

# **Respiratory Strength Training versus Respiratory Relaxation Training in the Rehabilitation of Physical Impairment, Function and Return to Participation Post-Stroke: Protocol for a Randomized Controlled Trial**

Dorian K. Rose, Gina Brunetti, Kathryn Cavka, J. Brooke Hoisington, Hannah Snyder, Wei Xue, Barbara K. Smith

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Table of Contents

Original Manuscript..... 5

Supplementary Files..... 28

    Figures ..... 29

        Figure 1..... 30

        Figure 2..... 31

    Multimedia Appendixes ..... 32

        Multimedia Appendix 0..... 33

Existing Peer-Review Reports from Funding Agencies (for protocols/proposals only)s ..... 34

    Existing Peer-Review Reports from Funding Agencies (for protocols/proposals only) 0..... 34

    Existing Peer-Review Reports from Funding Agencies (for protocols/proposals only) 0..... 34

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## Abstract

**Background:** Persistent disability in chronic stroke survivors is often attributed to arm or leg weakness; however, respiratory muscle weakness also impedes post-stroke rehabilitation, reduces quality of life, and increases risk of health complications. Respiratory complications are common after stroke and place patients at risk for both prolonged functional disability and mortality. Additionally, stroke survivors face ongoing cardiovascular disease that places them at risk for recurrent stroke.

**Objective:** The study objective is to compare the effects of two respiratory training programs, paired with an individualized flexibility, strengthening and cardiovascular exercise program, on physiologic, activity, and societal participation outcomes in chronic stroke survivors.

**Methods:** This study will be a randomized controlled trial. Participants are 80 community-dwelling adults with chronic stroke. In conjunction with a 24-session (3x/week for 8 weeks) American Heart Association (AHA)-informed whole-body exercise program, participants will be randomized to receive either respiratory strength training (RST) or respiratory relaxation training (RRT). Study intervention will be directed by a physical therapist and take place in a community fitness center. Outcome assessments will occur in a clinical research center. The primary outcome measures are maximal respiratory pressures. Secondary outcome measures include airway clearance, walking endurance, spatial-temporal gait characteristics, community walking, functional strength and fatigue, depression and societal participation measures. Longer-term societal participation is a complex domain that may be influenced by other factors beyond physical function.

Participants' health status will be monitored for 1-year following the intervention for falls, respiratory illness and hospitalizations. Additional sub-analyses will evaluate the effect of smoke exposure on short- and long-term outcomes. Outcome assessors are blinded to group assignment. RRT is an active comparator, but no pure control group is included.

**Results:** This study was funded March 2020 with enrollment commencing November 2020. Completion of enrollment is projected May 2025 with study projected end date of April 2026. Published results are anticipated Fall 2026. Results from this study will improve our understanding of the additive benefits of respiratory exercises on short and long-term physiologic, functional and societal gains for these individuals.

**Conclusions:** These data will be instructive to meet a current unmet rehabilitative need, to promote patient-centered care and contribute to decreasing morbidity and mortality in chronic stroke survivors. Clinical Trial: ClinicalTrials.gov: NCT05819333

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## Original Manuscript

**Title:** Respiratory Strength Training versus Respiratory Relaxation Training in the Rehabilitation of Physical Impairment, Function and Return to Participation Post-Stroke: Protocol for a Randomized Controlled Trial

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## ABSTRACT

**Background.** Persistent disability in chronic stroke survivors is often attributed to arm or leg weakness; however, respiratory muscle weakness also impedes post-stroke rehabilitation, reduces quality of life, and increases risk of health complications. Respiratory complications are common after stroke and place patients at risk for both prolonged functional disability and mortality. Additionally, stroke survivors face ongoing cardiovascular disease that places them at risk for recurrent stroke.

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**Results.** This study was funded March 2020 with enrollment commencing November 2020. Completion of enrollment is projected May 2025 with study projected end date of April 2026. Published results are anticipated Fall 2026. Results from this study will improve our understanding of the additive benefits of respiratory exercises on short and long-term physiologic, functional and societal gains for these individuals.

**Conclusion.** These data will be instructive to meet a current unmet rehabilitative need, to promote patient-centered care and contribute to decreasing morbidity and mortality in chronic stroke survivors.

**Trial registration.** ClinicalTrials.gov: NCT05819333

**Key words.** stroke, rehabilitation, exercise, clinical trial, respiration, wellness, community-based

## INTRODUCTION

Stroke is the leading cause of serious long-term disability in the United States.[1] A decrease in stroke mortality (36.9% decrease from 1999-2009), has led to a subsequent increase in those living with the consequences of stroke.[2] Recurrent stroke, cardiac disease and respiratory complications are the leading causes of mortality in stroke



survivors. There is therefore a critical need to prevent further cardiovascular and cardiorespiratory decline and reduce the incidence of cardiac and respiratory disease and functional disability.

Although stroke sequelae effect numerous body systems, automatic control of resting ventilation is typically spared in the majority of stroke cases, affected only in more severe brainstem strokes. Motor deficits are often the most debilitating to mobility and return to participation in life roles. Motor processing and the voluntary control of muscles of respiration engaged when speaking, upon exertion, coughing, or with exercise may be weakened following damage to directly to the cerebral cortex or the descending axonal projections. Consequently, individuals post-stroke may exhibit prolonged exercise intolerance, dyspnea, and airway clearance dysfunction. It is upon this conceptual framework we propose that respiratory muscle training is an important component in the rehabilitation of individuals following stroke. The purposes of this study are to 1) evaluate the effect of a combined Exercise Program (EP) with Respiratory Strength Training (RST) on measures of impairment, activity and participation, 2) evaluate its ability to maintain prospective respiratory health and 3) explore the effect smoking history may have on these outcomes.

