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AExaCTT – Aerobic Exercise and Consecutive Task-specific Training for the upper limb after stroke: Protocol for a randomised controlled pilot study

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ABSTRACT

Motor function may be enhanced if aerobic exercise is paired with motor training. One potential mechanism is that aerobic exercise increases levels of brain-derived neurotrophic factor (BDNF), which is important in neuroplasticity and involved in motor learning and motor memory consolidation. This study will examine the feasibility of a parallel-group assessor-blinded randomised controlled trial investigating whether task-specific training preceded by aerobic exercise improves upper limb function more than task-specific training alone, and determine the effect size of changes in primary outcome measures. People with upper limb motor dysfunction after stroke will be allocated to either task-specific training or aerobic exercise and consecutive task-specific training. Both groups will perform 60 hours of task-specific training over 10 weeks, comprised of 3 × 1 hour sessions per week with a therapist and 3 × 1 hours of home-based self-practice per week. The combined intervention group will also perform 30 minutes of aerobic exercise (70–85%HR_{max}) immediately prior to the 1 hour of task-specific training with the therapist. Recruitment, adherence, retention, participant acceptability, and adverse events will be recorded. Clinical outcome measures will be performed pre-randomisation at baseline, at completion of the training program, and at 1 and 6 months follow-up. Primary clinical outcome measures will be the Action Research Arm Test (ARAT) and the Wolf Motor Function Test (WMFT). If aerobic exercise prior to task-specific training is acceptable, and a future phase 3 randomised controlled trial seems feasible, it should be pursued to determine the efficacy of this combined intervention for people after stroke.

1. Introduction

1.1. Background

Currently 440,000 persons after stroke live in community settings in Australia [1]. Many with stroke experience chronic disability and although two-thirds receive care each day [1], the majority still have unmet needs [2]. Upper limb dysfunction is a persistent and disabling problem present in 69% of persons after stroke in Australia [3]. Upper limb dysfunction is a major contributor to poor well-being and quality-of-life [4–7]. Unsurprisingly, advancing treatments for upper limb recovery is a top ten research priority for persons after stroke and their carers [8].

In Australia, 87% of persons with stroke-attributable upper limb impairments receive task-specific training [3]. Task-specific training is a progressive training strategy that utilises practice of goal-directed, real-world, context-specific tasks that are intrinsically and/or extrinsically meaningful to the person, to enable them to undertake

Abbreviations: ARAT, Action Research Arm Test; BDNF, brain-derived neurotrophic factor; CERT, Consensus on Exercise Reporting Template; CM, centimetre; CONSORT, Consolidated Standards of Reporting Trials; ECG, electrocardiography; ELISA, enzyme-linked immunosorbent assay; FAS, Fatigue Assessment Scale; GP, general practitioner; HR_{max}, age-predicted maximal heart rate maximum; HR_{peak}, peak heart rate; IPAQ, International Physical Activity Questionnaire; MAL, Motor Activity Log; $mL.kg^{-1}.min^{-1}$, millilitres per kilogram per minute; MRI, magnetic resonance imaging; MS, Microsoft; m/s, millimetres per second; NAA, N-acetyl Aspartate; PV, Peak Velocity; PD, Peak Deceleration; REDCap, Research Electronic Data Capture; reps, repetitions; RPE, rating of perceived exertion; RPM, revolutions per minute; SIS, Stroke Impact Scale; s, seconds; VO_2, oxygen uptake; VO_{2peak}, peak oxygen uptake; WMFT, Wolf Motor Function Test; 6MWT, Six Minute Walk Test

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activities of daily living [9] and may improve upper limb motor function after stroke [9–11].

Improvements in motor function coincide with structural and functional reorganisation of the brain [12–15]. The brain's ability to undergo these changes is denoted as neuroplasticity. Capitalisation and enhancement of neuroplasticity in peri-infarct and non-primary motor regions may promote recovery via an increased response to motor training and other neurorehabilitative interventions [16–18].

