Title: A Novel Strategy to Decrease Fall Incidence Post-Stroke
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Protocol

1. Project Title: A Novel Strategy to Decrease Fall Incidence Post-Stroke

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3. Abstract:

Background/Purpose: Falls are a common and costly complication following stroke. While residual walking and balance deficits contribute substantially to long-term disability, of greater concern for this population is the incidence of falls. Between 40% and 70% of individuals fall within their first year post-stroke. Individuals who fall have increased incidence of serious adverse outcomes, including fractures, depression, and mortality. A primary goal of stroke rehabilitation is to improve mobility in the presence of motor, balance, and visual-spatial deficits. The conundrum all stakeholders must face is that increased mobility may increase risk for falls, whereas limiting walking and general mobility will lead to a multitude of deficits associated with inactivity, including recurrent stroke. Because of these serious consequences, there is an urgent need in the rehabilitation of Veterans with stroke to both identify those who are at fall risk and develop intervention strategies that will reduce fall incidence while increasing mobility. Backward walking has recently emerged as both a potential predictor of fall incidence as well as an intervention modality to prevent future falls. However, it has not yet been assessed under the rigors of a controlled trial. We will conduct a randomized controlled trial with three specific aims to examine 1) the effectiveness of Backward Walking Training (BWTraining) early poststroke in decreasing falls, 2) the timing of BWTraining delivery to increase Backward Walking speed (BWSpeed), and 3) the relationship between BWSpeed and prospective fall incidence.

Subjects: One-hundred twenty-eight individuals, 2 months post-stroke, will participate. Additional study criteria include: 1) ambulatory with gait speed < 0.8 m/s; 2) community-dwelling; 3) Berg Balance Scale < 42; 4) absence of other neurological conditions; 5) discharged from physical therapy services; 6) stable cardiac status; 7) absence of lower extremity orthopedic impairments or pain that limits gait ability.

Methods: Following baseline assessment, participants will be randomized to BWTraining at 2 months (Immediate group) or 1-year post-stroke (Delayed group). The intervention consists of 18 sessions (3X/week for 6 weeks) of BWTraining: 20–30 minutes of step training using a Body Weight Support and Treadmill system (BWST) followed by 15 minutes of overground gait training delivered by a physical therapist-led team. Participants will walk backward overground with assistance as warranted to transfer stepping skills from the BWST environment to overground. The Immediate group will be followed prospectively for 1-year and compared to the Delayed group to determine the effectiveness of BWTraining in decreasing falls (Specific Aim#1). BWSpeed post-intervention will be compared between groups to assess the timing effect of BWTraining (Specific Aim #2). The Delayed group will be followed prospectively for 1-year prior to BWTraining, to determine if BWSpeed at 2-months is a predictor of fall incidence in the first year post-stroke (Specific Aim #3).

Outcome Measures: Fall incidence 2-months to 1-year post-stroke is our primary outcome measure. Secondary measures include forward and backward walking gait speed, dynamic balance measured by the Functional Gait Assessment, fall self-efficacy measured by the Activities-Balance Confidence Scale and gait kinematics.
Data Analysis Plan: The total number of falls per patient month for the immediate and delayed intervention groups will be calculated, and using a nonparametric ratio estimate, point and interval estimates for the average hazard for each group will be determined. The ratio of the two individual group estimates, 95% confidence limits and P-values will be obtained. Forward stepwise ordinal logistic regression will be used to determine the independent relationship between BWSpeed at 2-months post-stroke and 1-year fall incidence of those in the Delayed intervention group.

4. Background:

Falls are a Common and Serious Complication after Stroke.
Stroke is the leading cause of chronic disability world-wide[1] and in the United States more than 795,000 persons experience a new or recurrent stroke each year.[2] Impairments of motor control and the subsequent functional limitations in ambulation ability are the most common manifestations of stroke. Falls among community-dwelling individuals with stroke are widely reported in the literature, with incidence of falls reported to be 40% and 70%.[3, 4] When tracked over a period of four to six months, community-dwelling individuals with stroke were two times more likely to fall than the average elderly population.[5, 6] Individuals post-stroke have a higher fall risk secondary to persisting neurological impairments such as motor,[7, 8] sensory[9] and vision[10] deficits. These deficits can directly affect balance and mobility, thereby increasing fall risk.

The consequences of falls can have a negative physical and psychosocial impact for individuals post-stroke. Physical injuries following a fall for those post-stroke include both fractures[7, 11] and soft tissue injuries[3, 11] with overall injury incidence reported to be 15%-50%.[3, 7, 9, 11] Hip fractures are the most common fractures reported; a 2.1% rate of hip fractures has been reported to occur in individuals with stroke after a fall.[7] There is a two-to four-fold increase in the risk of hip fractures in individuals with stroke than in those without.[12-14] Negative psychosocial impact of falls on individuals with stroke include fear of falling, reduced mobility, greater disability, depression, increased stress experienced by the caregiver, and social isolation.[3, 4, 6] Fear of falling often leads to activity restriction as reported by Mackintosh et al.,[11] who determined that 44% of individuals post-stroke restricted their activities due to fear of falling. Belgen reported that individuals with stroke who fell were 5.6 times more likely to be afraid of falling.[15] This fear of falling leads to reduced falls-related self-efficacy, resulting in a loss of functional independence.[15] Community-dwelling individuals with stroke who have fallen have also been found to be less socially active and more depressed.[3] Depression and reduction in social activity can result in further deconditioning and reduction in physical activity, further increasing the risk of falls in these individuals.[14] Given this devastating cascade of events that can occur following a fall in this population and the enormous health-care dollars associated with a fall and its potential sequelae, there is an urgent need to develop rehabilitation strategies that will decrease fall incidence in individuals post-stroke. Specific Aim 1 will examine the efficacy of BWTraining to decrease fall incidence in the first year post-stroke.

