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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Dorian K. Rose[1, 2, 3] PT, MS, PhD, FAPTA; Gina Brunetti[2] PT, DPT; Kathryn Cavka[2] PT, DPT; J. Brooke Hoisington[2] MPT; Hannah Snyder[2] MS, ACSM-EP; Wei Xue[4] PhD; Barbara K. Smith[1] PhD, MHS, MPT

[1]Department of Physical Therapy University of Florida Gainesville US
[2]Brooks Rehabilitation Jacksonville US
[3]Brain Rehabilitation Research Center Malcom Randall VAMC GAINESVILLE US
[4]Department of Biostatistics University of Florida Gainesville US

Corresponding Author:
Dorian K. Rose PT, MS, PhD, FAPTA
Department of Physical Therapy
University of Florida
College of PHHP; HSC; PO. Box 100154
Gainesville
US

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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Authors
Dorian K. Rose, PT, MS, PhD, FAPTA
Research Professor
Department of Physical Therapy
University of Florida
Clinical Research Scientist
Brooks Rehabilitation Clinical Research Center
Research Health Scientist
Malcom Randall VA Medical Center

Gina Brunetti, PT, DPT
Board-Certified Clinical Specialist in Neurologic Physical Therapy (NCS)
Clinician Scientist, Neuromuscular Research Program
Brooks Rehabilitation Clinical Research Center

Kathryn Cavka, PT, DPT
Board-Certified Clinical Specialist in Neurologic Physical Therapy (NCS)
Clinician Scientist, Neuromuscular Research Program
Brooks Rehabilitation Clinical Research Center

J. Brooke Hoisington, MPT
Brooks Rehabilitation Clinical Research Center

Hannah Snyder, MS, ACSM-EP
Senior Research Associate
Brooks Rehabilitation Clinical Research Center
Wei Xue, PhD
Research Assistant Professor
Department of Biostatistics
University of Florida

Barbara K. Smith, PhD, MHS, MPT
Assistant Professor
Department of Physical Therapy
Department of Pediatrics
University of Florida

Corresponding Author:
Dorian K. Rose
University of Florida
College of Public Health and Health Professions
Department of Physical Therapy
P.O. Box 100154, UFHSC
Gainesville, FL 32160-0154
Address all correspondence to Dr. Rose: dkrose@phhp.ufl.edu

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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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

Background

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] As such, it impacts the financial

status of patients, families, and healthcare systems.[3] A retrospective study of inpatient stroke care costs from 2000-2020 revealed mean hospital costs per stay were $15, 781 (± $330).[4] The mean lifetime cost of ischemic stroke is approximately $140,048 in the United States, placing stroke among the top ten most costly conditions among Medicare beneficiaries.[5] Recurrent stroke, cardiac disease and respiratory complications are the leading causes of mortality in stroke survivors. Given these financial and health costs, 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.

Economically, the total direct and indirect cost of ischemic stroke in the U.S. is estimated to be 65.5 billion

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.

Study Objective and Aims

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[6], a significant risk factor for aspiration. Cough is a critical mechanism to guard against aspiration and is often impaired post-stroke,[7] resulting in greater incidences of aspiration and chest infection.[8, 9] Furthermore, pneumonia is the leading cause of non-vascular death in acute[10] and chronic[11] 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.[12] Several small-scale studies have demonstrated that inspiratory[13-16] and expiratory[14] 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[17] 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.[18-20] Menezes et al.[17] 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. [21-23] A 2016 meta-analysis[17] 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.[24]

METHODS

Trial Design

This is a randomized, single-blind, controlled trial. Participants will be assessed at Brooks Rehabilitation Clinical Research Center (Jacksonville, FL, USA) and receive intervention sessions at the Brooks Family YMCA (Jacksonville, FL, USA). 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]

Ethics Approval

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 de-identify and 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.

Ethical Considerations

To evaluate not simply *how many* steps participants take but to understand *where* those steps are taken (i.e. within the confines of their home or actually outside their home, in the community) participants will wear a Global Positioning Device for seven days. This de-identified longitude and latitude coordinate data is not collected in real time, but rather will be downloaded to a password protected computer at the completion of the seven day wearing period.