Many studies show that aerobic exercise (prolonged, rhythmical activity using large muscle groups to increase heart rate) enhances neuroplasticity [19], grey matter volume, white matter integrity [20–22] and brain activation [23–25]. Furthermore increasing evidence indicates that lower limb aerobic exercise increases upper limb motor function. A single bout of aerobic cycling exercise can improve long-term retention of a motor skill in healthy individuals [26], regardless of whether performed immediately before or after motor training [27].

Aerobic exercise increases BDNF [28]. Improvements in motor skill learning and memory induced by aerobic exercise have been associated with increased peripheral blood concentrations of BDNF [26]. BDNF is involved with neurogenesis [29] and neuroprotection [30] in the human brain [31], thereby playing an important role in stroke recovery, including facilitating functional upper limb motor rehabilitation [32].

In chronic stroke, an 8-week programme of lower extremity endurance cycling enhanced upper extremity fine motor control [33]. Also, a single bout of aerobic treadmill exercise improved grasp function of the hemiparetic hand [34]. As aerobic exercise alone can enhance motor function after stroke, motor learning in stroke rehabilitation may be facilitated if aerobic exercise is paired with motor training [35,36].

1.2. Aims and objectives

The aims of this study are to 1) assess the feasibility of conducting a randomised controlled trial to compare the effects of task-specific training preceded by aerobic exercise to task-specific training alone on upper limb motor function after stroke; and 2) calculate the effect size of changes in primary clinical outcome measures to evaluate proof-of-concept and inform calculation of sample size for a future phase III trial. This includes investigating potential neural correlates of exercise-induced motor function changes using peripheral blood serum BDNF measurement and multi-modal MRI.

2. Methods

2.1. Study design

This is a parallel-group assessor-blinded randomised controlled pilot study (Fig. 1). One group will undertake task-specific training alone and the other group will undertake 30 minutes of aerobic cycling exercise prior to their task-specific training. The interventions will be delivered by a therapist 3 days per week for 10 weeks. Both groups will be provided with an individually-prescribed task-specific training programme to practice at home for 60 minutes, 3 times per week. Assessments will be conducted at baseline, within 1 week from the end of intervention, and 1 and 6 months following the end of the intervention period. Ethics approval has been obtained from the Hunter New England Human Research Ethics Committee (14/12/10/4.07) and registered with the University of Newcastle Human Research Ethics Committee (H-2015-0105). The study is registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12616000848404).

2.2. Sample size

As this is a feasibility study, the sample size will be determined by the number of participants that are feasible to recruit and study within the timescale of the project. Consecutive sampling will be used to recruit a target of 20 participants, which will provide sufficient information to indicate feasibility and provide estimates of effect sizes to inform a larger phase III randomised controlled trial to determine efficacy.

2.3. Participants

Eligibility criteria for participants are presented in Table 1. Participants will be recruited from the Hunter Medical Research Institute volunteer register, local hospitals, by advertisement on the website of the National Stroke Foundation and Stroke Recovery Association of New South Wales, and University of Newcastle and Hunter Medical Research Institute social media networks. In the clinical settings, physiotherapists and occupational therapists will identify eligible and interested potential participants, and refer them to the research team, who will then follow up by phone call. Informed written consent will be obtained for all participants.

2.4. Assignment to intervention group

Participants meeting inclusion criteria will be referred for baseline assessment, after which randomisation will occur. To obtain balanced groups with respect to numbers and severity of functional impairment, computer-generated [37] 2-4-6 block randomisation will be used with stratification using scores on the ARAT (Group 1: score 0–3; Group 2 score 4–28; Group 3 score 29–56) [38]. Randomisation will be concealed and performed via the REDCap system [39].

2.5. Interventions

2.5.1. Task-specific training

A Cochrane overview based on the synthesis of systematic reviews concluded that there is moderate quality evidence that a minimum of 20 h of task-specific training is required to achieve a beneficial effect [40]. Therefore, participants will receive a total of 30 h of task-specific training with a therapist and an additional 30 h of home-based practice to promote translation to activities of daily living.

