Cost-effectiveness and Efficacy of a Combined Intervention to Facilitate Motor Recovery Following Stroke

NCT Number: NCT03819764

Study Protocol and Statistical Analysis Plan

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Research Strategy

Significance: For the first time, an innovative application of aerobic exercise (AE) in facilitating upper extremity motor recovery for patients with stroke will be studied considering both the clinical effectiveness and economic impact. We will use tested concepts and methods and apply them to the field of stroke rehabilitation while building a framework that could be used in future stroke and rehabilitation studies.

Stroke, an endpoint of cardiovascular disease, is a leading cause of severe, long-term disability among older adults in the United States[12]. The total economic burden of stroke in the US is significant, with direct costs estimated at $38 billion and indirect costs approaching $30 billion annually[13-15]. Given the economic burden of stroke on individuals, families, and society, increased emphasis needs to be placed on innovative rehabilitation approaches that optimize motor recovery and reduce disability, thus lowering both direct and indirect costs. A fundamental gap exists in the rehabilitation of patients with stroke: lack of a rehabilitation model that is efficacious and cost-effective. The proposed project will, for the first time, simultaneously determine the effectiveness of a rehabilitation model from a motor recovery and cost perspective.

An abundance of randomized clinical trials focused on improving upper and lower extremity function have been conducted over the past decade[16-18]. Despite the demonstration of efficacy, cost and therapist time are reported as primary barriers to the clinical adoption of intensive, motor learning-based rehabilitation approaches such as constraint-induced movement therapy[3, 19, 20]. To overcome this barrier, cost-effectiveness analyses can be conducted in parallel with clinical research[21]. Cost-effectiveness analyses inform decisions about the application of new and existing interventions to guide the judicious use of clinical and financial resources[22, 23]. While reimbursement decisions cannot ethically or legally be based on economic analyses[22], resources in rehabilitation are finite. In the recently published Guideline for Adult Stroke Rehabilitation and Recovery, Winstein and colleagues acknowledged this disconnect, stating that **"Of central interest is the need for a better understanding of the impact of rehabilitation care on patient outcomes, especially relative to resource use and cost."[24]** Therefore, it is critical to consider, in parallel, the clinical efficacy and cost-effectiveness of approaches that maximize recovery while not exhausting clinical resources[25].

A novel application of aerobic exercise (AE) training in stroke rehabilitation may be more efficacious and cost-effective in improving motor recovery and reducing disability than traditional motor learning approaches. It has been shown that AE training administered immediately prior to motor task practice enhances motor skill acquisition[4]. The direct neurophysiological effects of AE training which may be responsible for this behavioral outcome include increased levels of neurotransmitters and neurotrophic growth factors[26, 27]. The schematic diagram in Figure 1 depicts the hypothesized mechanism by which these neurophysiological effects may prime the central nervous system, creating a global response and a neural environment supportive of plasticity[5, 26-28]. While AE alone is not likely to induce neuroplasticity, performing purposeful motor task practice in close temporal proximity to AE training may harness the neurophysiological effects of AE, and facilitate motor recovery[5].

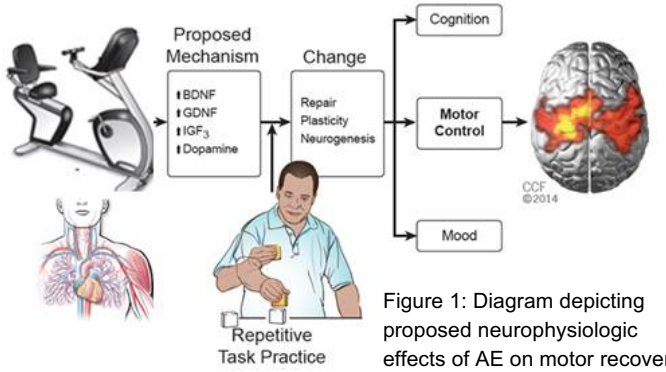

Figure 1: Diagram depicting proposed neurophysiologic effects of AE on motor recovery

The role of AE in facilitating motor recovery following stroke has not been tested empirically. Previous studies related to AE post-stroke have focused on feasibility, safety, cardiovascular endpoints, and its potential to improve fitness and reduce disability[29-37]. While these studies assess safety and efficacy of an AE regime post-stroke, it remains unknown if AE, which clearly alters central nervous system (CNS) function[5], can be used to facilitate motor recovery. We have conducted preliminary studies investigating whether AE training can enhance the motor learning benefits associated with task practice following stroke. Results from our R03 pilot study demonstrated safety, feasibility, and initial efficacy for individuals with stroke to complete an intensive AE intervention paired with upper extremity (UE) repetitive task practice (RTP)[6, 7]. Our outcomes indicated that those completing AE paired with an abbreviated session of UE RTP had greater improvements in motor recovery than time-matched UE RTP alone without an AE component (see preliminary data)[7]. Although we did not conduct a cost analysis, intuition indicates that our combined approach was more cost-effective in facilitating motor recovery. We anticipate that an economic analysis from both the health care and societal perspectives would demonstrate superiority of the combined AE and RTP approach compared to RTP alone[22].