The primary objective of this trial is to test the hypothesis that a combined EP with RST improves physiologic, activity and societal participation outcomes in chronic stroke survivors. In addition to limb and respiratory weakness, up to 78% of patients post-stroke present with dysphagia[3], a significant risk factor for aspiration. Cough is a critical mechanism to guard against aspiration and is often impaired post-stroke,[4] resulting in greater incidences of aspiration and chest infection.[5, 6] Furthermore, pneumonia is the leading cause of non-vascular death in acute[7] and chronic[8] phases after stroke. RST

could improve airway clearance as a protective function. The adoption of interventions capable of preventing the occurrence of respiratory complications may substantially improve long-term outcomes of these patients.[9] Several small-scale studies have demonstrated that inspiratory[10-13] and expiratory[11] muscles respond to strength training in patients post-stroke, but the impacts of respiratory strengthening on function are less clear. In a systematic review of post-stroke respiratory muscle training randomized controlled trials, Menezes et al[14] reported there were insufficient data to determine whether the benefits of respiratory muscle training are realized into gains in functional activity level or participation, concluding that future trials are needed to assess the effects of training on one's activity and participation in life roles. RST for individuals post-stroke has the potential to facilitate return to these important societal roles.

Our secondary objective is to prospectively monitor health status for 1-year following the exercise intervention. There is a clear link between the presence of respiratory dysfunction of individuals post-stroke and the incidence of respiratory complications such as aspiration or respiratory infections.[15-17] Menezes et al.[14] revealed that respiratory muscle training reduced the relative risk of respiratory complications immediately and 6 months after the commencement of intervention. Others have reported that expiratory muscle strength training exercises improve respiratory strength, cough, and swallowing function in stroke. [18-20] A 2016 meta-analysis[14] revealed that respiratory muscle training reduced the relative risk of respiratory complications immediately and 6 months after the commencement of the intervention. However, this conclusion was based on just two trials, and procedures for detecting the occurrence of respiratory complications were not sufficiently robust.

An exploratory objective will evaluate potential differential responses to respiratory muscle training based on smoke exposure. Cigarette smoking negatively impacts respiratory health and increases risk of cardiovascular events. While direct cigarette smoking is a known risk factor for stroke and post-stroke complications, individuals exposed to secondhand smoke also face high health risks. There is a strong, dose-dependent association between passive smoking and stroke.[21]

## METHODS

### Trial Design

This is a randomized, single-blind, controlled trial. Participants will be assessed at Brooks Rehabilitation Clinical Research Center and receive intervention sessions at the Brooks Family YMCA. Health status will be monitored monthly for one year following the intervention. This study is registered at ClinicalTrials.gov (trial no. NCT05819333). The trial will be reported according to SPIRIT, TIDieR, and CONSORT guidelines (Fig. 1).

[Insert Fig. 1 here]

### Ethical Considerations

This protocol and Informed Consent Form was reviewed and approved by the University of Florida's Institutional Review Board (#202000810). Participants will sign the IRB-approved Informed Consent Form prior to enrollment. Participants will be assigned a unique numerical identifier to assure privacy and confidentiality of all collected data. Compensation of \$15/study visit will occur in the form of a debit card with a total compensation of \$405.

### Participants

Participants will be recruited from an Institutional Review Board-approved Clinical Research Registry and study flier. We will enroll up to 95 participants. With a potential attrition rate of

up to 15%, we expect 80 participants to complete the study. Specific inclusion and exclusion criteria for study enrollment are presented in Table 1.

[Insert Table 1. Here]

### Randomization/Allocation/Blinding

Participants will be randomized to the Exercise Program (EP) plus Respiratory Strength Training (RST group) or EP plus Respiratory Relaxation Training (RRT group) using the Microsoft Excel RAND function. Participants and the intervention physical therapist will be aware of group assignment due to the nature of the intervention; however, study evaluators will remain blinded.

### Interventions

Twenty-four intervention sessions will be delivered three times a week over eight weeks. Intervention therapists will undergo standardized training and a structured intervention log with the three aspects of the EP and the Respiratory Training outlined will be followed each session to assure intervention fidelity.

Exercise Program. Both groups will participate in the Exercise Program consisting of three components recommended by the AHA's post-stroke exercise recommendations,[22] directed by the intervention physical therapist and individualized to participants' ability.

1. *Strengthening Exercise:* Resistance exercises will address primary muscles groups of the upper and lower limbs and trunk. Graded resistance will be provided via weight machines or resistance bands. *Progression:* Ability to perform an exercise with appropriate kinematics will determine initial resistance. Once the participant can perform 2 sets of 10 repetitions, resistance will be increased.

2. *Cardiovascular Exercise:* Exercise modalities may include treadmill, recumbent cross trainer, recumbent bicycle, stairs, elliptical stepper, Upper Extremity ergometer, Arc Trainer or provided via overground gait, sit to stand repetitions, shallow knee bends, step-ups,

marching in place. *Progression*: Participants will wear a heart rate monitor and exercise between 40-70% of Heart Rate Reserve. Exertion will be subjectively reported using the Rate of Perceived Exertion (RPE) scale.[23] Progression will occur by increasing exercise duration, resistance or speed.