Repetitions will be high (100–300 reps/session) to stimulate the neuroplastic changes necessary for motor learning to occur in the specific neural networks that mediate motor functions [41,42]. However, repetition of a movement alone is not sufficient to create cortical changes, as these are related to specific skill learning in line with a learning-dependent model of neuroplasticity [43–45]. The importance of the specificity of the task is indicated by the findings in animals that motor cortical reorganisation is best triggered by carrying out tasks which are meaningful in terms of function and usefulness [46]. Since goal-oriented training also enhances compliance, motivation and self-efficacy [47–49], task prescription will consider individual goals by allowing each participant to choose 5 activities that they would like to accomplish by the end of the programme. Appropriate exercises will then be selected from a task-specific upper limb training manual containing 142 predefined activities and movements [50] and adapted based on the individual participant's needs. Based on training principles from the disciplines of motor learning [51] and exercise physiology [52], the difficulty of each component exercise is graded, reviewed and progressed according to the individual ability of the participant.

Where required, everyday skills will be broken down into practice of functional components until each component is mastered and can be systematically reassembled into the original sequence to perform the whole task, or as much of the whole task as possible (chaining) [53]. Biomechanical analysis of the whole task will underpin choice of part-practice to facilitate transfer of learning to the whole task. The functional components will maintain a strong resemblance to the original skill itself (e.g., extend elbow and flex shoulder to reach to cup, open fingers and thumb to grasp cup, flex elbow and shoulder to transfer cup

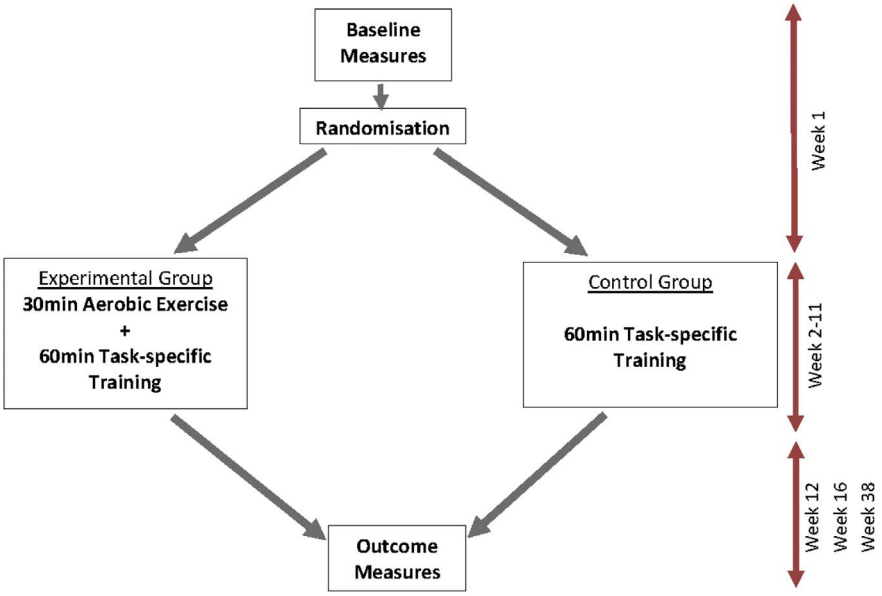

Fig. 1. Study design.

Table 1
Participants.

Inclusion Criteria
- Adults aged > 18 years old
- Clinical diagnosis of ischaemic or haemorrhagic stroke
- Upper limb movement deficit i.e., score < 63 on the WMFT or < 52 on the ARAT
- Able to perform the aerobic exercise training
- GP medical clearance

Exclusion Criteria
- Upper limb movement deficits attributable to non-stroke pathology
- Unable to lift hand off lap when asked to place hand behind head (gross motor task from the ARAT)
- Severe fixed contractures of elbow or wrist (i.e. grade 4 on the modified Ashworth scale)
- Moderate to severe receptive aphasia (< 10 on 'receptive skills' of Sheffield Screening Test for Acquired Language Disorders)

Other Participant Characteristics
- Neglect (Star Cancellation)
- Cognitive impairment (Montreal Cognitive Assessment)
- Disability (modified Rankin Scale)

to mouth), as functional movement arises from interaction between the individual, the task and the environment in which the task is being undertaken [54]. The significance of the role of the environment in the accomplishment of a task is reflected in the fact that movement kinematics of the upper limb can be different under real-life conditions compared to simulated conditions in humans [55]. For example, after stroke people exhibit different movement kinematics when simulating drinking from an empty glass compared to drinking from a glass of water [56]. Organisation of movement of the upper limb is positively influenced by the conditions in which it is being carried out [57].

