Aerobic exercise and cognitive health among stroke survivors

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i. Abstract

Background

In the United Kingdom (UK), there are 1.2 million stroke survivors; of which approximately 36% are living with severe movement impairments and 83% experience poor cognitive health. Evidence suggests that aerobic exercise is beneficial for improving cardiovascular and cognitive health. However, the nature of the relationship between cardiovascular and cognitive health among stroke survivors is yet to be quantified. Studies evaluating the impact of exercise in people with stroke tend to exclude those who are living with moderate to severe post-stroke movement impairments. The feasibility of appropriate outcome measures for evaluating the impact of exercise, and suitable exercise-based interventions are yet to be established for this population.

Aim

To explore the influence of exercise after stroke on cardiorespiratory fitness, with a view to maintain cognitive health.

Methods

A narrative systematic review was undertaken to explore the nature of the relationship between cardiorespiratory fitness and cognitive health, among stroke survivors.

A mixed method, randomised feasibility study was undertaken. Two modes of cardiopulmonary exercise testing (CPET) were explored: treadmill with body-weight support harness (BWS) and cycle ergometry. Participants were allocated to a six-week exercise-based intervention, of either aerobic exercise, strength training, or a combination of aerobic exercise and strength training. Outcomes included feasibility components, peak aerobic capacity (VO_{2peak}), cognitive function, quality of life and activities of daily living. The acceptability and satisfaction of CPET procedures and exercise-based interventions were explored in semi-structured interviews.

Results

There is a lack of evidence to quantify the relationship between cardiorespiratory fitness and cognitive functioning domains and the evidence that exists is of low quality. A systematic review of

eight studies found heterogeneity in assessment tools for cognitive function and little standardisation in CPET protocols.

Overall, CPET and a six-week exercise-based intervention of either aerobic exercise, strength training or a combination of aerobic exercise and strength training, was safe and feasible for stroke survivors with moderate to severe movement impairments. Participants found it to be acceptable and satisfactory. This was primarily attributed to their enjoyment, increased confidence and a feeling of a sense of community with other participants.

Conclusion

The evidence provided in this thesis provides preliminary work to support the implementation of exercise-based interventions, with a view to maintain the cognitive health of stroke survivors. There is a need for well-designed studies to understand the nature and the strength of the relationship between cardiorespiratory fitness and cognitive function among stroke survivors. The feasibility study demonstrated inclusive adaptations for CPET and exercise training for those who are living with moderate to severe post-stroke movement impairments. It is hoped that based on the learnings of the feasibility study, further research may determine optimal methods for implementing exercise after stroke interventions, with a view to maintain cognitive health.

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Acknowledgements

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ii. Conference presentations arising from this thesis

May 2018 - *Aerobic exercise and cognitive health among stroke survivors.* Neuro-Rehabilitation and Neuro-Repair World Congress, Maastricht

October 2017 - *Aerobic exercise and cognitive health among stroke survivors– a feasibility study protocol.* The Stroke Association Annual Conference, Liverpool

May 2017 - *Aerobic exercise and cognitive health among stroke survivors – a feasibility study protocol.* Faculty of Medicine and Health Post Graduate Student Conference, University of East Anglia

iii. Publications arising from this thesis

A. Welsh, K. Mares, R. Hill, A. Arthur (2020) The EXERCISES study: exercise and cognitive health in stroke survivors, a mixed methods feasibility study* **in preparation**

A. Welsh, K. Mares, R. Hill, A. Arthur (2020) The association between cardiorespiratory fitness and cognitive function among stroke survivors, a systematic review* **in preparation**

iv. List of figures

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vi. Acronyms and abbreviations

ACE-R	Addenbrooke's Cognitive Examination-Revised
ACSM	American College of Sports Medicine
ADLs	Activities of daily living
AE	Adverse event
AHA	American Heart Association
BP	Blood pressure
BPP	Brown-Peterson Paradigm
BWS	Body-weight support
CaO2	Arterial oxygen saturation
CERT	Consensus on Exercise Reporting Template
CPET	Cardiopulmonary exercise test
CPT	Continuous Performance Test
CRF	Cardiorespiratory fitness
CVD	Cardiovascular disease
CvO2	Venous oxygen saturation
DOMS	Delayed-onset muscle soreness
DST	Digit Span Test
EPHPP	Effective Public Health Practice Project
ESD	Early Supported Discharge Unit
EXERCISES	Exercise and Cognition in Stroke Survivors
F	Frequency
FAME	Fitness and Mobility Exercise for Stroke
FIM	Functional independence measure
GCP	Good Clinical Practice
HCPC	Health Care Professionals Council
HR	Heart rate
HRA	Health Research Authority
HRR	Heart rate reserve
HVLT-r	Hopkins Verbal Learning Test-Revised
I	Intensity
mL/kg/min	Millilitres of oxygen relative to body weight, per minute
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MoveEx Lab	Movement and Exercise Laboratory

MRC	Medical Research Council
MRes	Master's by Research
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute of Health Research
PMG	Project Management Group
PPI	Patient and Public Involvement
Q	Cardiac output
QoL	Quality of life
RCT	Randomised controlled trial
RPE	Ratings of perceived exertion
R**PMT**	Raven's Progressive Matrices Test
SAE	Serious adverse event
SSQoL	Stroke-specific Quality of Life Scale
T	Time
T	Type
TMT	Trial Making Test
UEA	University of East Anglia
VO_{2max}	Maximal aerobic capacity
VO_{2peak}	Peak aerobic capacity
WAIS	Wechsler Adult Intelligence Scale
WCST	Wisconsin Card Sorting Task
WHO	World Health Organisation

Chapter 1

Introduction to thesis

1.1 Development of thesis

My interest in exercise after stroke stems from previous research undertaken in fulfilment of my Master's by Research (MRes) degree. My research dissertation aimed to address the feasibility of implementing high intensity interval training into community cardiac rehabilitation. Throughout the study, individuals who had experienced a transient ischemic attack or mild stroke were integrated within the cardiac rehabilitation pathway, based on the premise they have similar risk factors to those with cardiovascular disease. However, at this particular NHS Trust, I noticed there was no provision for exercise rehabilitation for those who had experienced a more severe stroke, and as a result, had greater movement impairments. I therefore became interested in the inclusion of stroke survivors and those with disability within exercise referral schemes and the implementation of such schemes into the community.