While our intent is not to diminish the cardiovascular benefits of AE training post-stroke, it is critical to note that this project is not just another study investigating the role of AE in improving aerobic fitness. Rather, this project will for the first time simultaneously determine the clinical effectiveness and economic impact of an

innovative application of AE in facilitating UE motor recovery. Demonstrating efficacy and cost-effectiveness may foster the clinical adoption of AE into stroke rehabilitation programs, as typical 45-minute therapy sessions have been shown to occur with heart rate values in the aerobic zone for less than three minutes[38]. While our primary outcomes are related to the recovery of UE function, the concomitant improvements in aerobic fitness and cardiovascular health are likely to have an even greater *societal impact* than traditional approaches. Aerobic exercise coupled with a motor learning approach reflects an innovative model of rehabilitation that is scalable, fits within current clinical models and is complimentary to the focus on value in healthcare[25].

Scientific Premise

Several hypotheses have been proposed explaining the relationship between AE and the global behavioral responses observed related to brain function[39-45]. Aerobic exercise has been shown to increase cerebral blood flow, promote angiogenesis, and is associated with increased levels of dopamine, brain-derived neurotrophic factor (BDNF) and Insulin-like growth factor-1, all of which have been implicated in neuroplasticity and enhanced learning[5, 39, 46-48]. Increased concentrations of endogenous neurotrophins have been implicated as the mechanism for improved cognition, learning, and memory in healthy older adults[40, 41, 44]. Animal studies have shown enhanced motor training and recovery with high-intensity AE, resulting in lasting neuronal changes within the brain[47, 49]. In stroke rehabilitation, it has been posited that increased levels of neurotrophic factors and neurotransmitters are critical in facilitating the neural reorganization that likely underlies motor recovery[5, 42, 47, 50, 51]. Therefore, there is substantial scientific rationale to hypothesize that AE, which results in increased levels of neurotrophic factors and neurotransmitters, could be used to "prime" the CNS to further enhance motor recovery post-stroke. We fully acknowledge that while identifying the mechanism underlying improvements in motor recovery is important, it is beyond the scope of the proposed project.

Innovation

Given that medical expenditures represent 15% of the US Gross Domestic Product[13] and account for 60% of personal bankruptcies[52], there is an imminent need to investigate the efficiency of healthcare by applying analytical techniques to determine the clinical and economic impact of novel interventions[22]. The two research aims of this project demonstrate different, yet equally innovative goals in neurorehabilitation research and the impact of social determinants on health. The multi-faceted health economics aim demonstrates a commitment to investigating value-based care in addition to population health. The Cleveland Clinic has been recognized for pioneering efforts to transcend cost-cutting strategies and to focus instead, on improving the efficiency of medical care[25]. My team of mentors and collaborators have the background and resources in health economics to help me achieve this aim. Investigating the cost-effectiveness of AE as it impacts neuroplasticity post-stroke demonstrates a keen, yet unique perspective in rehabilitation research that emphasizes a necessary shift of focus from volume to value. The clinical aim will determine if AE training can be utilized to facilitate neuroplasticity associated with motor task practice. Although the cardiovascular benefits of AE have been well documented, the global effects of AE, particularly as they relate to improving brain function and health, have only recently been investigated[28, 45, 53, 54]. I am uniquely positioned to lead the field of stroke rehabilitation in investigating the systemic effects of AE in improving motor function. Our lab has a long history of studying the effects of AE in individuals with PD, having shown improvements in motor and non-motor function following intensive AE and enhanced functional connectivity and activation patterns on neuroimaging[55-58]. Our preliminary study in individuals with stroke has been completed which supported the safety and efficacy of AE.[6, 59] and a second study is in the final weeks of data collection. While field experts have theorized that AE training may facilitate neuroplasticity associated with task practice[5, 60], to our knowledge, no large-scale trial has paired AE with RTP in individuals with stroke to systematically investigate its potential to enhance motor recovery. My career plan is to investigate the clinical efficacy of this combined rehabilitation approach along with decision analytic methodologies including cost-effectiveness analysis. This will allow me to analyze health care interventions from clinical and economic standpoints. Addressing the economic impact is unique in rehabilitation studies is timely considering the aging population and shift from volume to value in health care. The proposed plan will serve as a blueprint for testing clinical efficacy and economic impact of various rehabilitation approaches to facilitate the clinical translation of effective and efficient models of care.