To ensure variability of training for better translation to everyday life, participants will be encouraged to use objects that vary in terms of shape, size, and texture (e.g., round/square object, narrow/wide object, empty/full cup, lightly/heavily spring-loaded clothes pegs, rough/smooth), and to reach different distances [58], speeds [59] and directions. Random practice will also be utilised in order to increase motor learning and retention via high contextual interference [60,61]. Exercises will be graded by choosing different weighted objects, altering the plane of movement relative to gravity and increasing numbers of repetitions. Task-specific training will be supervised by a physiotherapist or occupational therapist. Where necessary, activities will be performed with assistance (therapist guides the participants arm along the movement trajectory, or stabilises one body part while participant moves another) until active movement can be achieved without support, during which trajectory deviation can be corrected by the therapist or through feedback mechanisms (e.g., boundary markings/obstacles/objects). In order to maximally challenge each participant, the aim is to adjust each exercise as described above until they can perform the task successfully without requiring the use of compensatory strategies. Prior to commencing the programme, the principles of task-specific training will be explained to the participant, with emphasis on the importance of frequent training and high repetitions to optimise rehabilitation.

The home-based practice will be based on that of Cunningham et al., 2015 [50]. Each participant will be provided with a copy of the home-based upper limb task-specific training manual [50], from which the therapist will prescribe specific exercises to be completed at home each week and also provide demonstrations of variations and adaptations to suit individual abilities and their home environment. Carers will be advised to remind, encourage and assist participants to practise and record the number of repetitions and time spent on each activity in log sheets which will be returned to the therapist during the first visit of each week.

2.5.2. Aerobic exercise training

The aerobic exercise will be performed on a low entry level upright (928G3, Monark, Sweden) or semi-recumbent (RT2, Monark, Sweden) cycle ergometer. The specific ergometer will be prescribed according to individual ability and impairment. For example, where stroke-related balance deficits and lower limb dyscontrol preclude use of an upright ergometer, a semi-recumbent ergometer will be selected. Although exercise-induced increments of BDNF have a beneficial effect in facilitating neuroplastic processes that underlie recovery from brain injury, the optimum threshold required for these effects in humans are not yet known. Synthesised findings from post-stroke animal studies show that forced exercise at moderate-high intensity increases BDNF and synaptogenesis in multiple brain regions [19]. In humans, high-intensity aerobic exercise induces increases in motor learning, motor memory, BDNF and paired associative stimulation in healthy subjects [27,62]. Although the only studies investigating aerobic exercise and upper limb motor function after stroke in humans found that moderate intensity (70% age-predicted HR_{max}) increased motor learning [33,34], given the very strong correlations between peripheral lactate concentration and motor skill acquisition and retention in healthy subjects [26], it is plausible that larger effects may be obtained if a higher intensity of exercise is used. Continuous vigorous exercise may be challenging to sustain for many people after stroke, which may decrease exercise

adherence [63]. High intensity interval training involves concentrated bouts of relatively vigorous exercise interspersed with bouts of recovery of varying duration and intensity and is feasible in mild-moderate subacute people with stroke [64]. Therefore participants will be prescribed 4 × 4-minute intervals of high-intensity exercise (85% of HR_{peak}) with a 3-minute active recovery (70% of HR_{peak}) period between each interval per 30-minute session [64]. In the last 15 seconds of each interval, heart rate (via a heart rate monitor (T31, Polar, Australia)) and rating of perceived exertion (Borg 6–20 RPE scale) [65] will be recorded in the exercise logs by research assistants, as well as workload in Watts, cadence and duration of exercise achieved. The initial level of resistance will be prescribed based on data from an incremental cycle ergometer test performed prior to starting the training programme, and is progressively adjusted to maintain a high intensity (as indicated by 77–93% of HR_{peak} and an RPE of 14–16) [66]. Data from the aerobic exercise intervention will be reported according to the Consensus on Exercise Reporting Template (CERT) checklist [67].