3. *Flexibility Exercise*: Static stretching of trunk and upper and lower extremities, two repetitions of each stretch held for 20 seconds. Muscles groups will be individualized according to participants' needs.

Respiratory Training. Participants will be randomized to the RST or RRT group.

*Respiratory Strength Training (RST)*. RST will consist of a bout of inspiratory strength training at the start of each EP session, plus a bout of expiratory strength training at the conclusion of each EP session. RST devices (Oxygen Dual Valve, Forumed S.L.) provide up to 70 cm H<sub>2</sub>O of inspiratory and 80 cm H<sub>2</sub>O of expiratory pressure threshold loads. RST bouts include 5 sets of 5 maximal volume and speed breaths of both inspiratory and expiratory muscle training two times during each session. Initial intensity will be 25% of maximal inspiratory and expiratory pressures the subject can generate. *Progression*: The inspiratory setting of the training device will be increased up to 10% of the training load from the first set each session, to achieve an RPE of 6-8 (Modified 10-point Borg scale)[24] with complete valve opening. Expiratory settings will be progressed similarly.

*Respiratory Relaxation Training (RRT)*. RRT will consist of bouts of relaxation breathing at the start and conclusion of each EP session. Subjects will be guided to breathe slowly through a respiratory training device, (Threshold PEP, Respironics), with minimal resistance. RRT bouts include 5 sets of 5 breaths, two times during the session. While effects of relaxation breathing exercises may include a modest lowering of systolic BP in some hypertensive patients,[25] this group serves as an active control. *Progression*: There

will be no progression for this group.

### Outcome Measures

Participants will be assessed 1) at baseline, 2) after 12 sessions, 3) after 24 sessions by a physical therapist blinded to group assignment. Blinded assessors will undergo standardized training to assure assessment fidelity. Following intervention completion participants will complete monthly health status questionnaires.

Primary objective outcomes. The World Health Organization's International Classification of Functioning, Disability, and Health (ICF) model[26] recognizes that functioning and disability as a result of a health condition (stroke, in this trial), are multi-dimensional concepts, relating not simply to impairment at the level of one's body (i.e. muscle strength) but to limitations in activity one might experience, as well as one's restrictions in societal participation. To assess more broadly how addressing respiratory muscle weakness can improve quality of life post-stroke we will examine outcomes across these dimensions (Fig. 2).

[Insert Fig. 2 here]

Our primary outcome is Maximal Inspiratory Pressure (MIP). Participants will perform a seated MIP maneuver using a respiratory pressure manometer, from residual volume, in accordance with American Thoracic Society testing guidelines for respiratory muscle testing.[27] Additional respiratory measures include maximal expiratory pressure, forced vital capacity and forced expiratory volume in one second, and peak cough flow. Open circuit spirometry will provide breath-by-breath cardiopulmonary data while participants complete the Six Minute Walk Test.[28] Additional measures of physical function include the Five Times Sit to Stand Test[29] and spatial-temporal gait characteristics captured while walking across an instrumented walkway. Steps per day and GPS data will be obtained at

baseline and intervention conclusion for one week. A portable accelerometer will record participants' steps and a Global Positioning System (GPS) device will record location. A Walk Score [30, 31] and an Area Deprivation Index [32] score will objectively characterize the "walkability" and the socioeconomic status of participant's neighborhood.

Finally, self-report measures of participation and quality of life will also address our primary objective. These include the Participation subsection of the Stroke Impact Scale,[33] the abbreviated World Health Organization Quality of Life instrument,[34] which measures the domains of physical health, psychological health, social relationships and environment, the Functional Assessment of Chronic Illness Therapy Dyspnea and Fatigue Scales, the Fatigue Severity Scale, the Patient Health Questionnaire-9 depression assessment, the PROMIS-10, an assessment of health status after stroke,[35] the Satisfaction and Ability to Participate in Life Roles subscales of the Neuro-QoL, and a Pain Questionnaire.

Secondary objective outcomes. To investigate if RST in the chronic post-stroke period impacts the rate of respiratory complications, we will follow participants for 1 year post-intervention. Respiratory complications will be defined as onset of respiratory symptoms that require the evaluation and treatment by a medical provider or a hospitalization for respiratory causes. If the subject reports a respiratory complication, medical records will be obtained and a blinded assessor will review the record to confirm diagnosis.

Exploratory objective. To address this objective, participants will provide a urine cotinine test and complete a subset of key questions from the Global Adult Tobacco Survey (GATS), a validated self-report of tobacco consumption and passive smoking.[36] From the cotinine test results participants will be categorized as either: 1) no significant smoke exposure (NOSMK), or 2) significant smoke exposure (SMK). Cotinine is a metabolite of nicotine and

indicates exposure to tobacco products within the past 48 hours. GATS is a household survey created as a way to globally monitor adult tobacco use and indirectly measure the impact of tobacco control and prevention initiatives. A subset of questions will be asked about current and past tobacco use (if any), exposure to secondhand smoke. We will compare the outcome measures described above from our primary and secondary objectives to investigate differences between those categorized as NOSMK and SMK.

Safety of trial intervention and assessments will be monitored by reporting to the Institutional Review Board any adverse events that occur from enrollment to trial completion at 12 months following the intervention.