Approach

The proposed project determining the clinical effectiveness of AE in facilitating motor recovery and determining the cost-effective strategy could fundamentally alter current rehabilitation approaches and drive the adoption of AE into stroke rehabilitation.

Experimental Overview: A prospective, single-center, parallel group, rater-blind clinical trial is proposed. A schematic depicting workflow and outcomes is provided in Figure 2. A total of 60 individuals with chronic

stroke (>6 months) will be randomized to one of two time-matched groups: 1) AE and RTP or 2) RTP only. All groups receive an identical dose of contact time (36 hours) over a course of 8 weeks (3X per week). Upper extremity motor outcomes (Aim 1) will be collected at baseline, mid-treatment, end of treatment (EOT), and EOT+4 weeks. Data concerning participant demographics, social determinants, and intervention resource utilization (including personnel) will be collected during the clinical trial and at 6-months (primary outcome on full data set, Aim 2) and 12-months follow-up (secondary outcome on subset of sample, Aim 2).

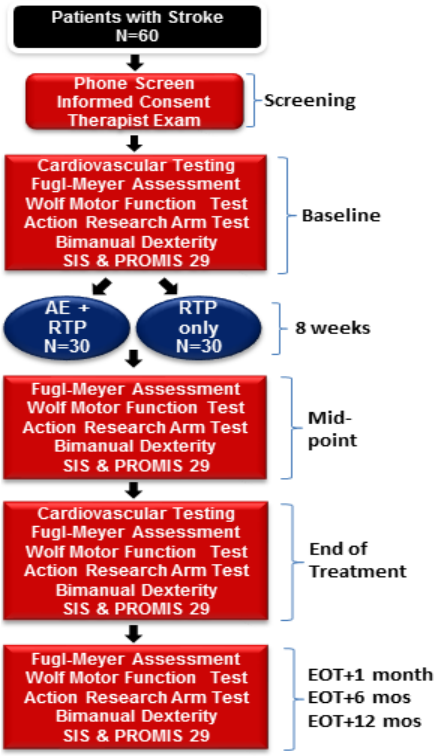

Figure 2: Study Workflow and Outcomes

The following elements of our experimental design ensure scientific rigor: 1) Randomization stratified according to baseline function and age; 2) Blinding of the rater; 3) Utilization of a time-matched control group; 4) Sample size justified to demonstrate group differences based on preliminary studies; and 5) Sound statistical analysis plan. An intent-to-treat approach will be used to address any missing data; to date <1% of data in our preliminary studies are missing.

Recruitment and Sample: Sixty individuals from the Cleveland Clinic Health System (CCHS) and adjacent medical community with chronic stroke and the following criteria for inclusion will be recruited: 1) ≥ 6 months following single ischemic or hemorrhagic stroke confirmed with neuroimaging, 2) Fugl-Meyer motor score 24-50 in the involved UE, 3) Ambulatory ≥ 20 meters with no more than contact guard assistance, and 4) 18-85 years of age. Exclusion criteria include: 1) hospitalization for myocardial infarction, heart failure or heart surgery within 3 months, 2) cardiac arrhythmia, 3) hypertrophic cardiomyopathy, 4) severe aortic stenosis, 5) pulmonary embolus, 6) significant contractures, 7), anti-spasticity injection within 3 months of enrollment and 8) other contraindication to exercise. The targeted population represents a collective cohort in whom spontaneous recovery is typically no longer occurring, potential exists for significant motor recovery, and risk associated with intensive AE training is minimized. Since our pilot R03 study, we established numerous collaborative relationships in the Cleveland stroke research community and achieved our targeted enrollment of 30 participants over a 21-month period for the current 2-year AHA study. Drs. Frederick Frost, Chairman of Physical Medicine and Rehabilitation, and Irene Katzan, neurologist in the cerebrovascular center, have endorsed our work and actively support our recruitment efforts. Based on the proposed criteria outlined above and in detail in Human Subjects section, during the past 12 months ~1200 CCHS patients would be eligible for the trial. To address transportation as a potential barrier to participation and adherence, the Cleveland Clinic offers free transportation to those who live within a 15-mile radius of the campus and free parking in an accessible, attached parking garage for those with their own vehicular transportation. Given our history and approach, recruiting 60 participants is feasible and will be accomplished.