2.6. Outcome measures

2.6.1. Feasibility

Feasibility outcome measures and their methods of evaluation are presented in Table 2.

2.6.2. Clinical efficacy

The following series of assessments will be administered at 4 time points – (a) Baseline, (b) Post-Intervention, and at (c) 1 month, and (d) 6 months, after the intervention period.

Table 2
Feasibility outcomes.

Rate of recruitment
- Percentage of potentially eligible participants who provide consent to participate relative to the total number of potentially eligible participants.

Compliance to the programme
- Percentage of training sessions attended and amount of home-based practice performed relative to the total prescribed.

Adherence to the intervention protocols
- Any variations to intervention protocol will be recorded in the participant training diaries by the researcher supervising the session and adherence to the home-based practice will be self-reported once a week.

Acceptability of the intervention
- Acceptability of the aerobic exercise and consecutive task-specific training intervention will be assessed by means of a dichotomous questionnaire administered within 1 week of completion of the intervention program.

Identification of post-exercise exertional fatigue
- Exertional fatigue during the treatment session will be measured by the Visual Analogue Scale once a week.

Rate of retention
- Percentage of participants who complete the intervention relative to the number randomised.

Completeness of outcome data
- Percentage of missing data relative to that expected.

Frequency of adverse events
- Adverse events will be recorded as adverse events and serious adverse events.
- All events will be reported to the Hunter New England Human Research Ethics Committee and the University of Newcastle Human Research Ethics Committee and Health and Safety Committee.

Suitability of eligibility criteria and screening procedures
- Any amendments to eligibility criteria and screening procedures will be documented by the trial coordinator.

Suitability of study questionnaires and data collection tools
- Any issues with data collection questionnaires and tools will be recorded by the trial coordinator.
- Results from the ARAT and WMFT will be compared with regards to sensitivity to measure change in motor function relative to the level of impairment of the population recruited by the study.

Rate and cause of unblinding events
- Percentage of correct group allocation guesses by the assessor.
- Any unblinding events will be recorded by the lead outcome assessor and reported to the trial coordinator for investigation.

2.6.2.1. Motor function. The standardised protocol for the ARAT [68] will be used to measure upper limb function. The ARAT has an ordinal scoring system (0, 1, 2 or 3 for each item) with higher values indicative of better performance. This 19-item test assesses motor ability by reaching and grasping sized, shaped and weighted objects and lifting them on to a shelf [69]. The test has high inter-rater and test-retest reliability (0.98 and 0.99 respectively), good validity and is sensitive to therapy-related changes after stroke [70]. The test is less suited to participants who lack hand function as they may only be able to score points in the Gross Motor section.

The WMFT will be used to measure motor impairment and function [71]. It requires the participant to perform 15 upper limb activities, and time to complete each task is measured. It is more sensitive to changes in motor impairment than the ARAT as it involves grasping objects in a greater variety of functional tasks, and includes a number of upper arm movements not requiring grasp. This assessment has high inter-rater reliability (0.97), test-retest reliability (0.95), internal consistency, and construct validity [72].

2.6.2.2. Self-reported upper limb use. The Motor Activity Log (MAL) will be used to ask participants to rate on a six-point scale their perceived amount and quality of use of the affected limb in performing 28 everyday tasks in their daily life [73]. The MAL has good internal consistency (0.94) and it is a reliable (0.82) and valid (0.72) assessment after stroke [74].

2.6.2.3. Self-reported health status. The Stroke Impact Scale (SIS) is a stroke-specific quality-of-life measure that will be used to assess multidimensional stroke outcomes, including strength, hand function, activities of daily living, mobility, communication, emotion, memory and thinking, and participation. Participants rate difficulty to perform each item on a five-point Likert scale. The hand function section of the SIS is considered to have excellent interrater reliability (0.82), internal consistency (0.95) and criterion validity (0.81) [75].