#### Data Analysis

Power calculations. Our primary outcome measure is MIP. The power calculation was based on work by Messaggi-Sartor et al.,[11] who examined the effect of RST on respiratory strength and respiratory complications following subacute stroke and measured MIP as the primary outcome. MIP mean gain was  $18.9 \pm 15.1$  cm H<sub>2</sub>O in the experimental RST group and mean MIP change was  $9.3 (\pm 10.1)$  cm H<sub>2</sub>O in the control (sham RST) group. With a total of 80 subjects (40 in each group) in the current study, a two-sided repeated measures ANOVA comparing 2 treatments across 3 time points, using a pooled standard deviation of 12.8 would detect a difference at power  $>0.8$  ( $f=0.16$ ,  $F = 3.067$ ,  $\rho=0.5$ ,  $\alpha=0.5$ ). For our secondary objective, the RST effect on lung infections may be even more robust. Messaggi-Sartor et al. reported a 70% lower lung infection rate for subjects who completed RST during subacute stroke rehab, compared to subjects allocated to the control group. The number needed to treat to prevent one lung infection event was seven. [11] The effect of RST on respiratory complications for those with chronic stroke is not yet known. Our exploratory objective is to distinguish responses to RST, based on smoking exposure. The primary intent of this objective is to collect data to power a future, larger



study. Specifically, baseline function is lower in current smokers without neurological disease/stroke, and their tolerated exercise training volume may be reduced. A sample size of 80 will provide an opportunity to evaluate whether smoking influences responses to the exercise interventions.

Statistical analysis. To analyze the data for each objective and investigate the intervention effects for EP+RST vs. EP+RRT, we will adopt a mixed effects model[37] to account for the correlation of repeated measurements within each participant. Depending on the outcome for each objective, we will include the baseline value as an independent covariate in addition to other independent variables including intervention effects at 4 weeks and 8 weeks, age, gender and Body Mass Index (BMI) by using a robust covariance matrix, i.e. unstructured covariance matrix.

## RESULTS

This study was funded March 2020 with enrollment commencing November 2020. Completion of enrollment is projected May 2025 with study projected end date of April 2026. Published results are anticipated Fall 2026.

Results from this study will improve our understanding of the additive benefits of respiratory exercises on short and long-term physiologic, functional and societal gains for these individuals.

## DISCUSSION

While multiple studies indicate potential for respiratory muscle training to improve respiratory strength, airway protection, and dyspnea during acute stroke rehabilitation,[11, 38, 39] limited information is available pertaining to benefits of respiratory training in community-dwelling adults with chronic stroke.[10, 18, 40] This study approaches the research aims from a wellness perspective, as opposed to a medical model of

rehabilitation. The AHA-informed exercise program and respiratory training sessions occur in a community-based gym that emphasizes wellness and secondary prevention of stroke. Previous respiratory training research has emphasized respiratory strength, with fewer studies reporting effects on activity-based metrics such as cough force, gait speed, or walking endurance.[13, 41] This trial utilizes an impairment-based primary study outcome measure (MIP) as a comparator to other published respiratory training studies in stroke. However, activity and participation-based outcome measures were also included to account for functional limitations participants might experience post-stroke, and to further quantify restrictions in their societal roles. Further, this study moves beyond patient-reported participation, by directly measuring impacts of the respiratory training on gains in community activity and societal roles for up to one-year following completion of the intervention. The carryover from a gain in body function or activity to improved community and societal participation is a recognized need in stroke rehabilitation research.[14]

This research will also contribute novel exploratory information regarding effects of the exercise program and respiratory training in people with chronic stroke with and without daily cigarette smoke exposure. Smoking is an independent risk factor for stroke that directly increases relative risk of stroke in a dose-dependent fashion.[42] Smoking induces vascular inflammation and endothelial dysfunction to accelerate the progression of atherosclerosis.[43, 44] Secondhand smoke exposure also independently increases both the risk of stroke and obstructive pulmonary disease,[45, 46] and no level of passive smoke exposure is considered safe.[21] Chronic smoke exposure increases work of breathing via dynamic hyperinflation and heightened airway resistance, despite an increased inspiratory neural drive, leading to dyspnea and airway clearance dysfunction.[47, 48] Despite the negative impacts of smoking on cardiovascular and respiratory health, its impact on post-stroke respiratory rehabilitation is poorly understood. Older adults with obstructive lung

disease who completed six weeks of inspiratory strength training achieved significant improvements in MIP, dyspnea, and reported physical quality of life, yet in contrast to adults without lung disease, no gains in walking endurance occurred. These results suggest that individuals with lung disease recovering from stroke may require additional training time or combinatorial exercises to improve walking[49]

We recognize some limitations of the study design. The study was powered to distinguish 8-week effects of RST from RRT on MIP. We acknowledge that societal participation is multi-dimensional, and longer-term changes may be influenced by many contributing factors beyond respiratory strength and walking endurance.[50, 51] The use of patient-reported outcome measures and assessment of the Area Deprivation Index will help identify some factors that contribute to societal participation. Since group assignment will be based on the type of respiratory training, it is possible there may be unequal proportions of smoke-exposed and non-smoking participants in each group. The monitoring of smoke exposure will enable us to explore whether the combined respiratory and whole-body exercise approaches offer distinct benefits to cigarette smoke-exposed individuals. While study assessors will be blinded to group assignment, patients and exercise supervisors will know their respiratory exercise assignment. A true control or “sham” respiratory training intervention was not included; rather, the RRT serves as an active comparator. The volume of respiratory exercises during exercise sessions will be the same for both groups, even though physiological effects of RST and RRT exercises likely differ.