Aim 1: To determine the effects of aerobic exercise paired with UE repetitive task practice compared to time-matched UE task practice on the recovery of UE motor function in individuals with stroke.

Rationale: Declines in UE function are common in the majority of patients with stroke. Aerobic exercise has been theorized to facilitate motor recovery following stroke[5, 51]; however, the proposed study will be the first to test this to theory empirically. Our preliminary data indicate that our AE approach combined with a reduced dosage of RTP resulted in significantly greater gains in motor function than time-matched RTP without an AE component, supporting the scientific hypothesis that AE facilitated motor recovery associated with RTP.

Outcomes: The primary clinical outcomes to evaluate changes in motor function and impairment are the Action Research Arm Test (ARAT)[8] and Fugl-Meyer Assessment (FMA)[9], respectively. To determine the impact on motor control processes, participants will complete a bimanual dexterity task in which grasping forces and torques will be quantified. Finally, the Wolf Motor Function Test[61] (WMFT) will serve as a secondary outcome.

Expected results and interpretation: It is hypothesized that the AE+RTP group will demonstrate greater improvements in UE motor function and impairment compared to RTP only. Animal and human studies suggest that intensive AE facilitates neurophysiologic changes in the brain, several of which have been implicated neuroplasticity[47, 48]. Preliminary data from our R03 study demonstrated improved motor outcomes in those completing AE+RTP compared to RTP only, implying that AE may exploit the motor learning benefits associated with RTP and could be used to decrease the dosage of RTP required for UE motor recovery[7].

Aim 2: To determine the cost-effectiveness of pairing aerobic exercise with UE repetitive task practice compared to UE repetitive task practice only to facilitate motor recovery following stroke.

Rationale: Stroke-related disability has a significant economic impact on patients, their families, and society as a whole. Novel approaches that improve recovery, overall health, and optimize resources including indirect costs borne by patients, are necessary to maximize the value of stroke rehabilitation[31]. The proposed intervention is hypothesized to increase value by providing an approach that improves outcomes and is delivered in a manner that is less resource intensive. As preliminary data suggest that outcomes were superior with the combined approach of AE+RTP, a cost-effectiveness analysis using a decision analytic model is proposed to address the clinical and economic differences between the two proposed interventions. The model will address: cost-effectiveness in the short and long term; cost-effectiveness from the healthcare provider and patient perspective, and identifying specific social determinants of health that impact the cost-effectiveness of the interventions. A tornado diagram from a study investigating the cost-effectiveness of primary stroke centers is presented in Figure 3. This diagram is included as a sample output, as it depicts one-way sensitivity analyses for variables which influence the ICER, and the magnitude and range of their contributions. The modeling techniques I learn as part of my training will produce comparable visualizations, demonstrating the impact of variables contributing to the ICER (such as absolute change in motor function, level of disability, change in cardiovascular function, employment, mortality, etc) in a quantitative manner.

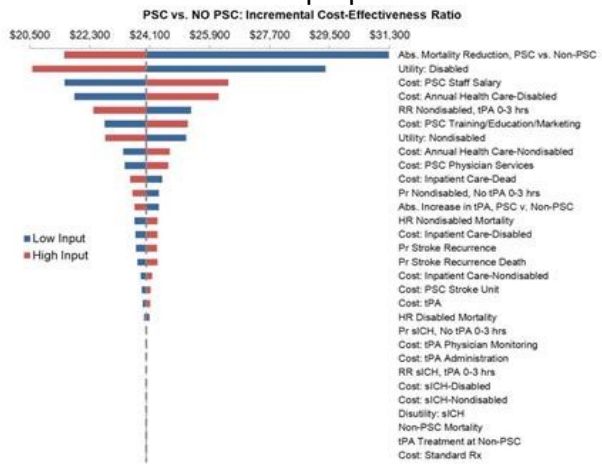

Figure 3: Sample tornado diagram depicting sensitivity analysis of variable impact on ICER

Outcomes: The primary outcome will be the ICER (change in dollars and QALY's[62] between interventions) at six months, while the secondary outcome will analyze the ICER on a subset of participants at 12 months.[22, 23]. The ICER is an analytic tool in which costs and effects of two or more interventions are calculated and presented in a ratio of incremental cost versus effect[22]. Quality metrics will be derived from the Stroke Impact Scale (SIS)[63, 64] and PROMIS 29[65]. Additional analyses will be conducted for the stroke recurrence, readmission, mortality, change in depression, return to work, and participation/compliance. All analyses will be conducted from the perspective of the healthcare sector and society, per recommendations by the second panel on cost-effectiveness in health and medicine[22]. Based on 6- and 12-month ICER outcomes, forecasting will be used to predict the optimal intervention at 2 and 5 years. Dr. Udeh has used these analytical approaches extensively and will oversee all aspects of the cost-effectiveness analyses[66-69].