I explored the opportunity to undertake a PhD with a goal of studying exercise provision after stroke. I was interested in learning more about the impact of stroke and how exercise training may be used as an adjunct therapy as part of, or following, formal rehabilitation. A studentship at the University of East Anglia (UEA) provided me with the opportunity to work towards developing feasible and practical ways of delivering exercise after stroke programmes, with an emphasis on including those living with the long-term consequences of a severe stroke.

1.2 Statement of the problem

There are 1.2 million stroke survivors in the United Kingdom (UK) (1). Of those who are living with the long-term consequences of a severe stroke, it is estimated that 36% are living with severe movement impairments and up to 83% experience deficits in cognitive health (2-4). The impact of a severe stroke often leads to a lack of physical activity participation, which may exacerbate cardiovascular deconditioning, in turn increase the risk of a recurrent stroke and the onset of vascular dementia (5-8).

1.3 Rationale for research

There is existing evidence to support the application of aerobic exercise to improve cardiovascular health among stroke survivors (9). There is also some suggestion that aerobic exercise may benefit cognitive health and reduce the risk of post-stroke vascular dementia (10). However, the extent to which outcomes of aerobic exercise, for example cardiorespiratory fitness, mediates improvements in cognitive health, are yet to be established among stroke survivors. Studies evaluating the impact of exercise in people with stroke tend to exclude those who are living with moderate to severe post-stroke movement impairments (11, 12). The feasibility and acceptability of appropriate outcome measures for evaluating the impact of exercise, and suitable exercise-based interventions are yet to be determined among this population.

1.4 Structure of thesis

The following chapters report the research undertaken to explore the influence of exercise after stroke on cardiorespiratory fitness among stroke survivors, with a view to maintain cognitive health. Figure 1 illustrates the structure of this thesis. The overall thesis aim was developed though a review of the literature and is addressed by means of a systematic review and a mixed methods feasibility study.

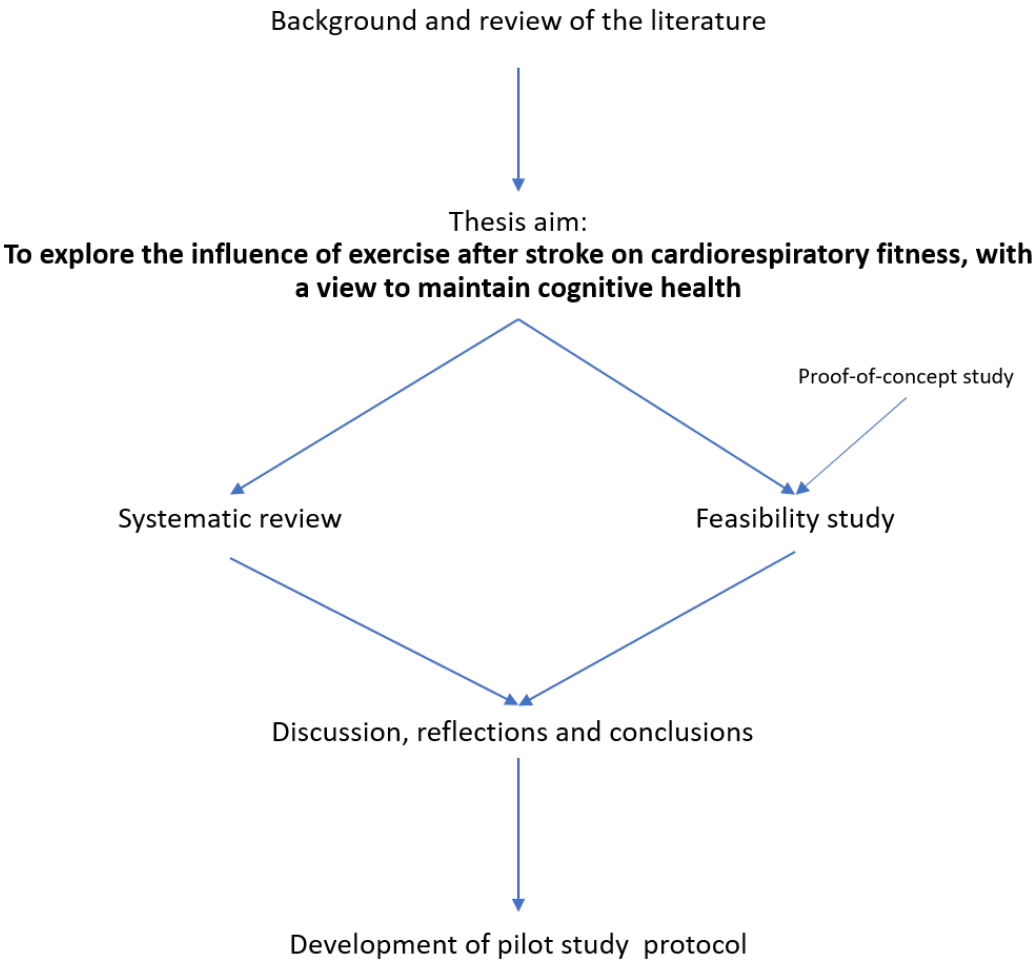

Figure 1: A model to describe the structure of this thesis

Chapter 2 defines key terms and sets the context of this thesis, by considering the burden of stroke, related to cardiovascular and cognitive health. It provides an overview of the current guidelines for exercise after stroke. The literature surrounding the implementation of aerobic exercise with a view to improving cognitive health among people with stroke is presented. There is a focus on the methods used for measuring cardiorespiratory fitness and exercise prescription. This chapter highlights the gaps within the current evidence-base, providing the rationale and justification for the research undertaken in this thesis.