Backward Walking Training is an Emerging Intervention for Post-Stroke Gait.
BWTraining has been used as a strategy in the rehabilitation of orthopedic conditions as it produces less mechanical strain on the knee joint[16] and it is an effective means for increasing the strength and power of the quadriceps.[17] BWTraining is also an option to improve aerobic capacity as backward walking can increase energy expenditure to levels high enough to maintain cardiorespiratory fitness.[18] BWTraining to improve gait and dynamic balance post-stroke is a more recent application of this modality. Yang et al.,[19] demonstrated in people 5-7 months post-stroke that the addition of a 30-minute BWTraining to each conventional care session delivered 3x/week for three weeks resulted in a significant improved forward walking speed, stride length, and gait symmetry when compared to conventional training alone. However, with the lack of an active control group it is not known if these benefits were simply due to the additional therapy. In high-functioning stroke survivors who were able to ambulate without an assistive device or orthotic, Weng and colleagues[20] reported that walking speed as well as balance and lower extremity motor function was significantly more improved for those in a BWTraining compared to those who received dose-matched conventional therapy. Although *total* training time was matched, these results need to be interpreted cautiously as the *amount of gait training* in the conventional therapy group was not standardized nor matched to the *amount of backward gait training*. The foundation for this current proposal resulted from our case-series with individuals post-stroke[21] and our recently conducted pilot RCT that compared BWTraining to standard balance training in subsequent balance and gait ability[22, 23] Individuals in the BWTraining group demonstrated larger improvements in forward and backward gait speed, balance confidence and balance ability compared to those in dose-matched balance training group. Despite the limitations of these small prior studies, they provide enticing evidence that BWTraining may be a post-stroke gait rehabilitation strategy superior to current approaches. A current gap in the investigation of this novel rehabilitation strategy is its efficacy in reducing future fall-incidence. Secondary to the relationship between BWSpeed and fall incidence in the elderly, we hypothesize that a BWTraining would be an effective modality in decreasing falls. Specific Aim 1 will test this hypothesis. BWTraining has been assessed in both the acute and chronic post-stroke population but the effects of timing of this intervention to increase BWSpeed have not been compared directly under the rigors of a randomized controlled trial. Specific Aim 2 will test the effects of intervention timing and will provide important information regarding when BWTraining may be most beneficial for those post-stroke in increasing BWSpeed, an indicator for fall-risk.
Identification of Fall Risk is Necessary to reduce Future Falls.
Identification of individuals at risk for falling is an important aspect of post-stroke rehabilitation in order to implement pro-active measures both intrinsically (related to the individual) and extrinsically (associated with their environment). Clinical tests of walking speed and postural balance to predict fall risk after stroke have been reported previously.[24-26] Gait speed has been reported to predict fall risk both in community-dwelling elderly[27-29] and in individuals post-stroke.[30] A recent, intriguing finding, worthy of further exploration is that backward, more so than forward walking identified, in a cohort of community-dwelling elderly, those that had fallen in the previous 6 months.[31] Walking backward at a speed less than 0.6 m/s identified 100% of fallers and those who walked backward at a speed less than 0.4 m/s had a 3.2 times greater likelihood of being a faller than those who walked faster. In comparison, forward walking velocity at a cut off of 1.0 m/s only identified 83% of fallers. If BWSpeed is a more reliable predictor of falls than forward walking speed in the post-stroke

population is not known. Given the difficulty post-stroke of combining hip extension with knee flexion, necessary to take a backward step, we hypothesize this BWSpeed-fall incidence relationship exists post-stroke as well. Specific Aim 3 will test the hypothesis that BWSpeed at 2-months post-stroke is a significant predictor of fall incidence over the next year 1 year period.

Backwards walking challenges postural stability in a controlled and safe environment with a dynamic task similar to the type known to induce falls*.*

Most falls leading to injuries occur while walking and of these falls the majority occurs in the sideways or backwards directions.[32] This is not surprising as there are greater postural demands in backward compared to forward walking.[33] Many everyday walking activities, such as opening a door to enter a room, approaching a chair to sit down, or opening the refrigerator require stepping backwards. Compensatory stepping in all directions is an important strategy necessary for preserving stability.[34] Because stepping responses are necessary for fall prevention, the difficulties in taking several consecutive large and rapid steps backward might be a factor contributing to fall incidence post-stroke. A decreased ability to take rapid compensatory steps has been shown to be closely related to measures of balance and fall risk.[35] Straube and colleagues[36] trained individuals post-stroke in variable stepping contexts (sideways, backwards) and reported subsequent improvements in dynamic balance activities. While we recognize that falls post-stroke are multifactorial[7], the inability to combine hip extension with knee flexion required for backward stepping may be a contributor to the prevalence of falls in this population. Repetitive practice of this movement combination in a controlled environment may facilitate its expression when necessary to prevent a fall. We hypothesize that BWTraining will improve balance and falls self-efficacy and decrease fall incidence in the first year post-stroke.