Participants

Participants will be recruited from an Institutional Review Board-approved Clinical Research Registry and study flier. Power calculations (see below) determined a study population of 80 participants. We will enroll up to 95 participants to allow for a potential attrition rate of up to 15%.. Specific inclusion and exclusion criteria for study enrollment are presented in Table 1. The cardiovascular and respiratory exclusion criteria were adopted from a previous exercise study with individuals post-stroke.[25, 26]

[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 (Microsoft Office Professional Plus 2016) 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,[27] 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.[28] 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 (Orygen Dual Valve, Forumed S.L.) provide up to 70 cm H2O of inspiratory and 80 cm H2O 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)[29] 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,[30] 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[31] 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). MIP is a measure of the strength of inspiratory muscles, primarily the diaphragm.[32] 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.[33] Additional respiratory measures include Maximal Expiratory Pressure (MEP a measure of the strength of expiratory muscles, primarily the abdominals and intercostals) [33], Forced Vital Capacity (FVC, the total volume of air blown out of the lungs during forced exhalation after maximal inspiration)[33] and Forced Expiratory Volume in one second (FVC_1 a measure of the amount of air that can be forced out of the lungs in one second following a full inhalation),[33] and Peak Cough Flow (PCF, maximum expiratory flow during the compressive phase of a cough).[34] Open circuit spirometry will provide breath-by-breath cardiopulmonary data while participants complete the Six Minute Walk Test.[35] Additional measures of physical function include the Five Times Sit to Stand Test[36] 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 [37, 38] and an Area Deprivation Index [39] 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,[40] the abbreviated World Health Organization Quality of Life instrument,[41] which measures the domains of physical health, psychological health, social relationships and environment, the Functional Assessment of Chronic Illness Therapy Dyspnea[42] and Fatigue[43] Scales, the Fatigue Severity Scale[44], the Patient Health Questionnaire-9 depression assessment[45], the PROMIS-10, an assessment of health status after stroke,[46] and the Satisfaction and Ability to Participate in Life Roles subscales of the Neuro-QoL[47].

[Insert Table 2 here]

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 outcomes. 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.[48] 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.,[14] 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 ±15.1 cm H_2O in the experimental RST group and mean MIP change was 9.3 (± 10.1) cm H_2O 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, ρ=0.5, α=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. [14] 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[49] 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

Anticipated Results

We hypothesize that the combined RST+EP will be more effective than the EP alone for stroke survivors with and without a smoking exposure history. Specifically, we hypothesize that combined RST+EP will be more effective in restoring post-stroke maximal respiratory pressure, in restoring both physical (walking endurance) and

respiratory (airway clearance) function and in restoring post-stroke life and social roles. We also hypothesize that RST+EP will be more effective than EP alone in reducing 1-year post-intervention incidence of adverse respiratory events.

Wellness Approach

While multiple studies indicate potential for respiratory muscle training to improve respiratory strength, airway protection, and dyspnea during acute stroke rehabilitation,[14, 50, 51] limited information is available pertaining to benefits of respiratory training in community-dwelling adults with chronic stroke.[13, 21, 52] 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.[16, 53] 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.[17]

Effects of Smoke Exposure

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.[54] Smoking induces

vascular inflammation and endothelial dysfunction to accelerate the progression of atherosclerosis.[55, 56] Secondhand smoke exposure also independently increases both the risk of stroke and obstructive pulmonary disease,[57, 58] and no level of passive smoke exposure is considered safe.[24] 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.[59, 60] 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[61]

Limitations

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 muti-dimensional, and longer-term changes may be influenced by many contributing factors beyond respiratory strength and walking endurance.[62, 63] 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.

Dissemination Plan

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.

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

GPS: Global Positioning System

ICF: International Classification of Function, Disability and Health

MIP: Maximal Inspiratory Training

Neuro-QOL: Neuro Quality of Life

NOSMK: No Significant Smoke Exposure

PROMIS 10: Patient Reported Outcomes Measurement Information 10

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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Data Availability

All data generated or analyzed during this study, once available will be included in the published results.

