, Pomeroy VM, Wang J, Schlaug G, Tulasi Marrapu S, Geva S, Rowe PJ, Chandler E, Kerr A, Baron JC; SWIFT-Cast investigators. Does stroke location predict walk speed response to gait rehabilitation? *Hum Brain Mapp*. 2016;37(2):689-703.

161. Luft AR, Forrester L, Macko RF, McCombe-Waller S, Whitall J, Villagra F, Hanley DF. Brain activation of lower extremity movement in chronically impaired stroke survivors. *Neuroimage*. 2005;26(1):184-194.

162. Forrester LW, Hanley DF, Macko RF. Effects of treadmill exercise on transcranial magnetic stimulation-induced excitability to quadriceps after stroke. *Arch Phys Med Rehabil*. 2006;87(2):229-234.

163. Tang A, Eng JJ, Krassioukov AV, Madden KM, Mohammadi A, Tsang MY, Tsang TS. Exercise-induced changes in cardiovascular function after stroke: A randomized controlled trial. *Int J Stroke*. 2014;9(7):883-889.

164. Tang A, Marzolini S, Oh P, McIlroy WE, Brooks D. Factors associated with change in aerobic capacity following an exercise program for individuals with stroke. *J Rehabil Med*. 2013;45(1):32-37.

165. Tang A, Sibley KM, Thomas SG, Bayley MT, Richardson D, McIlroy WE, Brooks D. Effects of an aerobic exercise program on aerobic capacity, spatiotemporal gait parameters, and functional capacity in subacute stroke. *Neurorehabil Neural Repair*. 2009;23(4):398-406.

166. Hoshino D, Tamura Y, Masuda H, Matsunaga Y, Hatta H. Effects of decreased lactate accumulation after dichloroacetate administration on exercise training-induced mitochondrial adaptations in mouse skeletal muscle. *Physiol Rep*. 2015;3(9):e12555.

167. Schiffer T, Schulte S, Sperlich B, Achtzehn S, Fricke H, Struder HK. Lactate infusion at rest increases BDNF blood concentration in humans. *Neurosci Lett*. 2011;488(3):234-237.

168. Skriver K, Roig M, Lundbye-Jensen J, Pingel J, Helge JW, Kiens B, Nielsen JB. Acute exercise improves motor memory: Exploring potential biomarkers. *Neurobiol Learn Mem*. 2014;116:46-58.

169. Roos MA, Rudolph KS, Reisman DS. The structure of walking activity in people after stroke compared with older adults without disability: A cross-sectional study. *Phys Ther*. 2012;92(9):1141-7.

170. Macko RF, Haeuber E, Shaughnessy M, Coleman KL, Boone DA, Smith GV, Silver KH. Microprocessor-based ambulatory activity monitoring in stroke patients. *Med Sci Sports Exerc*. 2002;34(3):394-399.

171. Hornby TG, Holleran CL, Hennessy PW, Leddy AL, Connolly M, Camardo J, Woodward J, Mahtani G, Lovell L, Roth EJ. Variable intensive early walking poststroke (VIEWS): A randomized controlled trial. *Neurorehabil Neural Repair*. 2016;30(5):440-50.

172. Flansbjer U, Holmback AM, Downham D, Patten C, Lexell J. Reliability of gait performance tests in men and women with hemiparesis after stroke. *J Rehabil Med*. 2005;37(2):75-82.

173. Collen FM, Wade DT, Bradshaw CM. Mobility after stroke: Reliability of measures of impairment and disability. *Int Disabil Stud*. 1990;12(1):6-9.

174. Maeda A, Yuasa T, Nakamura K, Higuchi S, Motohashi Y. Physical performance tests after stroke: Reliability and validity. *Am J Phys Med Rehabil*. 2000;79:519-25.

175. Lord SE, McPherson K, McNaughton HK, Rochester L, Weatherall M. Community ambulation after stroke: How important and obtainable is it and what measures appear predictive? *Arch Phys Med Rehabil*. 2004;85(2):234-239.