Backwards walking effectively engages cerebral pathways damaged by stroke.

In addition to the increased challenge to postural stability BWTraining affords, there are additional benefits to this rehabilitation strategy. Compared with forward, backward walking is more effective at inducing cerebral activation.[33, 37] Examination of cortical activity during backward walking revealed an increased oxygenated hemoglobin (oxyHb) response compared to forward, suggestive of increased cortical processing, in the Supplementary Motor Area (SMA), Primary Motor Cortex (PMC), and Superior Parietal Lobule.[33] This outcome is similar to that of an animal model study that demonstrated more intense activity in the medial motor cortices during backward compared to forward walking.[38] This greater cortical activation may promote cortical neural plasticity by more intensely engaging the circuits damaged by stroke. Backward walking also provides a means for high repetition of practice, which is known to be a prerequisite to induce cortical reorganization.[39]

Backwards walking allows patients to practice coordinated locomotion independent from the abnormal patterns that are characteristic of forward walking after stroke.

In humans, evidence suggests that the neural control of forward and backward walking may largely originate from the same basic neural circuitry.[40, 41] Hoogemaker et al.,[42] has postulated a conceptual framework suggesting pattern generating circuits in the spinal cord provide the basic rhythms of the respective gait pattern, but that the details of the pattern are dictated both by spinal and supraspinal circuits. Kinematic analysis of leg movements has supported this idea, especially for the proximal joints.[16, 40, 41, 43, 44] Due to the many similarities in the kinematics and kinetics of forward and backward walking, when a video of an individual walking backward is reversed, the differences with this same individual walking forward are barely noticeable.[45] Many authors have suggested that these two forms of locomotion are generated by the same basic neural mechanisms.[43, 44, 46, 47] Hip extension is more active in backward walking due to the concentric contraction of knee flexors during early swing phase[16, 44] which may be beneficial at improving lower limb coordination after stroke. Training under conditions with a greater demand for muscle activation may facilitate activity in muscles weakened secondary to stroke. An advantage of BWTraining in individuals post-stroke is that a backwards step requires hip extension with simultaneous knee flexion to bring the lower extremity posterior to the trunk. This movement combination is often difficult after stroke due to the re-emergence of the predominant flexion synergy[48] that often occurs following CNS damage. Repetitive movement that requires activation of hip extensors with knee flexors, out of the predominant flexor synergy pattern, as required in backward walking, may improve muscle activation and subsequent motor control to transfer to improved muscle activation and appropriate kinematics during forward walking. Although causes of falls are multifactorial, it is important to note that a primary physical contributing factor to a fall is the difficulty and/or inability to take a backward step to maintain balance.[49] Training in backward stepping may be an effective strategy to regain coordinated hip extension with knee flexion needed to efficiently take a backward step to maintain balance, remain upright and prevent a fall.

5. Specific Aims:

Aim #1: Test the hypothesis that 1-year fall incidence is decreased for participants randomized to BWTraining administered at 2-months post-stroke (versus usual care comparison group).
Hypothesis #1a: BWTraining at 2-months post-stroke reduces the number of falls over the next year.
Hypothesis #1b: BWTraining at 2-months post-stroke increases gait speed, improves balance and increases balance confidence over the next year.
Aim #2: Test the hypothesis that BWTraining at 2 months (immediate) vs. 1-year (delayed) post-stroke is more effective at improving BWSpeed.
Hypothesis #2a: BWSpeed improvement from 2- to 14-months post-stroke is greater when BWTraining is delivered at 2 months versus 1 year post-stroke.
Hypothesis #2b: Improvements in forward gait speed, Functional Gait Assessment and Activities-Balance Confidence Scale from 2- to 14-months post-stroke are greater when BWTraining is delivered at 2 months versus 1 year post-stroke.
Aim #3: This exploratory aim will test the hypothesis that BWSpeed at 2-months post-stroke is a significant predictor of fall incidence over the next year 1 year period, after adjusting for other covariates.
Hypothesis #3: BWSpeed at 2-months will be a significant predictor of fall incidence during the first year post-stroke, after adjusting for other covariates.

6. Research Plan:

This prospective, single-blind, RCT enrolling individuals at 2-months post-stroke is designed to address the study's three Specific Aims (See Figure below). Participants will be randomized to either Immediate (2-months post-stroke) or Delayed (1-year post-stroke) BWTraining. The primary endpoint for SA#1 and SA#3 will be Assessment D at 1-year post-stroke. The primary endpoint for SA#2 will be Assessment E at approximately14-months post-stroke. Secondary assessment time points (Assessments B and C) will allow us to examine potential mechanisms of recovery contributing to our primary results. Individual treatment allocations will be in sealed envelopes. Envelopes will be opened only on enrollment of the next eligible participant. We will recruit 142 individuals post-stroke. This will permit up to a 10% attrition rate and still provide a sufficient participant pool to address our Specific Aims.