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

Inclusion Criteria
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
Greater than 18 years of age
Exclusion Criteria
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

Table 2. Outcome Measures

Assessment	Outcome Measured	Time to Complete	Scoring	Psychometrics
MIP	Maximum pressure created during inspiration measured with a manometer	8 minutes	Pressure measured in cm H_2O	Reliability[64] Validity[64]
MEP	Maximum pressure created during expiration measured with a manometer	8 minutes	Pressure measured in cm H_2O	Reliability[64] Validity[64]
PCF	Strength of cough	5 minutes	Liters of air breathed out per minute; L/min	Reliability[65] Validity[65]
FVC	Maximum amount of air exhaled after fully inhaling and making a maximal effort.	5 minutes	Volume measured in Liters	Reliability[66, 67] Validity[66, 67]
FEV_1	Volume of air exhaled in the first second during forced exhalation after maximal inspiration	1 minute	Volume measured in Liters	Reliability[66, 67] Validity[66, 67]
6MWT	Participants walk for six minutes covering as much ground as possible. Participants permitted to stop and rest at any time during the test.	6 minutes	Distance measured in meters.	Reliability[68] Validity[69]
5XSTS	Participants stand up and sit down from a 16” solid seat as quickly as possible 5 times, with their arms folded across their chest.	1 minute	Time measured in seconds.	Reliability[70] Validity[70]
Steps/day	Number of steps taken over a seven-day period measured with an activity monitor	7 days	Number of steps completed each day	Reliability[71] Validity[72]
PHQ-9	Self-report	6 minutes	Nine items	Reliability[73]

	questionnaire to assess depressive symptoms		scored on a 0-3 Likert scale	Validity[73]
SIS-P	Self-report questionnaire to assess ability to participate in meaningful life activities	3 minutes	Eight items scored on a 1-5 Likert scale	Reliability[74] Validity[74]
WHO-QOL BREF	Self-report questionnaire to assess four QOL domains: physical health, psychological health, social relationships and environment.	12 minutes	26 items rated on a 5-point Likert scale. Each domain score is transformed into a scaled score, with a higher score indicating a higher QOL.	Reliability[75] Validity[75]
FSS	Self-report questionnaire to assess the impact of fatigue on life and functional activities	8 minutes	Nine items scored on a 1-7 Likert Scale; One item scored on a 0-10 visual analogue scale	Reliability[76] Validity[76]
FACIT-D	Self-report questionnaire to assess dyspnea severity during activities of daily living	5 minutes	Ten items scored on a 0-3 Likert Scale	Reliability[42] Validity[42]
FACIT-F	Self-report questionnaire to assess fatigue experience and impact on daily life	5 minutes	Thirteen items scored on a 0-4 Likert Scale	Reliability[77] Validity[77]
Neuro-QOL	Two self-report questionnaire subscales to assess 1) Ability to Participate in Social Roles and Activities and 2) Satisfaction with Social Roles and Activities	10 minutes	Total of sixteen items scored on a 1-5 Likert Scale	Reliability[47] Validity[47]
PROMIS-10	Self-report questionnaire to assess multiple	5 minutes	Ten items scored on a 1-5 Likert Scale	Reliability[78] Validity[78]

	domains of health			

Key: MIP – Maximum Inspiratory Pressure; MEP – Maximum Expiratory Pressure; PCF – Peak Cough Flow; FVC – Forced Vital Capacity; FEV_1 – Forced Expiratory Volume in 1 second; 6MWT – Six Minute Walk Test; 5XSTS – Five Times Sit to Stand; PHQ-9 – Patient Health Questionnaire -9; SIS-P – Stroke Impact Scale – Participation; WHO-QOL BREF – World Health Organization Quality of Life Abbreviated Version; FSS – Fatigue Severity Scale; FACIT-D – Functional Assessment of Chronic Illness Therapy – Dyspnea; FACIT-F – Functional Assessment of Chronic Illness Therapy – Fatigue; Neuro-QOL – Neuro Quality of Life; PROMIS-10 – Patient-Reported Outcomes Measurement Information 10.

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.

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Supplementary Files

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Figures

Flow chart of the clinical trial.