Since findings from this study may influence the health promotion, wellness, and secondary prevention societal roles of the physical therapy profession, dissemination efforts will be directed toward physical therapists and other rehabilitation providers. Study results will be presented at scientific conferences and published in peer-reviewed journals utilized by physical therapists and rehabilitation scientists.

In conclusion, this trial is an investigator-initiated, single-blind, randomized clinical study designed to evaluate effects of an AHA-informed exercise program and respiratory training on measures of impairment, activity, and societal participation. Implementation of this trial will help identify modes of exercise that lead to the greatest short- and long-term functional and societal gains in smoke-exposed and non-exposed, community-dwelling adults with chronic stroke.

### **List of abbreviations**

AHA: American Heart Association

BMI: Body Mass Index

EP: Exercise Program

GATS: Global Adult Tobacco Survey

ICF: International Classification of Function, Disability and Health

MIP: Maximal Inspiratory Training

NOSMK: No Significant Smoke Exposure

RPE: Rate of Perceived Exertion

RRT: Respiratory Relaxation Training

RST: Respiratory Strength Training

SMK: Significant Smoke Exposure

### **Conflicts of Interest**

None declared.

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no role in the design, implementation, analysis, or the decision where to publish manuscripts. The authors acknowledge the Brooks Clinical Research Center for the infrastructure necessary for participant recruitment, consenting and the conduction of study interventions and assessments and the Brooks Family YMCA for use of their facility.

#### Authors' contributions

DR and BS conceptualized and designed this study and obtained external funding. GB, KC, JBH and HS contributed to study intervention, assessment and data acquisition. WX conceptualized the statistical approach. All authors read, edited and approved the submitted manuscript and are personally accountable for their contributions and will investigate and resolve any questions regarding accuracy or integrity of any part of the work.

Table 1. Inclusion and Exclusion Criteria for enrollment into the trial

<b>Inclusion Criteria</b>
Diagnosis of stroke > 6 months post-onset
Signed letter of medical approval from primary care physician to participate
Community dwelling
Ability to attend the exercise program 3x/week for 8 weeks
Ability to follow directions or mimic exercises
Ability to communicate adverse effects such as pain or fatigue or the need for assistance
Able to ambulate 20 feet with no more than contact guard assist, with or without an assistive device or orthotic device
Able to access exercise equipment independently or with caregiver assist
➤ 18 years of age
<b>Exclusion Criteria</b>
Neurologic condition other than stroke (i.e. Parkinson's Disease, multiple sclerosis)
Severe, functional limiting arthritis
Orthopedic condition that limits mobility
Severe weight-bearing pain
Current participation in other physical rehabilitation services or exercise programs
Serious cardiac conditions (hospitalization for myocardial infarction or heart surgery within the past year, 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.
Severe hypertension with systolic > 200 mmHg and diastolic > 110 mmHg at rest, that cannot

be medically controlled into the resting range of 180/100 mmHg
Use of supplemental oxygen
Severe obstructive pulmonary disease (Classification of Global Initiative for Chronic Obstructive Lung Disease (GOLD) 3 or higher, indicating FEV1 < 50% predicted
Treatment for pneumonia or lower respiratory infection within the past month
Able to run one quarter mile without stopping

## Figures

Figure 1. Flow Chart of the Clinical Trial

Figure 2. Outcome Measures across World Health Organization's International Classification of Functioning, Disability and Health model.

## References

1. Centers for Disease Control and Prevention (CDC). Prevalence and most common causes of disability among adults: United States, 2005. *MMWR. Morbidity and Mortality Weekly Report*, 2009. **58**: p. 421-426. PMID: 19407734
2. Go, AS, et al., Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation*; 2013. **127**(1): p. e6-e245. PMID:23239837
3. Martino, R, et al., Dysphagia after stroke: incidence, diagnosis, and pulmonary complications. *Stroke*; 2005. **36**(12): p. 2756-63. PMID:16269630
4. Ward, K, et al., Acute ischaemic hemispheric stroke is associated with impairment of reflex in addition to voluntary cough. *Eur Respir J*; 2010. **36**(6): p. 1383-90. PMID:20413536
5. Addington, WR, R.E. Stephens, and K.A. Gilliland, Assessing the laryngeal cough reflex and the risk of developing pneumonia after stroke: an interhospital comparison. *Stroke*; 1999. **30**(6): p. 1203-7. PMID:10356100
6. Smith Hammond, CA, et al., Assessment of aspiration risk in stroke patients with quantification of voluntary cough. *Neurology*; 2001. **56**(4): p. 502-6. PMID:11222795
7. Katzan, IL, et al., The effect of pneumonia on mortality among patients hospitalized for acute stroke. *Neurology*; 2003. **60**(4): p. 620-5. PMID:12601102
8. Yamaya, M, et al., Interventions to prevent pneumonia among older adults. *J Am Geriatr Soc*; 2001. **49**(1): p. 85-90. PMID:11207848
9. Dexter, PR, et al., Inpatient computer-based standing orders vs physician reminders to increase influenza and pneumococcal vaccination rates: a randomized trial. *JAMA*; 2004. **292**(19): p. 2366-71. PMID:15547164
10. Britto, RR, et al., Inspiratory muscular training in chronic stroke survivors: a randomized controlled trial. *Arch Phys Med Rehabil*; 2011. **92**(2): p. 184-90. PMID:21272713
11. Messaggi-Sartor, M, et al., Inspiratory and expiratory muscle training in subacute stroke: A randomized clinical trial. *Neurology*; 2015. **85**(7): p. 564-72. PMID:26180145
12. Sutbeyaz, ST, et al., Respiratory muscle training improves cardiopulmonary function and exercise tolerance in subjects with subacute stroke: a randomized controlled trial. *Clin Rehabil*; 2010. **24**(3): p. 240-50. PMID:20156979
13. Jung, KM and DH Bang, Effect of inspiratory muscle training on respiratory capacity and walking ability with subacute stroke patients: a randomized controlled pilot trial. *J Phys Ther Sci*; 2017. **29**(2): p. 336-339. PMID:28265169
14. Menezes, KK, et al., Respiratory muscle training increases respiratory muscle strength and reduces respiratory complications after stroke: a systematic review. *J Physiother*; 2016. **62**(3): p. 138-44. PMID:27320833