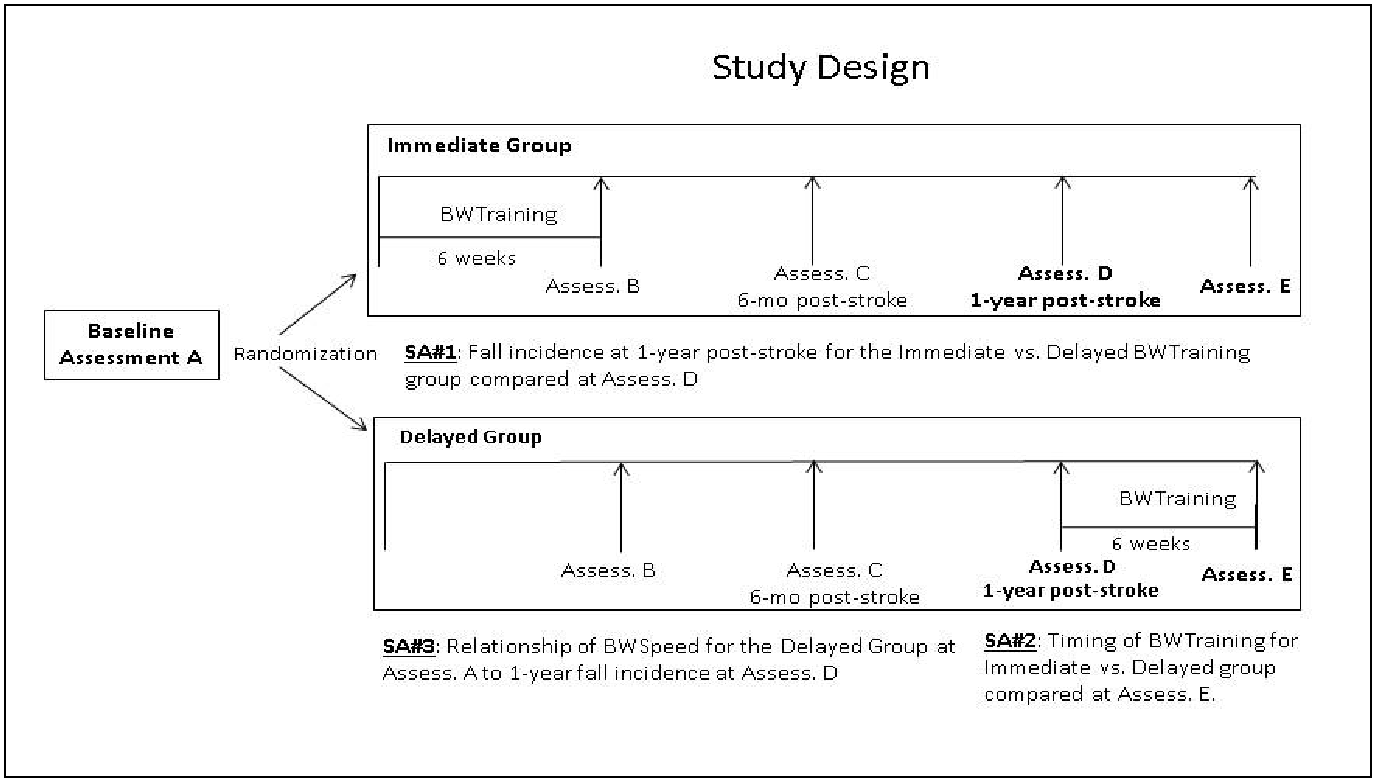

Figure. Participants will be randomized into an Immediate (BWTraining at 2-months post-stroke) or a Delayed (BWTraining at 1-year post-stroke) group. Primary assessment points are A (2-months post-stroke), D (1-year post-stroke) and E. Secondary assessment points are B and C (6-months post-stroke).