Chapter 3 is a statement of the aims and objectives of the research presented in this thesis.

Chapter 4 is a systematic review, aiming to explore the nature of the relationship between cardiovascular fitness (VO_2) and cognitive functioning among stroke survivors. This chapter includes an introductory section and a description and justification of the methodology used; followed by a summary and discussion of findings. A brief section discusses how findings of the systematic review informs the design of the subsequent feasibility study.

Chapter 5 presents the rationale for, and the methodological procedures of a feasibility study, entitled Exercise and Cognition in Stroke Survivors (the EXERCISES study). This study aimed (i) to investigate the feasibility of delivering two methods of CPET modes (treadmill with a body-weight supported harness and cycle ergometry); and (ii) to investigate the feasibility of delivering exercise-based interventions (aerobic exercise, strength training and a combination of aerobic exercise and strength training) to people with moderate to severe movement impairments as a result of stroke. This chapter also reports the methods and findings of a small proof-of-concept study, undertaken with healthy volunteers with the aim of refining CPET procedures.

Chapter 6 reports the quantitative and qualitative findings of the EXERCISES study.

Chapter 7 discusses the finding of the EXERCISES study, within the context of the current literature. Methodological triangulation, strengths, limitations and the implications of this study are presented in this chapter.

Chapter 8 integrates and discusses the findings of the systematic review and feasibility study presented in this thesis, in relation to the original aims and objectives. Implications for clinical practice, recommendations for future research and my reflections on the research process are described.

1.4.1 Notes on style

I have attempted to minimise the use of abbreviation, however, as is inevitable in any field, there is the use of discipline-specific language. To assist the reader a list of abbreviations is provided on page 12 and notes on frequently used terminology is provided on page 19.

To avoid ambiguity as to who has completed certain tasks, I have used the first-person where required. Any additional contributing persons are described by initials.

Where '*the research team*' is mentioned in this thesis, I am referring to a team made up of myself, the PhD supervisory team (AA, KMa and RH) and the supervising stroke consultant (KM). AA is a health services researcher with expertise in quantitative methodology and a registered nurse; KMa is a clinical academic and Health and Care Professions Council (HCPC) registered physiotherapist; and RH is a registered nurse with expertise in qualitative research methods.

Individuals photographed in this thesis have provided written informed consent for images to be used in this thesis and in the public domain.

1.4.2 Notes on terminology

The sample population explored in this thesis are described as stroke survivors. '*Stroke survivor'* is a term agreed by individuals who have experienced a stroke (1). For the purpose of this thesis, terms such as *chronic stroke survivors* or *those living with the long-term consequences of stroke*, describes any individual who experienced a stroke more than six-months ago. In this thesis, participants involved in the feasibility study are described as those living with moderate to severe movement impairments. This is defined as a score of two or three on the Functional Ambulation Category (FAC) (appendix 1) (13).

In this thesis, the term *cardiorespiratory fitness* is used to describe the overall fitness levels of stroke survivors; despite the use of terms such as exercise capacity and exercise tolerance used interchangeably across the exercise science literature. By definition, cardiorespiratory fitness is,

> '*the extent to which the cardiovascular system and respiratory system works together to provide oxygenated blood to working muscles; and the ability of an individual to perform large-muscle, dynamic, moderate to high intensity exercise over a prolonged period of time*' (14) pg. 72.

Maximal aerobic capacity (VO_{2max}) is a measure of cardiorespiratory fitness. Values reflect the maximal ability of an individual to inspire, transport and utilise oxygen during physical exertion. *Cardiopulmonary exercise testing* (CPET) is the gold standard method to determine values of $VO_{2max.}$ Testing provides an assessment of integrative physiological responses, including the pulmonary, cardiovascular and skeletal muscle systems, to incremental exercise. In this thesis, *CPET protocol* refers to the increments in exercise work rate. Specifically, the increase in treadmill speed or the increase in resistance on the cycle ergometer. The *CPET mode* refers to the exercise apparatus the incremental test is performed upon. Specifically in the feasibility study (chapters 5 to 7), the CPET modes explored are a treadmill with a body-weight supported (BWS) harness and an upright cycle ergometer. *CPET procedures* refers to the processes undertaken in the administration of the test, for example the steps taken to fit the face mask, assistance to step over the central frame of the cycle ergometer.

The term *exercise prescription* refers to the *dose* of exercise, specifically designed for an individual; tailored to their needs, abilities and goals. The *dose* of aerobic exercise is prescribed based on 'The FITT Principle': frequency (F) (how often), intensity (I) (how hard), type (T) (what mode or kind) and time (T) (For how long) (15).

Cognitive health encompasses processes of cognitive, emotional and sensory function. However, for the purpose of this thesis, where cognitive health is mentioned, this is only referring to processes of cognitive function. Cognitive health, and therefore cognitive function, is the combination of mental processes, leading to the acquisition of knowledge and information, for example attention, learning and memory, language and executive function (16).