2.6.2.4. Motion analysis. Kinematic variables of 10 trials of a reach-to-grasp task will be analysed (ProReflex system, Qualisys Inc., Sweden). Kinematic variables analysed will include:

- Transport Phase:
  - Movement Duration (s)
  - Peak Velocity (PV) (m/s)
  - Time to PV (s) and Time to PV expressed as a percentage of movement duration
  - Time to Peak Deceleration (PD) (s) and time to PD expressed as a percentage of movement duration
- Grasp Phase:
  - Start time of aperture opening (s)
  - Peak aperture size (cm)
  - Time of peak aperture (s)
  - Time of peak aperture expressed as a percentage of movement duration

2.6.2.5. Aerobic fitness. An incremental cycle ergometer test will be conducted on an upright cycle ergometer (928G3, Monark, Sweden) during which participants will wear a portable metabolic cart (K4b^2, Cosmed, Italy) to measure consumption of oxygen (VO_{2peak}, $mL.kg^{-1}.min^{-1}$), which is the gold standard for aerobic fitness testing. A portable ECG (Quark T12, Cosmed, Italy) will be used to monitor cardiac rhythm and to measure heart rate during exercise. Participants will pedal at a cadence of 50–60 revolutions per minute (RPM) beginning at a power output of 20 Watts. Power output will increase by 10 Watt increments every 30 seconds primarily by adjusting resistance. Heart rate and rating of perceived exertion (Borg 6–20 RPE scale) [65] will be recorded every 30 seconds. The test will be terminated when the participant reaches 85% of age-predicted HR_{max}

or is unable to continue due to volitional exhaustion. The formulas used to calculate age-predicted HR_{max} are as follows:

Age-predicted HR_{max} = (220 – age)

or

(164 – (0.7 × age)) if the participant is on beta-blocker medication [76].

2.6.2.6. Functional fitness. The 6-Minute Walk Test (6MWT) will be performed in accordance with the American Thoracic Society Guidelines [77]. The 6MWT is widely used in clinical practice to assess the distance walked in 6 min. The use of a walking aid is permitted if required. It will be conducted on a straight, hard-surfaced 20 m track due to space restrictions [78]. A portable metabolic cart (K4b^2, Cosmed, Italy) and ECG (Quark T12, Cosmed, Italy) will be worn for the duration of the test to measure oxygen consumption, cardiac rhythm and heart rate.

2.6.2.7. Fatigue. Fatigue is common after stroke [79,80]. The Fatigue Assessment Scale (FAS) will be administered to detect any changes in fatigue levels over the course of the study. It has good validity (0.71) and test-retest (0.77) and inter-rater (0.88) reliability after stroke [81].

2.6.2.8. Self-reported physical activity. Although participants will be asked not to alter current levels of physical activity during the trial, the International Physical Activity Questionnaire (IPAQ) will be administered to determine any changes in physical activity levels over the study period. The IPAQ has similar test-retest reliability (0.8), concurrent (0.67) and criterion (0.3) validity to other self-reported measures of physical activity [82].

2.6.3. Secondary analyses

The following assessments will be administered at baseline and one week after completion of the intervention.

2.6.3.1. Neuroimaging. To further elucidate exercise-induced neural changes participants will undergo multi-modal MRI. Scanning will consist of structural imaging (T1 and T2-weighted imaging) to identify stroke location, stroke volume and volumetric changes in white and grey matter. Diffusion tensor imaging will be obtained to identify changes in the structural connectivity of motor-related areas. Resting-state functional MRI will be used to assess changes in brain networks relating to motor learning. Magnetic resonance spectroscopy will be used to identify changes in brain metabolite concentrations (N-acetyl Aspartate (NAA), a marker for neuronal tissue; and glutamate/glutamine, excitatory neurotransmitters). Each scanning session will amount to 30 minutes of scanning time.