Participant Recruitment and Screening. Priority for participation in this study will be given to volunteers who are Veterans. To optimize our capability to recruit Veterans we will conduct the study's assessments and intervention at two locations: 1) The Malcom Randall VA Medical Center in Gainesville FL, and 2) Brooks Rehabilitation in Jacksonville, FL. Utilizing these two recruitment sites will assure us of reaching our planned recruitment of 142. Individuals post-stroke will be recruited from: 1) VA BRRC site: a. Database (IRB#457-1999) of the Malcom Randall VA BRRC, a VA RR&D Center of Excellence. The database contains over 400 individuals with stroke who have been screened by a neurologist and interdisciplinary team to gather preliminary information about medical, motor and cognitive status. All individuals in the database have signed informed consent and agreed to be contacted for research participation. b. VA Informatics and Computing Infrastructure (VINCI) is an initiative to improve researchers' access to VA data and to facilitate the analysis of those data while ensuring Veterans' privacy and data security. c. Clinician referrals from Select Rehabilitation – potential participants will be provided an IRB-approved study flier and if interested will provide signed authorization to be contacted by study personnel. 2) Brooks site: a. Brooks Active Research Registry: Brooks Rehabilitation in Jacksonville, FL is one of the nation's largest inpatient rehabilitation hospitals and stroke is their largest diagnostic category, with approximately 600 stroke admissions per year. Research studies within this entity are conducted under the auspices of their Clinical Research Center. Brooks Rehabilitation Clinical Research Center maintains an IRB-approved registry of individuals who have experienced a neurological injury, approximately 640 individuals with a stroke diagnosis who have signed HIPAA Authorization and can be contacted regarding research trial participation. Potential participants will be contacted via phone and a phone screen will be conducted. The phone screen script is provided in a separate document. If individuals pass the phone screen, they will be invited and scheduled for an in-person screen. Information obtained from the phone screen will only be shared with study personnel and will be stored in a locked cabinet in a locked room. b. Individuals who respond to an IRB-approved advertisement. They will undergo phone screen as above. c. Individuals who signed a Brooks Notice of Privacy Practices upon Brooks admission (which indicates their information may be used for research) will have their medical records reviewed by study personnel and if appropriate will be provided an IRB-approved study flier. If interested, they will have the opportunity to sign the Screening Informed Consent and complete the Screening Assessment while they are an inpatient. If they prefer to wait until they are discharged from inpatient rehabilitation,they will be contacted at six-weeks post-stroke to determine their continued interest and confirm eligibility. Women and members of diverse ethnic and racial groups will be actively recruited.

Inclusion criteria: 1) Diagnosis of unilateral stroke, 2) ≥ 2 months ≤ 4 months post-stroke, 3) Berg Balance Scale ≤ 42, 4) Self-selected 10 meter gait speed < 0.8 m/s, 5) Able to ambulate at least 10 feet with maximum 1 person assist, 6) Medically stable, 7) 18-95 years of age, 8) living in the community, 9) Unilateral lower extremity paresis confirmed by a score of < 32 on the Fugl-Meyer Motor Assessment[50], 10) Physician approval for patient participation.

Exclusion criteria: 1) Presence of neurological condition other than stroke, 2) Serious cardiac conditions (hospitalization for myocardial infarction or heart surgery within 3 months, history of congestive heart failure, documented serious and unstable cardiac arrhythmias, hypertrophic cardiomyopathy, severe aortic stenosis, angina or dyspnea at rest or during activities of daily living). Anyone meeting New York Heart Association criteria for Class 3 or Class 4 heart disease will be excluded, 3) Severe arthritis or orthopedic problems that limit passive ranges of motion of lower extremity (knee flexion contracture of -10°, knee flexion ROM < 90°, hip flexion contracture > 25°, and ankle plantar flexion contracture > 15°), 4) Severe hypertension with systolic greater than 200 mmHg and diastolic greater than 110 mmHg at rest, that cannot be medically controlled into the resting range of 180/100 mmHg. 5) Pain upon ambulation, , 6) Unable to ambulate at least 150 feet prior to stroke, or experienced intermittent claudication while walking less than 200 meters, 7) Living in a skilled nursing facility, 8) History of serious chronic obstructive pulmonary disease or oxygen dependence, 9) Non-healing ulcers on the lower extremity, 10) Uncontrollable diabetes with recent weight loss, diabetic coma or frequent insulin reactions, 11) On renal dialysis or presence of end stage liver disease, 12) Pulmonary embolism within previous 6 months, 13) History of major head trauma, 14) History of sustained alcoholism or drug abuse in the last six months, 15) Current enrollment in a clinical trial to enhance stroke motor recovery, 16) Intracranial hemorrhage related to aneurysmal rupture or an arteriovenous malformation, 17) Injection of lower extremity muscle relaxant in the past 6 months

Inclusion and Exclusion criteria will initially be determined by medical record review. If following the medical record review a potential participant remains eligible, they will be scheduled for an in-person screen to determine if they meet the criteria listed below. Potential participants will sign the screening Informed Consent Form and then the following screening assessments will be administered:

1. Berg Balance Scale[51]: This tool consists of 14 items that assesses static and dynamic standing balance, ability to sit, stand up and transfer.
2. 10 Meter Walk Test: Participants, wearing a gait belt and guarded by a licensed physical therapist, will traverse a total distance of 14 meters, two times at their self-selected walking pace. The time to traverse the middle 10 meters will be recorded with a stop watch.
3. Lower Extremity Fugl-Meyer Motor Assessment: The participant's ability to move their paretic lower limb will be assessed in the supine, sitting and standing position.
4. Range of Motion: Range of Motion of the hips, knees and ankles of both lower limbs will be assessed. This assessment will take place in the supine and sitting positions.
5. Three-Meter Backward WalkTest. The test consists of a 1 meter warm-up distance, a timed 3 meter distance, followed by an additional 1 meter to continue walking. Participants will walk this distance two times and the speed will be averaged.

Participants who meet eligibility criteria following the screening assessment will be invited to sign Part 2 Consent, the Intervention Informed Consent Form. Intervention Informed Consent allows for baseline testing and study participation.

Following baseline assessment (Assessment A) participants will be randomized to either the Immediate Group (initiate BWTraining within 1-week of Assessment A) or the Delayed Group (initiate BWTraining at 1-year post-stroke).