Chapter 2

Background and literature review

2.1 Introduction

This chapter sets the context of this thesis. It begins with an overview of the aetiology and epidemiology of stroke. The impact of stroke on cardiovascular and cognitive health is then described. Exercise after stroke is introduced with a brief summary of how it may influence cardiovascular and cognitive health. The current evidence surrounding cardiopulmonary exercise testing (CPET) and the use of aerobic exercise to promote cognitive health among stroke survivors is discussed. This chapter highlights gaps within the current evidence-base, providing a rationale for research.

2.2 Aetiology

Stroke is the most the common form of cerebrovascular disease and is defined by The World Health Organisation (WHO) (17) as,

> *"a syndrome of rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24-hours or longer or leading to death, with no apparent cause other than of vascular origin."*

Cerebral hypoxia or bleeding from the site of an aneurysm leads to cerebral dysfunction, resulting in significant neurological deficits, such as limb weakness or paresis, speech disturbance and visual loss (18).

2.2.1 Classification of stroke

There are two main classifications of stroke: ischaemic and haemorrhagic. Approximately 85% of strokes are ischaemic and occur as a result of complete or partial occlusion of cerebral arteries (19). Ischaemic strokes are often caused by a ruptured or eroded atherosclerotic plaque within the arteries (20). The remaining 15% of strokes are a result of either intracerebral (10%) or subarachnoid (5%) haemorrhage; where blood vessels burst within or on the surface of the brain

(20). The prognosis for haemorrhagic strokes is often worse than ischemic strokes, with mortality rates as high as 50% (21, 22).

2.3 Epidemiology of stroke

Stroke is the leading cause of mortality and disability worldwide (23). It is estimated that globally, there are 5.5 million deaths attributed to stroke (23). In the UK, there are more than 100,000 events each year, with an annual cost to the National Health Service (NHS) of £8.6 billon (1, 24).

There are currently 1.2 million stroke survivors living in the UK (1). Of these, 30% of stroke survivors will experience a recurrent stroke within five years (1). Despite the emphasis on reducing stroke incidence through risk factor management, treatment and rehabilitation; stroke-related illness, disability and early death is set to double by 2035 (25).

2.3.1 Risk factors

Non-modifiable risk factors for stroke include increased age (over 55 years), gender, family history and ethnicity (1, 26). Men are more likely to experience a stroke at a younger age than women, possibly due to an increased prevalence of obesity, smoking and alcohol consumption (27). Black people are almost twice as likely to have a stroke as white people (26). People who live in socioeconomically deprived areas are also at a greater risk of a severe stroke, due to a greater prevalence of health problems, such as diabetes and inadequate access to healthcare services (28, 29).

There are also several potentially modifiable risk factors attributed to stroke, including hypertension, atrial fibrillation, diabetes mellitus and high cholesterol (30-33). Approximately 30% of stroke risk is attributed to a lack of physical activity (34). This is primarily due to the association between physical inactivity and the aforementioned potentially modifiable risk factors (35). A sedentary lifestyle is associated with chronic diseases such as cardiovascular disease and diabetes mellitus (36). Research has estimated that taking part in regular physical activity is associated with a 25% to 30% first stroke risk-reduction (37). This is also true for the prevention of recurrent strokes (38).

2.4 The impact of stroke

Stroke is the leading cause of acquired disability in the UK (39). Almost two thirds of the 1.2 million stroke survivors in the UK, are living with some form of disability (1).

The type and severity of residual disabilities varies depending on the location of the brain lesion (40). For a stroke that occurs in the right hemisphere of the brain, impairments may include left-sided movement disorders, hemianopia (impaired vision), neglect and spatial unawareness (40). For strokes that occur within the left hemisphere, speech and language difficulties such as aphasia, apraxia, dysarthria and dysphagia are common; in addition to right-sided movement disorders (40). Fatigue is prevalent in 77% of stroke survivors (41) and instabilities in mental and emotional health in approximately 30% (42). Stroke can impact a person's ability to perform their usual activities of daily living, reduce quality of life and limit a survivors' potential for physical rehabilitation and social functioning (43, 44). With more severe strokes, individuals may experience poorer functional outcomes, symptoms of depression and worse quality of life, when compared to those with milder impairments (45-47).

2.4.1 Movement impairments

Post-stroke movement impairments are characterised by hemiparesis or a weakness on one side of the body (48). Significant muscular atrophy and reduced motor unit function are common after stroke (49). Movement impairments may be exacerbated by the presence of spasticity, limited balance control and perceptual or sensory disturbances, which may lead to compensatory movement patterns or even learned non-use (50, 51). Motor impairments and weaknesses in muscular function may lead to stroke survivors relying on a wheelchair and dependence in performing activities of daily living (52). As a result of movement impairments, research has shown that people with stroke are highly sedentary (53). Sedentary behaviour, characterised by any waking behaviour characterized by an energy expenditure less than 1.5 metabolic equivalents (METs) (54), is known to impact cardiovascular health, increase vascular risk factors and exacerbate the risk of a recurrent stroke (36).

2.4.2 Effect of stroke on cardiovascular health

After stroke, myocardial damage and arrhythmia have been reported (55-57). Such complications are associated with a greater risk of myocardial infarction or cardiac arrest after an acute stroke (57). In addition, 75% of stroke survivors are diagnosed with co-morbid cardiac disease, which already, is acknowledged as a risk factor of stroke (14, 58).