15. Kulnik, ST, et al., Higher cough flow is associated with lower risk of pneumonia in acute stroke. *Thorax*; 2016. **71**(5): p. 474-5. PMID:26834183
16. Lee, SJ, et al., Voluntary Cough and Swallowing Function Characteristics of Acute Stroke Patients Based on Lesion Type. *Arch Phys Med Rehabil*; 2015. **96**(10): p. 1866-72. PMID:26184890
17. Masiero, S, et al., Pneumonia in stroke patients with oropharyngeal dysphagia: a six-month follow-up study. *Neurol Sci*; 2008. **29**(3): p. 139-45. PMID:18612760
18. Hegland, KW, et al., Rehabilitation of Swallowing and Cough Functions Following Stroke: An Expiratory Muscle Strength Training Trial. *Arch Phys Med Rehabil*; 2016. **97**(8): p. 1345-51. PMID:27130637
19. Jo, MR and NS Kim, Combined respiratory muscle training facilitates expiratory muscle activity in stroke patients. *J Phys Ther Sci*; 2017. **29**(11): p. 1970-1973. PMID:29200637
20. Moon, JH, et al., Effects of expiratory muscle strength training on swallowing function in acute stroke patients with dysphagia. *J Phys Ther Sci*; 2017. **29**(4): p. 609-612. PMID:28533594
21. Oono, IP, DF Mackay, and JP Pell, Meta-analysis of the association between secondhand smoke exposure and stroke. *J Public Health (Oxf)*; 2011. **33**(4): p. 496-502. PMID:21422014
22. Billinger, SA, et al., 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): p. 2532-53. PMID:24846875
23. Borg, GA, Psychophysical bases of perceived exertion. *Med Sci Sports Exerc*; 1982. **14**(5): p. 377-81. PMID:7154893
24. Borg, GA, Borg's Perceived Exertion and Pain Scales. 1998, Champaign, IL: Human Kinetics. ISBN:9780880116237
25. Mahtani, K.R., et al., Device-Guided Breathing for Hypertension: a Summary Evidence Review. *Curr Hypertens Rep*; 2016. **18**(4): p. 33. PMID:27059041
26. Kostanjsek, N, Use of The International Classification of Functioning, Disability and Health (ICF) as a conceptual framework and common language for disability statistics and health information systems. *BMC Public Health*; 2011. **11 Suppl 4**(Suppl 4): p. S3. PMID:21624189
27. American Thoracic Society/European Respiratory, S., ATS/ERS Statement on respiratory muscle testing. *Am J Respir Crit Care Med*; 2002. **166**(4): p. 518-624. PMID:12186831
28. Fulk, GD, et al., Predicting home and community walking activity in people with stroke. *Arch Phys Med Rehabil*; 2010. **91**(10): p. 1582-6. PMID:20875518
29. Silva, PF, et al., Measurement properties and feasibility of clinical tests to assess sit-to-stand/stand-to-sit tasks in subjects with neurological disease: a systematic review. *Braz J Phys Ther*; 2014. **18**(2): p. 99-110. PMID:24839043
30. Ludwig, J, et al., Neighborhoods, obesity, and diabetes--a randomized social experiment. *N Engl J Med*; 2011. **365**(16): p. 1509-19. PMID: 22010917
31. Singh, GK, Area deprivation and widening inequalities in US mortality, 1969-1998. *Am J Public Health*; 2003. **93**(7): p. 1137-43. PMID: 12835199
32. Duncan, DT, et al., Validation of walk score for estimating neighborhood walkability: an analysis of four US metropolitan areas. *Int J Environ Res Public Health*; 2011. **8**(11): p. 4160-79. PMID:22163200
33. Lai, SM, et al., Physical and social functioning after stroke: comparison of the Stroke Impact Scale and Short Form-36. *Stroke*; 2003. **34**(2): p. 488-93. PMID:12574565
34. Skevington, SM, et al., The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report