176. Studenski S, Perera S, Wallace D, Chandler JM, Duncan PW, Rooney E, Fox M, Guralnik JM. Physical performance measures in the clinical setting. *J Am Geriatr Soc*. 2003;51(3):314-322.

177. Crouter SE, Antczak A, Hudak JR, DellaValle DM, Haas JD. Accuracy and reliability of the ParvoMedics TrueOne 2400 and MedGraphics VO2000 metabolic systems. *Eur J Appl Physiol*. 2006;98(2):139-151.

178. Dobrovolsky CL, Ivey FM, Rogers MA, Sorkin JD, Macko RF. Reliability of treadmill exercise testing in older patients with chronic hemiparetic stroke. *Arch Phys Med Rehabil*. 2003;84(9):1308-1312.

179. Marzolini S, Oh P, McIlroy W, Brooks D. The effects of an aerobic and resistance exercise training program on cognition following stroke. *Neurorehabil Neural Repair*. 2013;27(5):392-402.

180. Marzolini S, Oh P, McIlroy W, Brooks D. The feasibility of cardiopulmonary exercise testing for prescribing exercise to people after stroke. *Stroke*. 2012;43(4):1075-1081.

181. American Thoracic Society, American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med*. 2003;167(2):211-277.

182. Guazzi M, Adams V, Conraads V, Halle M, Mezzani A, Vanhees L, Arena R, Fletcher GF, Forman DE, Kitzman DW, Lavie CJ, Myers J; European Association for Cardiovascular Prevention & Rehabilitation; American Heart Association. EACPR/AHA scientific statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Circulation*. 2012;126(18):2261-2274.

183. Mezzani A, Hamm LF, Jones AM, McBride PE, Moholdt T, Stone JA, Urhausen A, Williams MA; European Association for Cardiovascular Prevention and Rehabilitation; American Association of Cardiovascular and Pulmonary Rehabilitation; Canadian Association of Cardiac Rehabilitation. Aerobic exercise intensity assessment and prescription in cardiac rehabilitation: A joint position statement of the European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitation, and the Canadian Association of Cardiac Rehabilitation. *J Cardiopulm Rehabil Prev*. 2012;32(6):327-350.

184. Keteyian SJ, Brawner CA, Savage PD, Ehrman JK, Schairer J, Divine G, Aldred H, Ophaug K, Ades PA. Peak aerobic capacity predicts prognosis in patients with coronary heart disease. *Am Heart J*. 2008;156(2):292-300.

185. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med*. 2002;346(11):793-801.

186. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Piña IL; HF-ACTION Investigators. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA*. 2009;301(14):1439-1450.

187. Danielsson A, Willen C, Sunnerhagen KS. Measurement of energy cost by the physiological cost index in walking after stroke. *Arch Phys Med Rehabil*. 2007;88(10):1298-1303.

188. Fredrickson E, Ruff RL, Daly JJ. Physiological cost index as a proxy measure for the oxygen cost of gait in stroke patients. *Neurorehabil Neural Repair*. 2007;21(5):429-434.

189. Hornnes N, Larsen K, Boysen G. Little change of modifiable risk factors 1 year after stroke: A pilot study. *Int J Stroke*. 2010;5(3):157-162.

190. Tudor-Locke C, Craig CL, Aoyagi Y, Bell RC, Croteau KA, De Bourdeaudhuij I, Ewald B, Gardner AW, Hatano Y, Lutes LD, Matsudo SM, Ramirez-Marrero FA, Rogers LQ, Rowe DA, Schmidt MD, Tully MA, Blair SN. How many steps/day are enough? For older adults and special populations. *Int J Behav Nutr Phys Act*. 2011;8:80.

191. Kang M, Bassett DR, Barreira TV, Tudor-Locke C, Ainsworth B, Reis JP, Strath S, Swartz A. How many days are enough? A study of 365 days of pedometer monitoring. *Res Q Exerc Sport*. 2009;80(3):445-453.