2.6.3.2. Peripheral serum BDNF concentration. At baseline and within 1 week post-intervention 10 ml of peripheral blood will be drawn from the participant's median cubital vein. Samples will be collected in the fed state between 8am and 11am, after the participants have rested for 15 minutes after arrival. The samples will be placed on ice for 60 minutes, then centrifuged at 2000g for 15 minutes, and stored at −80 °C until assayed. Serum BDNF concentrations will be measured using a commercial enzyme-linked immunosorbent assay (ELISA) according to instructions provided by the manufacturer.

2.7. Blinding of assessors

As per established blinding procedures [83], although it is not possible to blind participants and therapists providing the trial intervention to treatment allocation, the independent outcome assessor will be blinded to treatment allocation for the primary clinical efficacy outcome measures used in the trial, i.e., the ARAT and the WMFT, as well as the peripheral serum BDNF and motion analysis. The SIS, MAL, IPAQ and FAS are self-reported measures, and since participants will not be blinded to treatment allocation, it will not be possible to achieve blind outcome assessment for these outcomes. VO_2 data during the 6MWT and the Incremental Cycle Ergometer Test will be obtained objectively by a portable metabolic cart (K4b^2, Cosmed, Italy) thus presenting no risk of bias for these measures.

The blinded assessor for outcome measures will be a physiotherapist. These assessments are to be conducted by the same physiotherapist if possible. In the event of this assessor being unavailable or unblinded, assessments will be performed by another blinded and experienced physiotherapist. This assessor will be based at a different site than the therapist delivering intervention for the duration of the trial. All trial participants will be informed about the importance of blinded assessments during their baseline assessment and reminded not to disclose the intervention they are receiving to the assessor at the commencement of each assessment appointment. A trial questionnaire to check the success of blinding will be completed by the assessor at all outcome measure time points, which includes a field to record the details and circumstances of any unblinding events.

2.8. Data collection and management

Data from baseline and outcome assessments will be recorded by the assessor in REDCap (Research Electronic Data Capture) tools hosted at the Hunter Medical Research Institute [39]. REDCap is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Data from intervention delivery sessions will be logged in training diaries by the treating therapist.

Initially all raw participant data will be stored on REDCap and in a locked filing cabinet located on level 4 in the Hunter Medical Research Institute building. Only the research assistants and the chief investigators will have access to the raw data. Once data collection has concluded, the data will be entered into MS Excel and imported into a statistics program. All participants will be identified by alphanumeric code only, and all electronic files stored on a password-protected file will only be accessible by the chief investigators. Following completion of the trial, all data will be stored at Hunter Medical Research Institute for 8 years. The results of the study will be published in general terms according to CONSORT guidelines for randomised pilot and feasibility trials [84] and will not allow the identification of individuals.

2.9. Data analysis

Feasibility data will be reported using descriptive statistics. The mean change over time and 95% confidence interval for each group will be calculated for the proposed primary outcome measures. The effect size of differences over time will be calculated using the Cohen's d. An intention to treat approach will be used.

3. Discussion

Improvements in motor skill learning and memory in response to aerobic exercise have been associated with increased peripheral blood concentrations of BDNF [26]. If aerobic exercise alone can enhance motor function after stroke, motor learning in stroke rehabilitation may be enhanced if aerobic exercise is paired with motor training. This study will investigate the feasibility of a randomised controlled trial comparing combined aerobic exercise and consecutive task-specific training versus task-specific training alone to improve upper limb function after stroke. The number of participants recruited, ease of

recruitment, compliance with the program, retention in the study and acceptability of the interventions will provide sufficient information to indicate feasibility. Outcome data will be utilised to inform a larger phase III efficacy trial by assessing effect sizes, variability and completeness of data. This study will carry out a preliminary investigation into the potential enhancement of a currently used intervention, with an expected effect size of ≥ 0.2 based on Cohen's *d*. This would be deemed supportive of a larger phase III trial to determine efficacy which may contribute to changes in future clinical practice. This study follows recommendations for progressive staging of pilot studies of motor interventions [85] and guidelines for the evaluation of complex interventions [86], and meets the criteria of a randomised pilot study [87].

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