- from the WHOQOL group. *Qual Life Res*; 2004. **13**(2): p. 299-310. PMID: 15085902
35. Cella, D, et al., The Patient-Reported Outcomes Measurement Information System (PROMIS): progress of an NIH Roadmap cooperative group during its first two years. *Med Care*; 2007. **45**(5 Suppl 1): p. S3-S11. PMID:17443116
  36. Global Adult Tobacco Survey Collaborative Group. Tobacco Questions for Surveys: A Subset of Key Questions from the Global Adult Tobacco Survey (GATS); 2011: Atlanta, GA.
  37. Mallinckrodt CH, C.W., David SR, Type I Error rates from Mixed Effects Model Repeated Measures versus Fixed Effects ANOVA with Missing Values Imputed via Last Observation Carried Forward. *Drug Information Journal*; 2001. **35**(4): p. 1215-1225. doi:[10.1177/009286150103500418](https://doi.org/10.1177/009286150103500418)
  38. Kulnik, ST, et al., Does respiratory muscle training improve cough flow in acute stroke? Pilot randomized controlled trial. *Stroke*; 2015. **46**(2): p. 447-53. PMID:25503549
  39. Parreiras de Menezes, KK, et al., High-Intensity Respiratory Muscle Training Improves Strength and Dyspnea Poststroke: A Double-Blind Randomized Trial. *Arch Phys Med Rehabil*; 2019. **100**(2): p. 205-212. PMID:30316960
  40. Lee, K, D Park, and G Lee, Progressive Respiratory Muscle Training for Improving Trunk Stability in Chronic Stroke Survivors: A Pilot Randomized Controlled Trial. *J Stroke Cerebrovasc Dis*; 2019. **28**(5): p. 1200-1211. PMID: 30712955
  41. Vaz, LO, et al., Effects of inspiratory muscle training on walking capacity of individuals after stroke: A double-blind randomized trial. *Clin Rehabil*; 2021. **35**(9): p. 1247-1256. PMID: 33706569
  42. Pan, B, et al., The relationship between smoking and stroke: A meta-analysis. *Medicine (Baltimore)*; 2019. **98**(12): p. e14872. PMID: 30896633
  43. Mazzone, P, et al., Pathophysiological impact of cigarette smoke exposure on the cerebrovascular system with a focus on the blood-brain barrier: expanding the awareness of smoking toxicity in an underappreciated area. *Int J Environ Res Public Health*; 2010. **7**(12): p. 4111-26. PMID: 21317997
  44. Wylam, ME, et al., Mechanisms of Cigarette Smoke Effects on Human Airway Smooth Muscle. *PLoS One*; 2015. **10**(6): p. e0128778. PMID: 26075746
  45. Flouris, AD, et al., Acute and short-term effects of secondhand smoke on lung function and cytokine production. *Am J Respir Crit Care Med*; 2009. **179**(11): p. 1029-33. PMID: 19264972
  46. Lin, MP, et al., Association of Secondhand Smoke With Stroke Outcomes. *Stroke*; 2016. **47**(11): p. 2828-2835. PMID: 27729574
  47. Bazzan, E, et al., Symptomatic smokers without COPD have physiological changes heralding the development of COPD. *ERJ Open Res*; 2022. **8**(2). PMID: 35769419
  48. Elbehairy, AF, et al., Mechanisms of exertional dyspnoea in symptomatic smokers without COPD. *Eur Respir J*; 2016. **48**(3): p. 694-705. PMID: 27492828
  49. Huang, CH, et al., Comparison of inspiratory muscle strength training effects between older subjects with and without chronic obstructive pulmonary disease. *J Formos Med Assoc*; 2011. **110**(8): p. 518-26. PMID: 21783021
  50. Della Vecchia, C, et al., Contextual determinants of participation after stroke: a systematic review of quantitative and qualitative studies. *Disabil Rehabil*; 2021. **43**(13): p. 1786-1798. PMID: 31646906
  51. Shi, Y, et al., Poststroke activity engagement in community dwellers: Association with illness perceptions and perceived environment. *Clin Rehabil*; 2023. **37**(1): p. 132-142. PMID: 35785999

Table 1. Inclusion and Exclusion Criteria for enrollment into the trial

<b>Inclusion Criteria</b>
Diagnosis of stroke > 6 months post-onset
Signed letter of medical approval from primary care physician to participate
Community dwelling
Ability to attend the exercise program 3x/week for 8 weeks
Ability to follow directions or mimic exercises
Ability to communicate adverse effects such as pain or fatigue or the need for assistance
Able to ambulate 20 feet with no more than contact guard assist, with or without an assistive device or orthotic device
Able to access exercise equipment independently or with caregiver assist
➤ 18 years of age
<b>Exclusion Criteria</b>
Neurologic condition other than stroke (i.e. Parkinson's Disease, multiple sclerosis)
Severe, functional limiting arthritis
Orthopedic condition that limits mobility
Severe weight-bearing pain
Current participation in other physical rehabilitation services or exercise programs
Serious cardiac conditions (hospitalization for myocardial infarction or heart surgery within the past year, 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.
Severe hypertension with systolic > 200 mmHg and diastolic > 110 mmHg at rest, that cannot be medically controlled into the resting range of 180/100 mmHg
Use of supplemental oxygen
Severe obstructive pulmonary disease (Classification of Global Initiative for Chronic Obstructive Lung Disease (GOLD) 3 or higher, indicating FEV1 < 50% predicted
Treatment for pneumonia or lower respiratory infection within the past month
Able to run one quarter mile without stopping

## Supplementary Files

## Figures

Flow chart of the clinical trial.