Stroke survivors often experience profound cardiovascular deconditioning (58). Cardiovascular deconditioning refers to symptoms of orthostatic intolerance, increased resting heart rate, a reduced capacity to exercise and diminished physical capability (59). Contributing factors to cardiovascular deconditioning include gross muscular atrophy, changes in metabolism, diminished peripheral blood flow dynamics and reduced cardiorespiratory fitness (58).

Cardiorespiratory fitness refers to,

> '*the extent to which the cardiovascular system and respiratory system works together to provide oxygenated blood to working muscles; and the ability of an individual to perform large-muscle, dynamic, moderate to high intensity exercise over a prolonged period of time*' (14) pg. 72.

The gold standard for quantifying levels of cardiorespiratory fitness is through a direct measure of VO_{2max} via cardiopulmonary exercise testing (CPET) (60-62). Cardiopulmonary exercise testing provides an assessment of integrative exercise responses involving the pulmonary, cardiovascular and skeletal muscle systems, by directly measuring ventilatory gas, during incremental exercise (63). A further description of CPET procedures is described in section 2.7.

Cardiorespiratory fitness is as expressed as maximal aerobic capacity VO_{2max}, which is defined as,

> '*the maximal rate of oxygen utilized by skeletal muscles during exercise and is considered the most precise measure of the functional limit of the cardiorespiratory system'* (64) pg. 57.

Values reflect the maximal ability of an individual to inspire, transport and utilise oxygen during physical exertion (64). It is the product of maximal cardiac output (Q) and arterial-venous oxygen difference ($CaO_2 – CvO_2$); where cardiac output is defined as the amount of blood pumped through

the circulatory system in one minute, and arterial-venous oxygen difference is the difference between the oxygen content in arterial and venous blood (63):

$$VO_{2max} = Q \times (CaO_2 - CvO_2)$$

Units of measurement are millilitres of oxygen relative to body weight, per minute (mL/kg/min). Normative values of VO_{2max} for those with chronic stroke are within the range of 8 to 22 ml/kg/min (65). For context, a healthy adult male aged 60 to 69 years would have a VO_{2max} of approximately 30 mL/kg/min and a healthy adult female 20 mL/kg/min (66). Data from cross-sectional and longitudinal studies have estimated that the cardiorespiratory fitness of stroke survivors is approximately 50% lower when compared to age- and gender-matched controls (65, 67). However, this figure may be an overestimation, as stroke survivors with moderate to severe movement impairments have often been excluded from research studies (65). This is because they tend to be older, have a poorer health status or are thought to be unable to tolerate CPET (68).

Combined with age-related decline, Billinger et al. (69) described the physiological consequences of stroke, offering some justification as to why cardiorespiratory fitness is significantly lower than healthy individuals. As a result of stroke, cardiovascular regulation, including autonomic control, vascular function and respiratory function are all altered, leading to reduced cardiovascular fitness (69). Ivey et al. (58) also proposed that reduced levels of cardiorespiratory fitness post-stroke were related to functional and metabolic implications. Authors described an inverse relationship between VO_{2max} and body composition, muscular metabolism, inflammatory markers and peripheral haemodynamics, all of which stroke survivors often experience (58). Similarly, Smith et al. (65) suggest that neurological sensory disturbances may also influence values of cardiorespiratory fitness.

For stroke survivors, low levels of cardiorespiratory fitness may limit functional independence and engagement in activities of daily living (58). It has been suggested that a loss of independence is likely if VO_{2max} levels fall below 18 ml/kg/min and 15 ml/kg/min for men and women, respectively (70). To independently complete activities of daily living, an amount of oxygen relative to the level of exertion is required. For example, the energy cost of walking on a flat surface would require approximately 12 mL/kg/min for a healthy individual (71). For those who have experienced a stroke,

the energy cost of ambulation is almost doubled, attributed to motor inefficiencies and increased metabolic demands (72). There has also been some suggestion from a longitudinal study involving older adults, that low cardiorespiratory fitness is associated with a reduction in cognitive health (73).

2.4.3 Effect of stroke on cognitive health

Reduced cognitive health is reported in approximately 83% of stroke survivors, in varying degrees of type and severity (4). Most commonly after stroke, functions related to attention, executive function and memory are affected (10, 74). Poor cognitive health is associated with higher post-stroke disability (75), dependency on caregivers (76) and worse quality of life (77). There is also a greater rate of institutionalization (78) and higher health-care costs (79).

A battery of neuropsychological tests, with normative information for comparison, is the gold standard for determining the extent of cognitive deficits (80). Measures such as Montreal Cognitive Assessment (MoCA) (81), Mini-Mental State Examination (MMSE) (81), and the Addenbrooke's Cognitive Examination (ACE) (82) are routinely administered with stroke survivors to determine global and domain-specific deficits in cognitive health (74, 83).

Memory impairments are estimated to affect up to 31% of individuals in the first-year post-stroke (76, 84). Consequently, stroke survivors are at a greater risk of developing subsequent cerebrovascular diseases, specifically vascular dementia (5-7). Vascular dementia is a form of dementia; occurring as a result of the interaction between vascular risk factors, infarcts and haemorrhages, white matter changes and brain atrophy (85).

One in three stroke survivors are at risk of developing vascular dementia within five years of stroke onset (86). But, despite the prevalence and the implications of vascular dementia and poor cognitive health, there is limited evidence for effective prevention and treatment (87). Methods of improving cognitive health post-stroke has been identified as a priority for research in stroke rehabilitation (88).

2.4.4 Summary of the impact of stroke

The impact of stroke effects movement ability (49), cardiovascular (58) and cognitive health (4). The combination of such impairments may lead to limitations in physical activity and exercise participation, further exacerbating the impact of stroke. As a result, risk factors to stroke and the risk of developing subsequent cerebrovascular diseases, such as vascular dementia, is heightened (9) (figure 2).