BWTraining Intervention. The intervention consists of 18-21 sessions, 3x/week for 6 weeks. BWTraining will occur both on a treadmill and overground. BW training will consist of 20–30 minutes of step training with a BWST system, manual assistance provided by trainers, with rest periods provided as warranted followed by 15 minutes of overground gait training. A 20–30 min period of actual stepping on the treadmill is the goal with rest periods as needed. Each training session may last up to 1 hour and 30 minutes including time for warm-up, stretching, and cool down. Participants will be fitted with a harness around their hips and torso, which will be attached to an overhead support system directly above the treadmill. From a stationary position, the treadmill belt will gradually be increased in speed with intervention trainers assisting participant to step backward with their paretic leg, their non-paretic leg (if needed) and at the hips for weight-shift.
Training targets: The overall goal is to enable the participant, by the end of training, to walk independently for a total of 20 minutes in four, 5 minute bouts at 0% BWS with good stepping kinematics. Progression of training will be accomplished by: (1) gradually decreasing BWS from 40% to 0%, (2) initiating treadmill speed just below participant's overground backward walking speed, increasing as able and as tolerated, and (3) providing manual assistance initially when the participant is unable to independently step or control upright posture, and decreasing manual assistance to afford skill and control progression by the participant.

Outcome Measures. Participants' assessments will be stored in a secured study database, password protected, accessible only to study employees. Each participant will be given a study ID with assessments recorded and stored under the study ID. Hard copy folders will be stored in a locked filing cabinet in a locked room with access only available to study personnel. Participants in both groups will be assessed in parallel throughout the study timeline. Assessments will be conducted five times according to the study design above:

1. Assessment A (baseline, prior to randomization)
2. Assessment B 6 weeks following randomization
3. Assessment C 6-months post-stroke
4. Assessment D 1-year post-stroke
5. Assessment E 6 weeks following Assessment D.

The assessment battery will be conducted in a 1.5 hour appointment. Assessments are similar to those encountered in physical rehabilitation and should not result in undue fatigue, but participants will be able to rest as needed. All outcome measures will be conducted by licensed physical therapists, blinded to group assignment. The physical therapist will be beside the participant during all physical assessments of gait and balance. All therapists will receive standardized training and will be required to pass a competency exam to ensure standardization of the outcome measure protocol across assessors. Assessments are:

10 Meter Walk Test. Individuals will be given a 3 meter warm-up distance for walking, preceding the 10 meter distance and 3 meters beyond the 10 meters to continue walking. The time that it takes to traverse the 10 meters at the subject's usual pace will be recorded. Participants will walk this distance two times and the speed will be averaged.
Three-Meter Backward WalkTest. We will use this test to collect our variable of interest, BWSpeed. The test consists of a 1 meter warm-up distance, a timed 3 meter distance, followed by an additional 1 meter to continue walking. Participants will walk this distance two times and the speed will be averaged.
Functional Gait Assessment (FGA),[52] a 10-item clinical gait and balance test during which participants perform the following activities: walk at normal speeds, at fast and slow speeds, with vertical and horizontal head turns, with eyes closed, over obstacles, in tandem, backward and while ascending and descending stairs. Excellent test-retest[53] and intra- and inter-rater reliability[54] has been established patients post-stroke.
Activities-Specific Balance Confidence Scale (ABC): This 16-item self-report measure is used to assess perceived efficacy (self-reported confidence) in maintaining balance while performing a number of activities common in community-dwelling older adults.
Berg Balance Scale (BBS):[51] This tool consists of 14 items that assesses static and dynamic standing balance, ability to sit, stand up and transfer. From our previous work characterizing and identifying risk factors for falls post-stroke[55], BBS scores $\leq$ 42/56 was the single best predictor of multiple/injurious falls. This assessment is ubiquitously used in stroke rehabilitation and will aide in describing our study cohort. This has been tested in a stroke population and has well-established reliability and validity.
Lower-Extremity Fugl-Meyer Motor Score:[56] This tool consists of 17 items that assess motor control of the lower extremity as participants move their hip, knee and ankle in lying, sitting and standing is probably the most widely known scale of motor and sensory recovery after stroke. This assessment will provide a description of lower extremity impairment and aide in describing our study cohort.
Four-Step Square Test:[57] This clinical test of dynamic standing balance examines the ability to step over small objects, change direction and includes taking a backwards step. In a

study that confirmed the feasibility and validity of this assessment for individuals post-stroke, those who reported a fall scored > 15 sec to complete the assessment.[58]

Timed Up and Go Test: This clinical assessment of gait and balance consists of a participant standing up from a chair, walking three feet straight ahead, turning around and returning to the chair to sit down.

Modified Falls Efficacy Scale (MFES)[59] is a 14-item questionnaire based on the Falls Efficacy Scale (FES),[60] modified for people with chronic stroke. It includes the 10 items from the FES plus 4 items considered complex for people with stroke and is designed to measure self-perceived fear of falling during task performance. Significant differences in MFES scores between patients in a Falls and Balance Clinic and healthy older adults ($p < 0.05$) attests to the scales' validity.[59]

Modified Rankin Scale (mRS): This 0-5 scale is a functional outcome measure of stroke that reflects the overall level of disability. The clinician assessor scores the participant based on their impression and observation of the participant over the course of the evaluation process.