Expected results and interpretation: Reimbursement for medical and rehabilitation services in the US is shifting from a model of volume-based to value-based[25]. A result is the advent of Accountable Care Organizations (ACO), in which insurers partner with healthcare organizations to manage population health, and reward them for optimization of cost and quality[70]. Based on preliminary data, it is hypothesized that AE+RTP will be optimal in terms of the ICER at six and 12 months. Demonstrating value, by improving outcomes and reducing cost, is novel and would serve to engage ACO's in terms of potential adoption of the proposed rehabilitation approach. It is also hypothesized that the ICER will improve for the optimal strategy as the time frame is increased. Given the significant potential for AE to impact overall cardiovascular health, disability, morbidity, and mortality, it is hypothesized that the ICER will be most improved from the societal perspective, favoring AE+RTP.

Clinical Trial Methodology

Cardiopulmonary Exercise Fitness Testing Protocol: As in our R03 and AHA projects with stroke and our R01 with PD patients, prior to randomization, all subjects satisfying initial screening criteria for participation will undergo cardiopulmonary exercise (CPX) testing on an electronically controlled Lode cycle ergometer and a MedGraphics CardiO_2/CP system with Breeze software. Briefly, a 12 lead electrocardiogram will be assessed prior to exercise and monitored continuously throughout exercise and recovery. A continuous incremental protocol starting at 20 Watts (W) and increasing in 20W stages every two minutes will be employed. Subjects will be encouraged to continue exercise to the point of volitional fatigue or onset of test termination criteria as described in the ACSM Guidelines for Exercise Testing and Prescription[71]. Within 5 days of completing their final session, all subjects will repeat the CPX testing. Similar to our previous studies, Dr. Blackburn, Director of Cardiac Rehab, will conduct and interpret the results of the CPX testing to ensure participant safety. All participants in the R03 and AHA projects completed the protocol, as respiratory exchange ratio values ≥1.1.

Aerobic Exercise Intervention: Individuals in the AE group will participate in a supervised exercise protocol on a stationary semi-recumbent cycle ergometer, comprised of three 45-minute sessions per week for eight weeks. Target heart rate (HR_{target}) zone for each subject, based on ACSM recommendations, will be

determined using the Karvonen formula at the 60-80% range, based on the results of initial CPX testing[72]. Participants will be instructed to exercise within their HR_{target} during the 35-minute main exercise set, occurring between a 5-minute warm-up and cool-down phase. The high-rate AE protocol will be used, based on methodology used in our previous studies[6, 56, 59]. This mode of AE is safe and has been found most efficacious in our pilot studies[6, 59]. Furthermore, it allows participants who may be deconditioned to tolerate the 45-minute AE session without compromising aerobic intensity. Figure 4 depicts continuous HR monitoring of a single, representative participant on visit 8 (left panel) and visit 18 (right panel). The participant was able to exercise within his HR_{target} for ~ 90% of the main 35-minute set between the warm-up and cool-down phases. As in our previous studies, if any patient exhibits signs of cardiac distress or hemodynamic compromise, the session will be stopped immediately and the on-call physician will be paged to the laboratory. All training will be under the supervision of a physical therapist or exercise physiologist certified in Basic Cardiac Life Support.

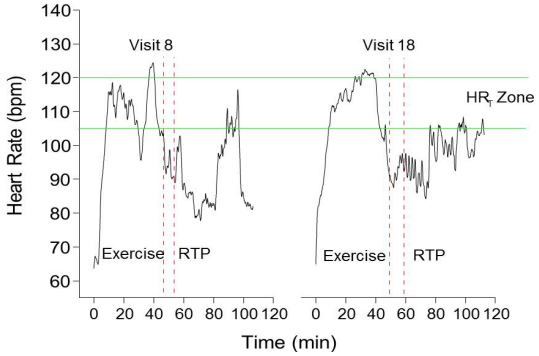

Figure 4: Heart rate response for the same participant on two separate visits demonstrating increased time spent within HR_{target} zone and sustained elevated HR response.