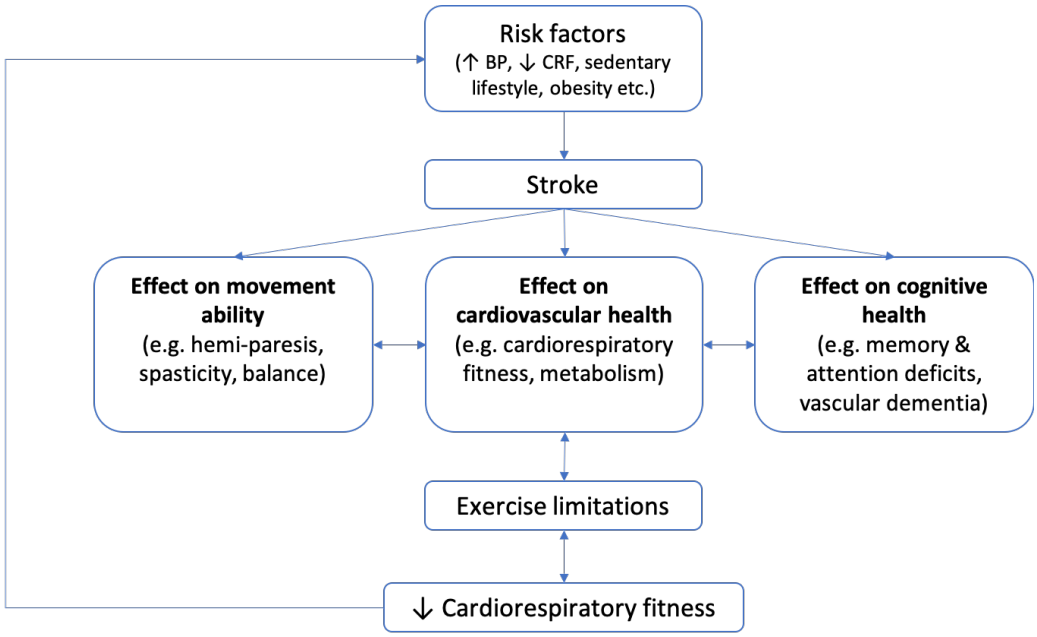

Figure 2: The cyclical process of the impact of stroke and exercise limitations, adapted from Saunders et al. (9)

The risk of a recurrent stroke and developing vascular dementia calls for research to investigate appropriate and effective interventions to protect against a decline in cognitive health. The secondary consequences of stroke and subsequent stroke prevention may be met with the benefits of exercise (89). This is in line with the top 10 research priorities relating to life after stroke, as identified by stroke survivors, caregivers and healthcare professionals (88). Exercise after stroke has been shown to improve cardiorespiratory fitness and in turn, has the potential to attenuate post-stroke cognitive decline and reduce the risk of a secondary diseases such as vascular dementia (10, 44).

2.5 Exercise after stroke

The provision of exercise after stroke is recommended to be integrated within stroke rehabilitation; for the purpose of improving functional outcomes, vascular risk reduction and secondary stroke

prevention (90). This includes acute and in-patient phases, early-supported discharge and community services (90, 91). Exercise after stroke is supported by clinical guidelines (12, 90, 92). Clinical guidelines encourages the combination of both aerobic exercise and strength training (12, 91, 93). Combined aerobic exercise and strength training has been found to produce significant improvements in cardiorespiratory fitness and muscular strength, superior to aerobic exercise or strength training alone among stroke survivors (94). Global disability (9), gait and walking ability (95, 96) and psychosocial measures (97) have been found to improve with participation in exercise after stroke.

There has been a plethora of research undertaken to explore the benefits of exercise and fitness programmes, since it was highlighted as a research priority, relating to life after stroke (9, 88). An update of the 2016 Cochrane review exploring physical fitness after stroke (98) was published in March 2020 (9) and examined the effects of exercise after stroke on several outcomes. Outcomes included death, dependence and disability, physical fitness and function, quality of life, mood, and cognitive function. Key findings included improvements in cardiorespiratory fitness (VO_{2peak}), muscular strength, walking speed and balance, as a result of exercise. The 2020 update included 17 newly published studies, totalling 75 studies of 3617 participants. Although conclusions suggested there was enough evidence to support the application of exercise after stroke, the optimal parameters or dose of exercise prescription is yet to be defined.

2.5.1 Exercise prescription

The prescription of exercise after stroke is based on several underlying concepts of exercise training, pertinent to the field of exercise physiology. Concepts are specificity, overload, progression, initial values and reversibility (99). *Specificity* refers to the application of exercise training that is particularly suited to an activity or skill; for example, the implementation of aerobic exercise to improve cardiorespiratory fitness. *Overload* describes how the body adapts to exercise as a stimulus. It refers to the need of applying a greater than normal stress or load, for physiological adaptations to take place. *Progression* is the gradual and systematic increases in *overload* over a period of time; for example, increasing the intensity or frequency of exercise as an individual's tolerance to the dose of exercise increases. Systematic progression results in greater physiological

adaptations over time, with minimal risk of injury. The *initial value* of an individual's performance determines the capacity for improvement, i.e. baseline measures. Individuals with low initial values are more likely to have the most to gain. *Reversibility* suggests that with the removal of a stimulus, i.e. the cessation of exercise training, physiological adaptations are lost. An example of this is muscular atrophy and decreases in cardiorespiratory fitness with decreased exercise activity (100). With the cessation of exercise training cardiorespiratory fitness can be reduced by as much as 14% within four weeks (101).