Kinesiologic assessment of walking: To more explicitly describe changes in participants' gait as a result of the intervention, secondary outcome measures will include:

1) Assessment of kinematics using a passive motion-capture system:Hip, knee and ankle angle data from the LE's will be acquired by placing reflective markers on the participant using a modified Helen Hayes marker set with rigid clusters on the pelvis and each thigh, shank and foot segments and recording the movement of these markers at 100 Hz using a 12 camera motion capture system (Vicon Motion Capture Systems, Oxford, UK). Data will be processed using Visual 3D (C-Motion, Inc., Germantown, MD). Intersegmental joint moments (normalized to body mass) will be calculated using standard 3D inverse dynamics techniques.

2) Assessment of kinetics and spatio-temporal movement characteristics:Three-dimensional ground reaction forces will be acquired under each foot as participants walk across force plates. The force plates are flush with the floor and are not an obstacle or tripping hazard. The participant will be asked to stand or walk in a specific location corresponding with the force plates embedded in the floor. This will be done while they also are wearing the EMGs and reflective markers so that all data are captured simultaneously. GRF data will be normalized to body weight. Sagittal plane hip, knee and ankle joint moment impulses and the vertical GRF will be calculated.

3) Spatial-Temporal gait variables of stride time, stride length, step time, step length and step width will be captured during forward and backward walking across a GAITRite instrumented walkway (CIR Systems Inc, Havertown, PA). Additionally, the participant will be asked to walk over a 12' instrumented walkway. The walkway appears like a basic carpet with embedded switches to record foot falls and placement. The edges of the carpet walkway will be taped down to minimize the possibility of tripping on the edge of the carpet. Participants will be guarded by the physical or occupational therapist at all times and/or an overhead harness may be used. The instrumented walkway (carpet) will provide quantitative data regarding the spatial and temporal characteristics of standing and walking.

4) Assessment of muscle activation using surface electromyography (EMG) By analyzing the electrical activity generated during muscle contraction or limb movement, EMG allows us to develop a better understanding of how the nervous system's control of movement is disrupted following stroke and whether this control is affected by the intervention. Using standard surface preparation (cleaning the skin with water or alcohol pad, shaving of excess hair) and electrode placement, surface EMGs will be collected from lower extremity and trunk muscles using surface EMG electrodes. EMG sensors will be attached

to the skin with double-sided hypoallergenic medical tape. Before the data collection, functional tests will be performed while each EMG channel is examined to assure clear signals and to check for crosstalk.

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Fall Incidence. In addition to the assessments described above that will be conducted at the 5 specific time points, fall incidence will be monitored throughout the study for each participant using the international standards for defining and reporting falls,[61] including the following definition for a fall: "A person has a fall if they end up on the ground or floor when they did not expect to. Most often a fall starts while a person is on their feet, but a fall could also start from a chair or bed. If a person ends up on the ground, either on their knees, their belly, their side, their bottom, or their back, they have had a fall." This explanation will be provided to participants and caregivers and printed on monthly calendars issued at randomization. Participants and/or caregivers will place an "X" on the corresponding date if a fall occurs, and submit to their study site each month (even if no falls occurred). If a calendar is not received within one week of its expected return, study personnel will contact participants. Participants will be contacted to follow-up on reported falls using the Fall Characterization Questionnaire. Information collected for each fall will include presence and nature of any injury, location of the fall, and ability to get up independently after the fall. Three categories will be used to characterize falls outcome poststroke: multiple or injurious (M/I); single, noninjurious (S/NI); and nonfallers. Injurious falls will be defined as those resulting in serious injury: fracture, loss of consciousness, or hospital admission. This information will be collected in-person for those currently receiving the study intervention and via phone for participants who have either completed or have yet to begin BWTraining.

Monitoring Delayed BWTraining. Participants randomized to Delayed BWTraining (Usual Care) will be assessed at the same time points as the Immediate BWTraining Group, at Baseline (Assessment A), at 6-weeks post-enrollment (Assessment B) and at 6-months post-stroke (Assessment C). In addition to these on-site assessments, this group (as well as the Immediate BWTraining Group) will be monitored throughout the first year post-stroke for 1) Any usual and customary rehabilitation services and 2) Fall incidence.

1. Usual and Customary Rehabilitation services: Throughout study participation, for ethical reasons, subjects will be permitted to engage in usual and customary clinical rehabilitation services. Any rehabilitation services received outside of the study intervention will be tracked and described in written logs. All subjects will be provided a health utilization log and will complete a daily checklist to report the type (PT, OT, Speech) and the length (0.5 hr.; 0.75 hr.; 1.0 hr.). These logs will be returned (via post mail or email) on a monthly basis. Participants will receive a reminder email or phone call three days prior to the submission date. This monthly contact with those randomized to Delayed BWTraining will facilitate participant retention. Upon receipt of the intervention logs the study coordinator will call the participant to thank them. There will be no restrictions on the type of clinical rehabilitation service except that participants will be required to abstain from any that involve backward walking either over ground or on a treadmill.