192. Tudor-Locke C, Burkett L, Reis JP, Ainsworth BE, Macera CA, Wilson DK. How many days of pedometer monitoring predict weekly physical activity in adults? *Prev Med*. 2005;40(3):293-298.

193. Barak S, Wu SS, Dai Y, Duncan PW, Behrman AL, Locomotor Experience Applied Post-Stroke (LEAPS) Investigative Team. Adherence to accelerometry measurement of community ambulation poststroke. *Phys Ther*. 2014;94(1):101-110.

194. 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.

195. Manns PJ, Tomczak CR, Jelani A, Haennel RG. Oxygen uptake kinetics: Associations with ambulatory activity and physical functional performance in stroke survivors. *J Rehabil Med*. 2010;42(3):259-264.

196. Vellone E, Savini S, Fida R, Dickson VV, Melkus GD, Carod-Artal FJ, Rocco G, Alvaro R. Psychometric evaluation of the Stroke Impact Scale 3.0. *J Cardiovasc Nurs*. 2015;30(3):229-41.

197. Chou CY, Ou YC, Chiang TR. Psychometric comparisons of four disease-specific health-related quality of life measures for stroke survivors. *Clin Rehabil.* 2015;29(8):816-29.

198. Duncan PW, Wallace D, Lai SM, Johnson D, Embretson S, Laster LJ. The stroke impact scale version 2.0. evaluation of reliability, validity, and sensitivity to change. *Stroke.* 1999;30(10):2131-2140.

199. Duncan PW, Bode RK, Min Lai S, Perera S, Glycine Antagonist in Neuroprotection Americans Investigators. Rasch analysis of a new stroke-specific outcome scale: The stroke impact scale. *Arch Phys Med Rehabil.* 2003;84(7):950-963.

200. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: Guidelines for the six-minute walk test. *Am J Respir Crit Care Med.* 2002;166(1):111-117.

201. Fulk GD, He Y, Boyne P, Dunning K. Predicting home and community walking activity post-stroke. *Stroke.* 2017;48:406-411. PubMed PMID: 28057807.

202. Donovan K, Lord SE, McNaughton HK, Weatherall M. Mobility beyond the clinic: The effect of environment on gait and its measurement in community-ambulant stroke survivors. *Clin Rehabil.* 2008;22(6):556-563.

203. Muren MA, Hutler M, Hooper J. Functional capacity and health-related quality of life in individuals post stroke. *Top Stroke Rehabil.* 2008;15(1):51-58.

204. Fulk GD, Echternach JL, Nof L, O'Sullivan S. Clinometric properties of the six-minute walk test in individuals undergoing rehabilitation poststroke. *Physiother Theory Pract.* 2008;24(3):195-204.

205. Eng JJ, Dawson AS, Chu KS. Submaximal exercise in persons with stroke: Test-retest reliability and concurrent validity with maximal oxygen consumption. *Arch Phys Med Rehabil.* 2004;85(1):113-118.

206. Wevers LE, Kwakkel G, van de Port IG. Is outdoor use of the six-minute walk test with a global positioning system in stroke patients' own neighbourhoods reproducible and valid? *J Rehabil Med.* 2011;43(11):1027-1031.

207. Kosak M, Smith T. Comparison of the 2-, 6-, and 12-minute walk tests in patients with stroke. *J Rehabil Res Dev.* 2005;42(1):103-107.

208. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, Coke LA, Fleg JL, Forman DE, Gerber TC, Gulati M, Madan K, Rhodes J, Thompson PD, Williams MA; American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology, Council on Nutrition, Physical Activity and Metabolism, Council on Cardiovascular and Stroke Nursing, and Council on Epidemiology and Prevention. Exercise standards for testing and training: A scientific statement from the American Heart Association. *Circulation.* 2013;128(8):873-934.

209. National Cancer Institute. Common terminology criteria for adverse events (CTCAE) version 4.0. *NIH Publication No 09-5410.* 2009.