The *dose* of aerobic exercise is prescribed based on 'The FITT Principle': frequency (F), intensity (I), type (T) and time (T) (15). *Frequency* describes the number of sessions to take place over a period of time; for example, twice weekly. *Intensity,* although a relative term, pertains to the work rate or amount of effort; for example, cycling at 70% of age-predicted maximum heart rate or walking at a rating of perceived exertion (RPE) of 11 to 14. Intensity defined as the rate of energy expenditure during physical exercise (102). *Time* may either describe the duration of each prescribed exercise activity (for example, cycling for ten minutes); the duration of the entire exercise session (for example, forty-five minutes); or it may also describe the length of the intervention (for example, eight-weeks). *Type* refers to the mode of exercise; for example, treadmill walking or stationary cycling.

It is expected that research studies explicitly report components of the FITT principle in order to support the design of future studies and the implementation of exercise-based interventions. However, in the exercise after stroke literature, reporting of the FITT principle and other concepts of exercise training, has been found to be inconsistent (99, 103). Amman et al. (99) undertook a systematic review evaluating the extent to which components of the FITT principle are reported in previous randomised controlled trials involving stroke survivors. Overall, authors described inconsistent and incomplete reporting of components of the FITT principle and participant adherence to exercise prescription. Therefore, it is difficult to verify whether or not the intended dose of exercise was actually delivered and adhered to by participants (96, 99). Reporting exercise intervention adherence to exercise prescription is important for transparency and reproducibility of exercise interventions.

2.5.2 Clinical guidelines for exercise after stroke

Clinical guidance has been developed for the provision of exercise after stroke (92). The purpose of clinical guidance is to support healthcare professionals and researchers in prescribing the appropriate dose of exercise for that individual, with the aim of inducing sufficient stress for effective adaptations to exercise to occur (104).

There appears to be plethora of guidance and recommendations for exercise after stroke available to stroke survivors, clinicians and researchers. For example, the dose of aerobic exercise recommended by the Stroke Association (2017) is a total of 150 minutes of moderate intensity aerobic exercise per week (105). Interestingly, this recommendation is the same as what is advocated for healthy older adults (106). General guidance in this way may be problematic for stroke survivors, given the prevalence of motor function impairments (107) and the reported lack of knowledge regarding exercise (107). It may also be discouraging for stroke survivors if they are unable to achieve what is recommended.

In an attempt to summarise exercise prescription guidelines for the stroke population, I undertook a small scoping exercise. I searched key databases, including Allied and Complementary Medicine Database (AMED); MEDLINE and MEDLINE Complete; PsychARTICLES and PsychINFO; SportDiscuss; Cumulative Index to Nursing and Allied Health Literature (CINAHL); and the grey literature, including policy documents, to gather stroke-specific resources that detailed recommendations for exercise after stroke.

I found six clinical guidance documents advocating exercise after stroke. The guidelines described components of the FITT principle. An overview of exercise prescription for both aerobic exercise and strength training, where applicable, is detailed in table 1.

Table 1: A description of available guidance for exercise after stroke

			Aerobic exercise				Strength training
	Type of publication	**Provided by whom?**	**Frequency**	**Intensity**	**Time**	**Type**	**Sets/repetitions**
Aerobic Exercise Recommendations to Optimize Best Practices in Care after Stroke (90)	Best practice guidance	Physiotherapists or cardiac rehabilitation specialists	3 x week	Individually tailored	≥20 mins	Any mode that activates a large muscle mass for a prolonged period	NR
American College of Sports Medicine: The management of persons with chronic diseases and disabilities (108)	Best practice guidance	Therapists	2 x week	≥ 50% HRR	30 mins	Treadmill, modified cycle ergometry	NR
Exercise after Stroke Services (93)	Best practice guidance	Level 4 specialist exercise instructor	3 x week	'Moderate'	40 mins	Walking, stepping & cycling	4-6 exercises
Fitness and Mobility Exercise (FAME) Programme for Stroke (91)	Best practice guidance	Clinician with experience in & exercise prescription	2-3 x week	70–80% HRR	30 mins	Walking	3 x 10 reps
National Clinical Guidelines for Stroke (92)	Evidence-based guidelines	Therapists & fitness instructors	5 x week	'Moderate'	30 mins	Walking	NR
Physical Activity & Exercise Recommendations for Stroke Survivors (AHA) (12)	Evidence-based guidelines	NR	3-5 x week	40%-70% VO2; 55%-80% HR_{max}; or RPE 11–14	20-60 mins	Walking, stationary cycle ergometry, arm/arm-leg ergometry	1-3 x 10-15 reps 8-10 exercises

Abbreviations

ACSM American College of Sports Medicine **AHA** American Heart Association **HR_{max}** maximum heart rate **HRR** Heart rate reserve **mins** Minutes **NR** Not reported **reps** Repetitions **RPE** rating of perceived exertion **VO_2** maximal aerobic capacity

Exercise mode

Walking was found to be the most frequently recommended mode of aerobic exercise across the clinical guidelines identified. An established evidence-base exists to support the benefits of walking after stroke (11, 109, 110). Other recommended modes of aerobic exercise included cycling and stepping. In recognition of the complex nature of post-stroke movement impairments (40), one set of clinical guidance recommended that the mode of aerobic exercise should be based on the comorbidities, personal preference, cardiorespiratory fitness, stroke severity, time since stroke and the goals of the individual (90).