2. Falls: As described above participants will be provided Monthly fall calendars upon enrollment, and asked to submit the monthly calendar (via post mail or email) whether they have fallen or not. Participants will receive a reminder email or phone call three days prior to the submission date. Upon receipt of the fall calendar, the study coordinator will call the participant to either: 1) thank them for returning the calendar, and/or 2) conduct a standardized questionnaire regarding fall specifics. Participants will have email and phone

access to the Study Coordinator and the Principal Investigator whom they will be instructed to contact with questions at any time.

Videorecording. For participants who signed the video recording consent, we will periodically videorecord training sessions. This will allow the intervention therapists to view the participant's training and strategize on how to progress the intervention. Videorecordings will also provide the therapists feedback on how they can best assist the participant. Assessment sessions will also be periodically recorded. This will provide assessment therapists feedback on their implementation of the assessments. Videorecordings may also be used in scientific presentations. Participants will be informed when videotaping is occurring

Data Analysis Plan: For Specific Aim #1 (primary outcome for entire study is the average fall rate per year), we will calculate the total number of falls per patient year for the Immediate intervention and Delayed intervention (control) groups, and use the actuarial method described below to estimate the average hazard rate in each group, and the overall hazard ratio. We will compare the Immediate and Delayed groups' fall rate at Assessment D, 1-year post-stroke. The analysis takes repeated falls within the same subject into account. Consider the number of falls, Y_{ij} for the j-th patient on treatment i (i=1,2) in the year, and T_{ij}, the time at risk for the subject (usually 1 year, less for withdrawals before then). The estimated average fall hazard for treatment i is the ratio estimator $H_i = \Sigma Y_{ij} / \Sigma T_{ij}$. Under nonparametric considerations, if the true average hazard over subjects and time for treatment i is Θ_i, then by the delta method, $\mathrm{Log}(H_i) - \log(\Theta_i)$ (Log=natural log) is asymptotically normal with mean zero and variance V_i, i=1,2 defined by

$$V_i=[\{ Var(Y_{ij})/(Mean\ Y_{ij})^2\} +\{ Var(T_{ij})/(Mean\ T_{ij})^2\} -\{2\ Cov\ (Y_{ij}, T_{ij})/(Mean\ Y_{ij})/(Mean\ T_{ij})\}]/N_i$$

with the means, variances, and covariance, the sample moments, and N_i is the sample size for treatment i. The log of the estimated average hazard ratio $\mathrm{Log}(H_2/H_1)$ is asymptotically normally distributed with mean $\mathrm{Log}(\Theta_2/\Theta_1)=\mathrm{Log}(\Theta_2)-\mathrm{Log}(\Theta_1)$ and asymptotic variance (V_1+V_2). This enables us to obtain a two-sided P-value and after taking natural anti-logs, a point estimate and 95% confidence interval for the true average hazard ratio.

Power analysis: The study is powered around Specific Aim 1, comparison of fall incidence at 1-year post-stroke for those in the Immediate versus the Delayed BWTraining groups. Although the analysis is valid for any within patient distribution of the number of falls and time at risk, we must make additional assumptions to calculate power. Dean and colleagues[62], in a study of post-stroke fall incidence reported an average of 1.5 falls per patient year, and hence we will plan for a 33% reduction from 1.8 falls per year to 1.2 falls per year, with 80% power at p=0.05. Using a Poisson rate of 1.8 vs. 1.2 falls per year we would require 64 subjects randomized to each group to be followed for one year. Although all data for withdrawals will be used up to the time of withdrawal, we shall recruit an additional 14 subjects (142 total) to assure we observe 128 patient years. We expect the actual distribution of falls to be more compact (less variable) then the Poisson, which allows unlimited falls for a patient. This suggests the real variance within a group will be lower than that suggested in the Poisson, making power a bit higher than stated here. We cannot quantify this, however. Power was derived via large sample approximations, and verified via 10,000 simulations.

All hard copy records will be stored in a locked filing cabinet in a locked office accessible only to study personnel. All electronic data will be stored on a VA secured server. Hard copy data collected at Brooks Clinical Research Center will be transported to the Gainesville VA BRRC via the Principal Investigator in a locked briefcase.

7. Possible Discomforts and Risks:

The risks undertaken in the walking therapy programs of the study are no greater than those in everyday physical therapy clinics where persons who have had a stroke are challenged daily to exercise, train, practice and improve beyond their current abilities. Safety in therapy is mandatory. Research personnel will walk beside participants during all aspects of the exercise intervention and all aspects of the assessment that assess gait and balance. Participants may experience some fatigue while being tested or during the therapy sessions. Should they become tired, they will be allowed to rest. Participants may experience temporary muscle soreness as they increase the use of their trunk and limbs during the walking intervention. There is a risk of falling during walking activities, but guarding by research personnel will minimize the risk. Stroke patients, including those in this study, are at risk for another stroke, coronary heart disease related event and cardiac related death, regardless of intervention.

8. Possible Benefits:

Subjects participating in this study may see improvements in their walking speed, balance, and/or the amount of walking that they are able to do. They may become more confident in their balance and walking ability.

9. Conflict of Interest:

There are no conflicts of interest apparent for any of the investigators.

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