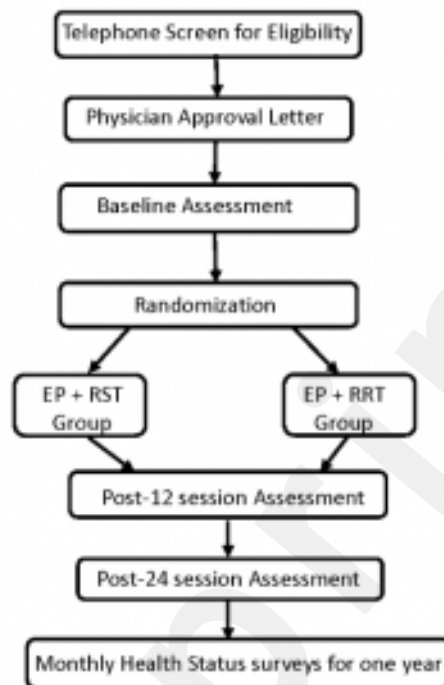
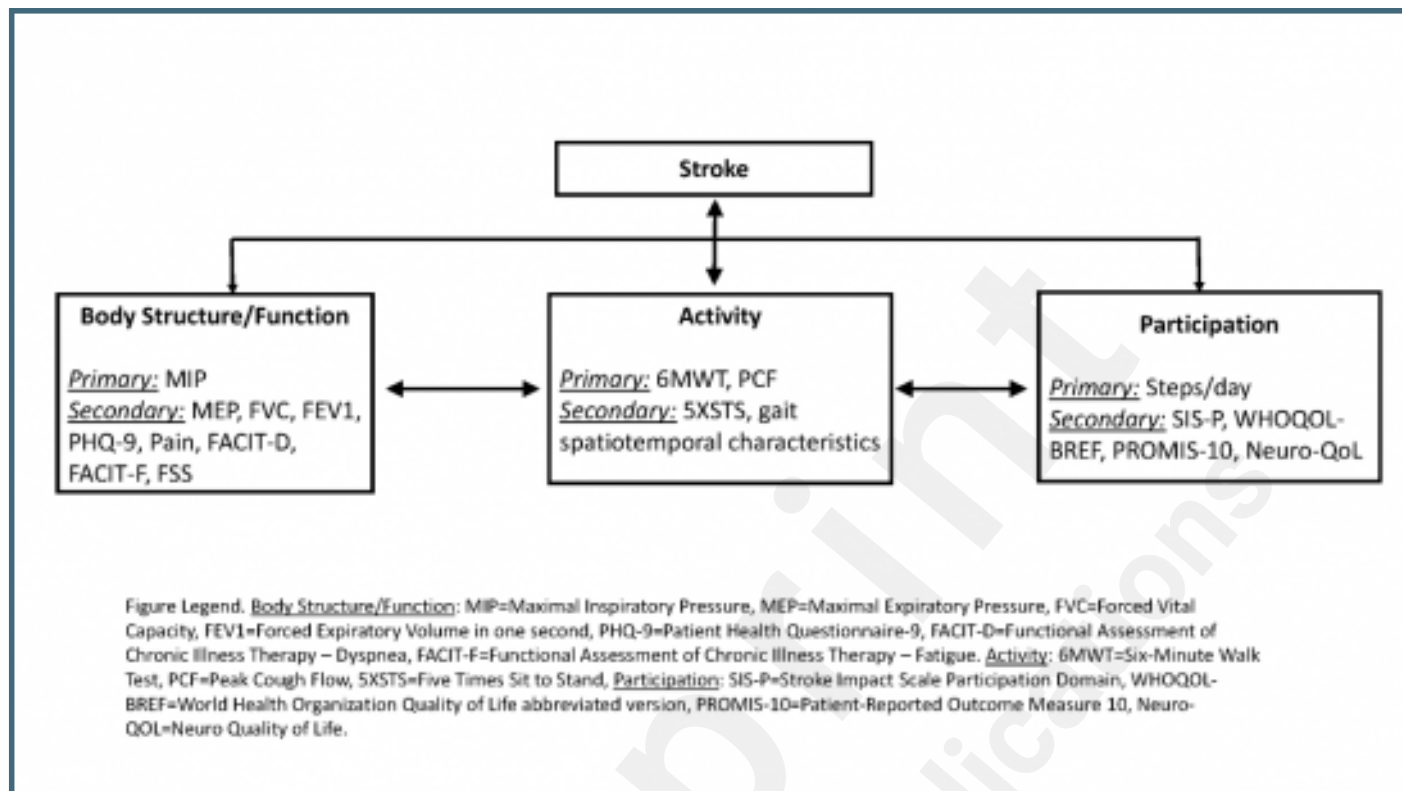


Figure Legend. EP=Exercise Program, RST=Respiratory Strength Training, RRT=Respiratory Relaxation Training

Outcome measures across World Health Organization's International Classification of Functioning, Disability and Health model.



## **Multimedia Appendixes**



Award letter following peer-review of proposal submission.

URL: <http://asset.jmir.pub/assets/27041dc892f9c3f574476c60e0a9b4e0.pdf>



## **Existing Peer-Review Reports from Funding Agencies (for protocols/proposals only)s**

Peer-Review Document #1 resulting from original submission to FL Dept. of Health. Reviews were responded to which resulted in funding (funding letter attached previously).

URL: <http://asset.jmir.pub/assets/e39efee1e9dc07771df85ed07a91cd61.pdf>

Peer-Review Document #2 resulting from original submission to FL Dept. of Health. Reviews were responded to which resulted in funding (funding letter attached previously).

URL: <http://asset.jmir.pub/assets/6f5321cbb7a3cb9b93fa12910c133a59.pdf>