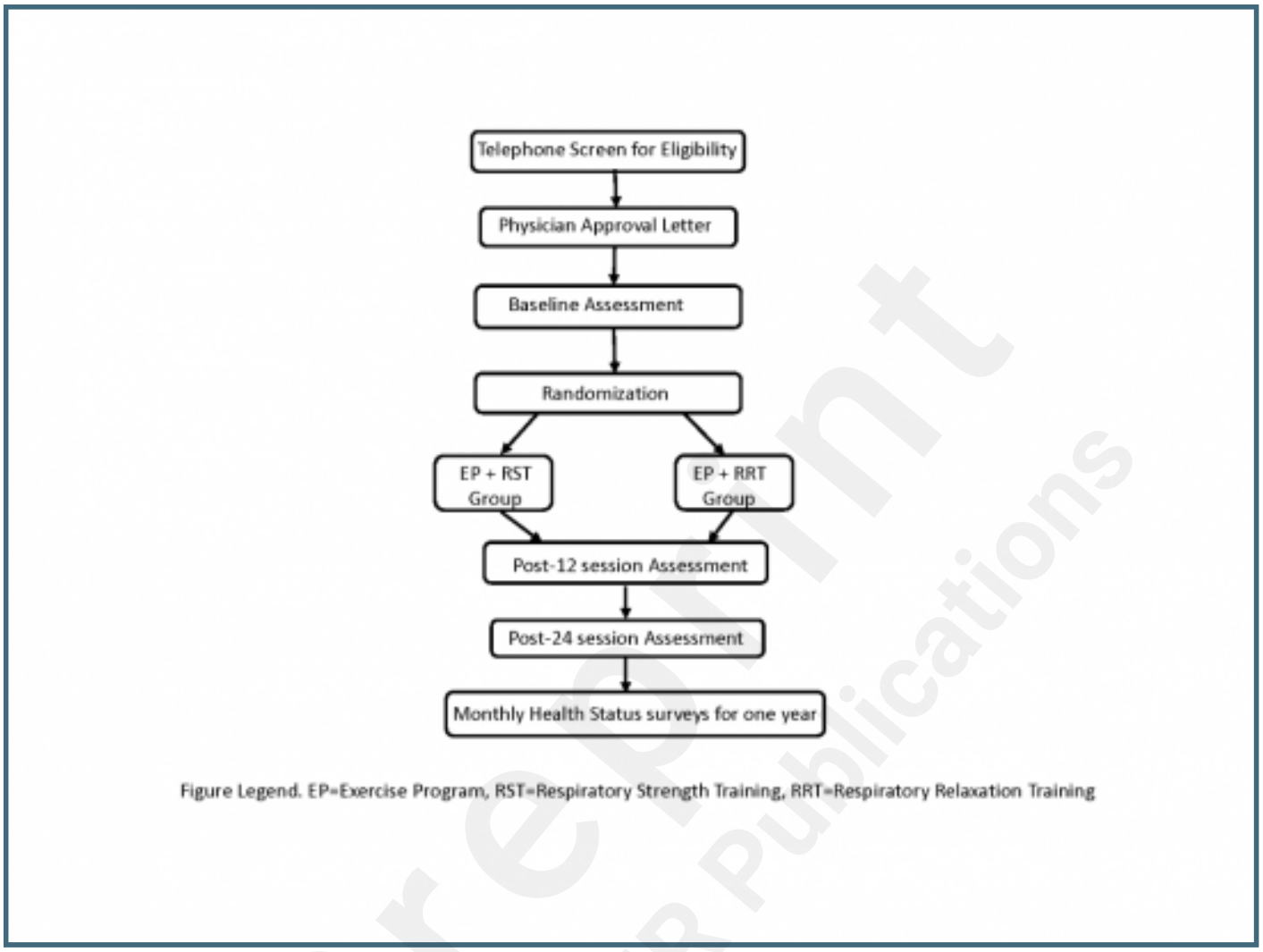

Figure Legend. EP=Exercise Program, RST=Respiratory Strength Training, RRT=Respiratory Relaxation Training

Outcome Measures across the WHO-ICF Model.