210. Kluding PM, Pasnoor M, Singh R, D'Silva LJ, Yoo M, Billinger SA, LeMaster JW, Dimachkie MM, Herbelin L, Wright DE. Safety of aerobic exercise in people with diabetic peripheral neuropathy: Single-group clinical trial. *Phys Ther.* 2015;95(2):223-234.

211. Roig M, Skriver K, Lundbye-Jensen J, Kiens B, Nielsen JB. A single bout of exercise improves motor memory. *PLoS One.* 2012;7(9):e44594.

212. Southwick SM, Davis M, Horner B, Cahill L, Morgan CA 3rd, Gold PE, Bremner JD, Charney DC. Relationship of enhanced norepinephrine activity during memory consolidation to enhanced long-term memory in humans. *Am J Psychiatry.* 2002;159(8):1420-1422.

213. Mang CS, Campbell KL, Ross CJ, Boyd LA. Promoting neuroplasticity for motor rehabilitation after stroke: Considering the effects of aerobic exercise and genetic variation on brain-derived neurotrophic factor. *Phys Ther.* 2013;93(12):1707-1716.

214. Winter B, Breitenstein C, Mooren FC, Voelker K, Fobker M, Lechtermann A, Krueger K, Fromme A, Korsukewitz C, Floel A, Knecht S. High impact running improves learning. *Neurobiol Learn Mem*. 2007;87(4):597-609.

215. Ivey FM, Hafer-Macko CE, Macko RF. Exercise training for cardiometabolic adaptation after stroke. *J Cardiopulm Rehabil Prev*. 2008;28(1):2-11.

216. Ivey FM, Macko RF, Ryan AS, Hafer-Macko CE. Cardiovascular health and fitness after stroke. *Top Stroke Rehabil*. 2005;12(1):1-16.

217. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381.

218. Fitzmaurice GM, Laird NM, Ware JH. *Applied longitudinal analysis*. 2nd ed. Hoboken, NJ: John Wiley & Sons, Inc.; 2011.

219. Lang CE, Strube MJ, Bland MD, Waddell KJ, Cherry-Allen KM, Nudo RJ, Dromerick AW, Birkenmeier RL. Dose response of task-specific upper limb training in people at least 6 months poststroke: A phase II, single-blind, randomized, controlled trial. *Ann Neurol*. 2016;80(3):342-354.

220. Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. *J Am Geriatr Soc*. 2006;54(5):743-749.

221. Guo Y, Logan HL, Glueck DH, Muller KE. Selecting a sample size for studies with repeated measures. *BMC Med Res Methodol*. 2013;13:100-2288-13-100.

222. Friedman L, Furberg C, DeMets D. *Fundamentals of clinical trials*. 4th ed. New York, NY: Springer; 2010.

223. Benjamini Y, Hochberg Y. Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J R Statist Soc B*. 1995;57(1):289-300.

224. Danks KA, Roos MA, McCoy D, Reisman DS. A step activity monitoring program improves real world walking activity post stroke. *Disabil Rehabil*. 2014;36(26):2233-2236.

225. Broderick J, Brott T, Kothari R, Miller R, Khoury J, Pancioli A, Gebel J, Mills D, Minneci L, Shukla R. The Greater Cincinnati/Northern Kentucky Stroke Study: Preliminary first-ever and total incidence rates of stroke among blacks. *Stroke*. 1998;29(2):415-421.

226. Kissela B, Schneider A, Kleindorfer D, Khoury J, Miller R, Alwell K, Woo D, Szaflarski J, Gebel J, Moomaw C, Pancioli A, Jauch E, Shukla R, Broderick J. Stroke in a biracial population: The excess burden of stroke among blacks. *Stroke*. 2004;35(2):426-431.

227. Kleindorfer D, Broderick J, Khoury J, Flaherty M, Woo D, Alwell K, Moomaw CJ, Schneider A, Miller R, Shukla R, Kissela B. The unchanging incidence and case-fatality of stroke in the 1990s: A population-based study. *Stroke*. 2006;37(10):2473-2478.