RTP Intervention: RTP is the current standard of care for UE stroke rehabilitation, with Class IA evidence supporting its use[12, 24]. Tasks performed with the more impaired UE are modeled after Birkenmeier and Lang[73], and identical to the approach used in our preliminary studies[6, 59]. Tasks that require a combination of reaching, grasping, manipulating and/or moving, and releasing an object are included. Tasks are designed to challenge each individual's abilities, practiced repeatedly, and graded to increase difficulty by requiring movement out of synergy, increasing range of motion requirements for task accomplishment, incorporating increasingly difficult grasp types, increasing force requirements, varying the sizes of the objects, and varying the use of adaptive equipment. An example of a task is grasping a mug with a handle versus a hard plastic tumbler, a Styrofoam cup, or a 3 ounce Dixie cup. A simple iteration may be to grasp the tumbler, push it to a target, release it, and repeat. A complex iteration would be to grasp a 3 ounce Dixie cup filled with water, pour the water into a bowl and place the empty cup onto a shelf, all while standing. Repetitions and time dedicated to RTP are recorded. All RTP is administered by a neurologic PT experienced in stroke rehabilitation and trained in RTP.

Experimental Groups

Aerobic Exercise and Repetitive Task Practice (AE+RTP): Participants in the AE+RTP group (N=30) will complete 24 intervention sessions, each ~90 minutes in length. The first 45 minutes will be spent performing AE as described in detail above under "aerobic exercise intervention". Hemodynamic response will be monitored via continuous heart rate monitoring and blood pressure measurements obtained prior to initiating, every 10 minutes during, and immediately following the exercise protocol. A 45-minute session of UE RTP as described in detail above will occur within ~10 minutes of exercise session completion.

Time-matched Upper Extremity Repetitive Task Practice (RTP only): Participants in the RTP only group (N=30) will complete two back-to-back 45-min sessions of RTP (90 min total) with a 5-10 min break between sessions. The RTP intervention will be administered in the same manner using the same approach by the same personnel as with the AE+RTP group. The planned dose of RTP has been found to be efficacious to elicit improvements in motor recovery[73]; and the protocol ensures similar contact time across both groups.

Data Variables

Exercise Training Variables: The customized software that controls the cycle records overall time, active exercise time, and monitors and stores heart rate, speed, cadence and power. The primary training variables of interest for each exercise session are: AE intensity measured as percent heart rate reserve (%HRR) during main 35-minute exercise set, average cadence and work (power) produced by the patient and motor.

Clinical and Biomechanical Measures of UE Function (Aim 1): The 33-item UE motor portion of the Fugl-Meyer Assessment (FMA) will be used to determine change in UE motor impairment[9]. The ARAT (primary outcome) and WMFT (secondary outcome), will be used as measures of motor function[8, 74]. To ensure rigorous experimental design, all measures of UE function will be obtained by an occupational therapist who has undergone training in the standardized administration of each test, has administered all testing for our previous studies, and is blinded to group assignment[59, 75-77]. The FMA, ARAT, and WMFT have been used in our previous studies, and have provided sufficient sensitivity in demonstrating change in motor function despite the heterogeneity of our sample. In addition to obtaining clinical measures of motor function, we have also used biomechanical measures of bimanual dexterity in our previous studies with stroke (see preliminary data) [11, 78-80] and other neurological diseases[10, 81-83]. Grasping forces and torques produced by both limbs are recorded by 6-DOF ATI force-torque transducers. Participants will complete 10 trials at each testing session: 5 trials in which

each hand fulfills the role of the stabilizing limb and manipulating limb. These biomechanical data will provide greater insight into motor control mechanisms underlying functional recovery. Dr. Alberts developed this device and has published results extensively[10, 80-82]. He will provide the equipment and assist with data interpretation.
Cost-Effectiveness Analysis Variables (Aim 2): Extensive participant demographics including age, gender, education, employment, support system, and social responsibilities will be collected at each time point in addition to the SIS[63] and PROMIS 29[65]. These measures will ensure the accurate calculation of quality indices and indirect costs. Direct medical costs including personnel time, equipment, and additional resources and consumables associated with each intervention will be collected throughout the intervention period. Labor prices will be sourced from the Bureau of Labor and Statistics using US averages. All costs will be adjusted to the same base year using the Medical Component of the Consumer Price Index. Discounting will be applied in line with the Recommendations of the 2nd Panel on Cost-Effectiveness in Health and Medicine[22].