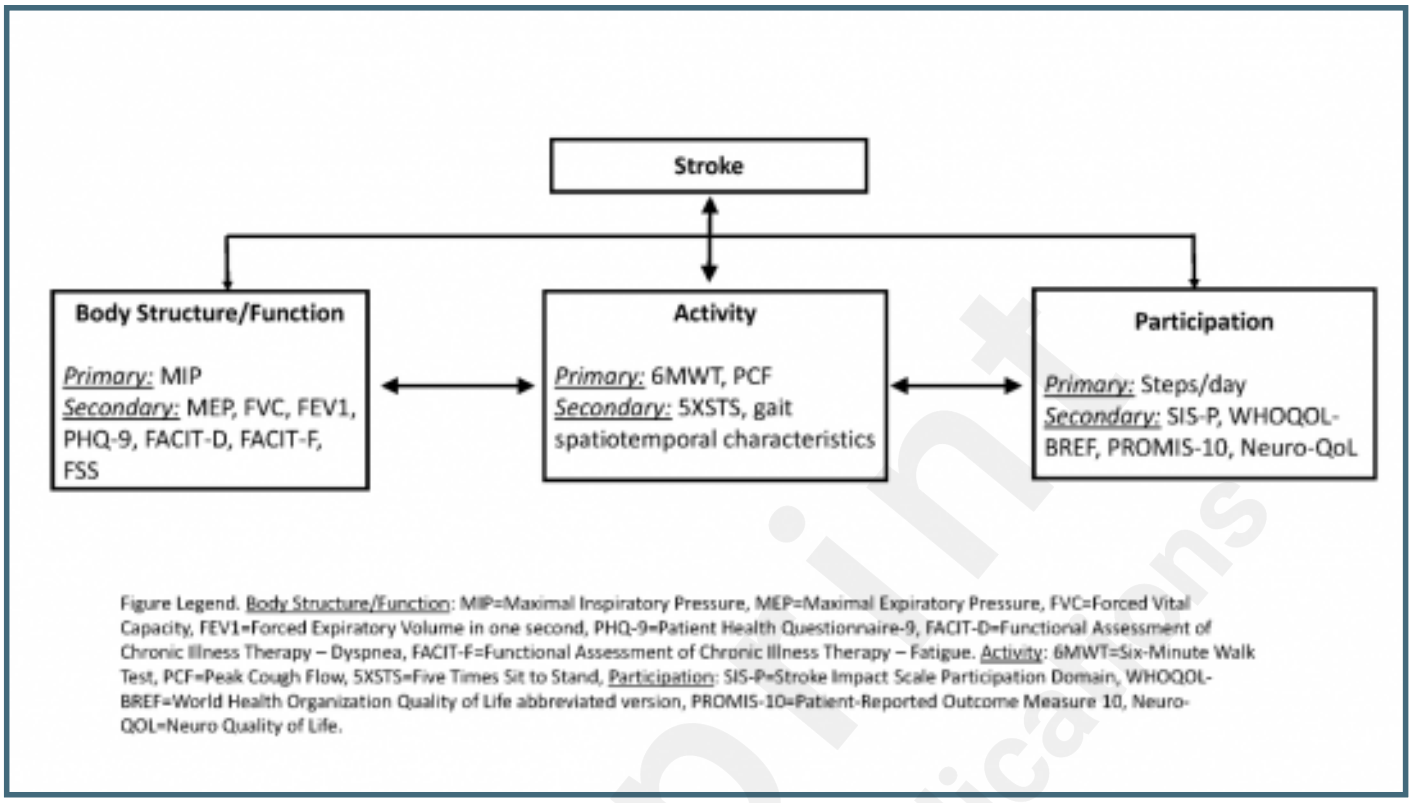

Figure Legend. Body Structure/Function: MIP=Maximal Inspiratory Pressure, MEP=Maximal Expiratory Pressure, FVC=Forced Vital Capacity, FEV1=Forced Expiratory Volume in one second, PHQ-9=Patient Health Questionnaire-9, FACIT-D=Functional Assessment of Chronic Illness Therapy – Dyspnea, FACIT-F=Functional Assessment of Chronic Illness Therapy – Fatigue. Activity: 6MWT=Six-Minute Walk Test, PCF=Peak Cough Flow, 5XSTS=Five Times Sit to Stand, Participation: SIS-P=Stroke Impact Scale Participation Domain, WHOQOL-BREF=World Health Organization Quality of Life abbreviated version, PROMIS-10=Patient-Reported Outcome Measure 10, Neuro-QOL=Neuro Quality of Life.

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