Data analysis

Consideration of Relevant Biological and Sociological Variables: Participants in both groups will be compared on potentially confounding baseline variables (age, gender, socio-economic status, education, fitness, co-morbidities, degree of hemiplegia, location/type of stroke, side of lesion) to assess the extent of any imbalances across groups. Baseline variables in which there is a clinically important difference between groups may be included as covariates. Participants will also be compared using participation and adherence metrics. While recent evidence has shown that genetic polymorphisms may influence motor recovery following stroke[84-87], it is beyond the scope of this project due to cost and lack of expertise to consider these as covariates.
Analysis of Motor Outcomes (Aim 1): Motor outcomes for each group will be compared at baseline, mid-treatment, EOT, and EOT+4. The group effect on ARAT, FMA, and WMFT will be estimated using separate linear mixed effects models with a random effect for subject, fixed effects for group, examination time, and baseline value of the outcome. An appropriate covariance structure (e.g.: unstructured, compound symmetric, autoregressive) will be used as determined using Akaike's information criterion[88]. The effects of group, time, and the group-by-time interaction will be assessed for each outcome. To adjust for multiple comparisons, the family-wise error rate will be controlled via Bonferroni-type adjustment required for multiple comparisons[89]. Tukey's and other post-hoc comparisons will be used to explore pairwise differences in main effects of group membership. To further investigate the effect of the intervention group assignment on the various sub-scales of the ARAT, a multivariate analysis of variance will be used along with a separate principle component analysis to study if further dimension reduction is possible in using these two tests in the study. Transformations of the data will be made to achieve normality or other model assumptions. The overall alpha level will be set at 0.05.
Bimanual dexterity data: All force and torque data will be filtered with a phase-symmetric low-pass filter using Woltring's algorithm with existing Matlab programs[11, 80]. The primary kinetic and kinematic outcomes will be: coordination of grip-load coupling, time delay between grasping force initiation for each limb, overall time to task completion and rate of grip force production for each limb[11, 80, 90].
Cost-Effectiveness Analysis (Aim 2): A decision analytic model using a systematic, quantitative approach using Treeage Pro® will be developed comparing AE+RTP and UE RTP only. All possible outcomes will be incorporated into the model. A hospital/payer perspective will be adopted and include all relevant costs and outcomes. All outcome probabilities used in the model will be determined from the clinical trial's data collection at the 6 time points. As part of my training, I will learn cost-effectiveness methodologies, including approaches to analyze variability and uncertainty in the model and the population, and methods to evaluate model generalizability (sensitivity analysis) in accordance with current recommendations[22, 23, 62]. For this analysis, a cost effectiveness summary will be produced, including the costs and effects of each intervention, the cost-effectiveness ratio of the interventions, and the incremental cost-effectiveness ratio between the interventions from two perspectives: healthcare sector and society. Deterministic and probabilistic sensitivity analyses will be used to evaluate result uncertainty attributable to the model and population variability[91]. Sensitivity analyses will be summarized to show that the optimal strategy is the choice strategy in 'what' percentage of time and for 'what' variable values and be reported as a cost-effectiveness acceptability curve[91].

Power and Sample Size Justification:

The power and sample size calculation is based on FMA scores from our R03 study. A minimal clinically important difference (MCID) range of 4.25-7.25 points has been reported for the FMA[92] with baseline subject standard deviation of 5.7 – 6.3 points. To be conservative, we have assumed the MCID to be 4.25 for the purposes of our power calculations. Based on results from our R03 which included 3 intervention groups, the forced AE+RTP group, voluntary AE+RTP group, and RTP only groups improved on the FMA by a mean of 12.33(4.13), 4.83(4.91), and 4.4(4.87), respectively. In the sample size and power computation, it is assumed that there is an increase of 2*MCID for the AE+RTP group and 1*MCID for the RTP only group, along with

statistically significant differences between the groups at EOT. Further, it is assumed that subject SD will remain ~10 points within the group. Based on these assumptions, with n=30 in each of the intervention groups, we will have a .87 power at the 0.05 significance level to detect pairwise group differences equivalent to an effect size of .4. All computations were completed using the PASS 13 program (East Kaysville, Utah).

Preliminary Studies

Our preliminary study in patients with stroke[7] and larger studies in Parkinson's disease[55-58] **(NIH R01HD056316, R21 HD056316)** have provided the majority of clinical efficacy data and technology that will be utilized for the proposed project. Cost-effectiveness analyses have not been conducted on prior studies. The primary goals of the stroke study were to determine feasibility and initial efficacy of utilizing two different modes of AE in patients with stroke as a means to promote functional motor recovery. In our R03, patients were randomized to forced-rate aerobic exercise (FE) along with RTP (FE+RTP), voluntary-rate aerobic exercise (VE) along with RTP (VE+RTP) or time-matched RTP only without an AE component. Preliminary data are presented from 17 participants who completed all study-related interventions and testing. Using a more rigorous study design from our R03, we recently achieved our target enrollment of 30 participants for our ongoing AHA study within a 22 month time period. No data from the ongoing AHA study are reported, as the trial remains active.

Cardiopulmonary Testing is Safe and Effective for Screening Individuals with Stroke: The pre-CPX medical screen and subsequent CPX testing protocol in this proposal was used successfully in all participants in our preliminary studies in determining the *safety* of individuals with history of stroke and cardiovascular co-morbidities to participate in the study intervention. Both AE groups demonstrated improvements in peak VO_2 with the VE+RTP improving by a mean of 2.4 mL/kg/min and the FE+RTP group improving by a mean of 1.3 mL/kg/min.

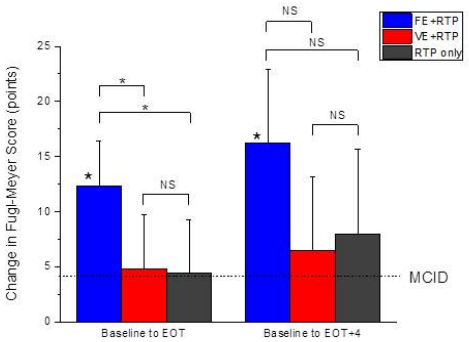

Fig 5: Mean (SD) change in Fugl-Meyer Assessment impairment for each group.

Individuals with Stroke can safely exercise at moderate to high aerobic intensity: Continuous heart rate monitoring was used to ensure participant safety and to monitor compliance[31, 32]. On average, participants in the FE+RTP and VE+RTP groups exercised at mean intensities of 56.5 [±15.7%] and 55.9 [±8.7%] HRR, well above minimum recommendations[93].

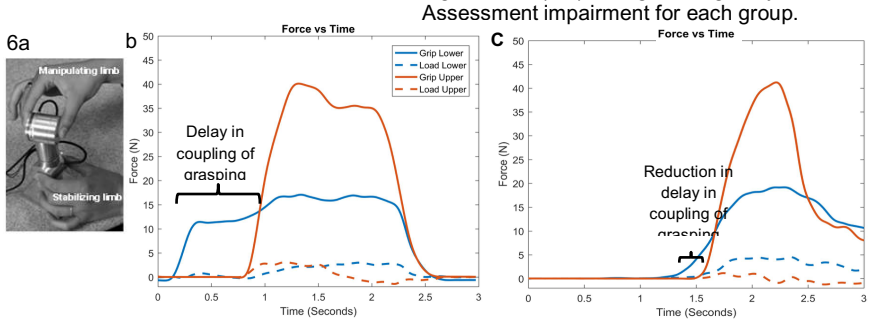

Fig 6a: Bimanual dexterity assessment system. At baseline (6b) the patient exhibited a sequential activation of grasping forces while following AE+RTP (6c), grasping forces were initiated nearly simultaneously.

Aerobic exercise improves motor function following stroke, despite smaller RTP dose: All three groups demonstrated decreased motor impairment from baseline to EOT as measured by the FMA, exceeding MCID values[92]. The RTP group completed ~75% more reps of RTP per visit than the AE groups[7]. Despite this significant difference in RTP dosage, the forced AE group was the only of the three groups to exhibit *and maintain* significant improvements as evaluated by the FMA ($p<0.01$), with a mean improvement of 12.3 [±1.6] points from baseline to EOT. Fig 5 depicts the mean change (SD) in the FMA from baseline to EOT and EOT+4 for all groups[47]. Improvements were significantly greater for the FE group from baseline to EOT compared to the VE and RTP only groups[41]. Biomechanical data were obtained during a bimanual task (Figure 6a), in which the participant attempts to disconnect the top and bottom portions of the device. Two force transducers measure the coordination of grasping forces from the stabilizing limb and manipulating limb. Data from a representative AE group participant in our AHA study shows a delay in the coupling of grasping forces and diminished force production from the involved UE (solid blue tracing) at baseline (Fig 6b), with improved coordination and quality of inter-limb grasping forces at EOT (Fig 6c).

Limitations and Future Directions: While we have provided theoretical rationale regarding mechanisms associated with motor recovery as a result of the proposed interventions, we have opted to focus on objective clinical and biomechanical outcomes rather than attempting to identify the potential mechanism(s) responsible for enhanced neuroplasticity as a result of AE. Additionally, in order to obtain all data within the 5-year span of the study, the primary economic analysis is for a timeframe of 6 months with an interim analysis for a subset of the sample at 1 year. Nonetheless, the training I obtain from this K award will provide me with the foundational knowledge to conduct clinical research with scientific rigor, and will create a template for formal longitudinal cost effectiveness analyses on larger datasets, comparing the value of various rehabilitation approaches.