Three clinical guidance documents stipulated that strength training should be performed two to three times per week (12, 91, 93). Strengthening activities should focus on functional tasks and the amount of repetitions should be tailored to the individual and be progressed systematically over time. Examples of strengthening activities include sit to stand, as a leg strengthening exercise and arm pole lift from a seated position, as an arm and back strengthening exercise.

Given the examples of exercise modes provided within the clinical guidance, all of which require significant movement ability, it may be assumed that guidelines are more suited to people with mild post-stroke movement impairments. It is estimated that approximately 20% of stroke survivors will remain non-ambulatory, irrespective of rehabilitation efforts (47). Therefore walking, which is the most common mode of aerobic exercise recommended, may be unattainable for a fifth of the stroke population (47). This raises questions regarding the inclusivity of exercise prescription guidelines currently published for stroke survivors.

Exercise intensity

The prescription of exercise intensity ranges from 50% to 80% of either, age-predicted maximum heart rate (HR) or heart rate reserve (HRR). Parameters of exercise intensity are calculated as follows (14, 111):

- Age-predicted maximum heart rate = *208 – (0.7 x age in years)* (112), or for those prescribed beta blockers, age-predicted maximum heart rate = *164 – (0.7 × age in years)*
- Heart rate reserve = *(HR_{max} - resting HR) x target % + resting HR*

Physical activity and exercise recommendations for stroke survivors, authored by the American Heart Association (AHA) (12) and within guidelines for exercise after stroke services in the UK (87), recommended stroke survivors to exercise at an RPE ranging from 11 to 15. The Borg 6 to 20 RPE scale (described in section 5.7.4, figure 9) is validated for defining self-reported perceptions of effort (106). Physical activity and exercise recommendations for stroke survivors by the AHA also referred to outcomes of CPET for exercise prescription (12). For example, 40% to 70% of VO_{2peak} or 55% to 80% of peak heart rate. However, there may be challenges in the application of this due to limited access to CPET in community exercise after stroke services (113). The use of CPET for exercise prescription is described later in this chapter (section 2.7.1).

Table 2 describes how each intensity parameters correspond to a low, moderate, vigorous or high category. Overall, three clinical guidelines recommended moderate-intensity exercise (14, 83, 93), two vigorous-intensity (12, 91) and one to be individually tailored (90).

Table 2: Categories of exercise intensity (114)

Intensity parameter	**Light**	**Moderate**	**Vigorous**	**High**
HRR	≤39%	40-59%	60-84%	≥85%
APHRmax	40-54%	55-69%	70-89%	≥90%
RPE	8-10	11-13	14-16	≥17
VO_{2peak}	≥39%	40-59%	60-84%	≥85%

Abbreviations
APHRmax Age-predicted maximum heart rate **HRR** Heart rate reserve **RPE** Rating of perceived exertion **VO_{2peak}** maximal aerobic capacity

For stroke survivors, the variation in how exercise intensity is defined and prescribed may cause some confusion. For researchers and healthcare professionals, differences in how intensity is defined may make it difficult to compare exercise intensities across guidance documents and across research studies.

Exercise rehabilitation context

Exercise after Stroke guidelines by Best et al. (93) referred to the integration of exercise across the stroke pathway, including acute, in-patient, and early-supported discharge phases. However,

according to stroke guidelines, formal rehabilitation is usually only offered for up to six-months post-stroke (115).

The importance of exercise training extends to the longer-term post-stroke (116). Eighty percent of time is spent sedentary in the first year following a stroke event, and it is suggested that it is unlikely to improve within the chronic phases of living with stroke (117). The impact of sedentary behaviour is known to contribute to a higher risk of a recurrent stroke and may have detrimental effects on cardiovascular and cognitive health (118-120). Access to exercise after stroke services beyond six-months is therefore important for chronic stroke survivors, to maintain general health and for the secondary prevention of a recurrent stroke event.

In response to the need for long-term exercise provision for stroke survivors', two clinical guidance documents (90, 91) recommended the implementation of aerobic exercise into community settings. Health and leisure centres or church halls are recommended as potentially appropriate venues for exercise after stroke programmes. Similar settings are known to be feasible and are used in clinical practice for cardiac rehabilitation schemes (121, 122). However, barriers, such as access and travel to community venues, were identified from research exploring adapted cardiac rehabilitation schemes for stroke survivors (123-125). In addition, for those who have more severe post-stroke movement impairments, it is likely individuals will require one-to-one supervision from healthcare professionals and would require access to suitable adaptive equipment (126). Understanding the feasibility and appropriateness of community-based exercise training programmes for chronic stroke survivors, including the use of similar venues or settings to cardiac rehabilitation schemes, is yet to be robustly established.

2.5.3 Summary of clinical guidelines for exercise after stroke

Despite the availability of several clinical guidance documents, there is variation in the recommended dose of exercise after stroke. For stroke survivors themselves, the inconsistency in exercise and physical activity recommendations may cause confusion.

It appears that clinical guidance is tailored towards those with mild movement impairments and is generally promoted within formal phases of stroke rehabilitation. Poltawski (127) undertook a review of practice guidelines for the development of community-based exercise programmes after

stroke. It was noted that much of the evidence cited to support the exercise after stroke guidance, derived from research involving stroke survivors with mild impairments who were able to ambulate independently. The transferability of research findings and recommendations to those who cannot ambulate independently, is therefore limited. More high-quality research is needed to produce exercise after stroke guidance documents for stroke survivors who are more severely disabled.

2.6 Aerobic exercise for cardiorespiratory fitness

Aerobic exercise, as previously highlighted, is advocated for stroke survivors with a view to improve functional outcomes, reduce vascular risk factors and secondary stroke prevention (90). There is evidence to suggest that aerobic exercise interventions share similar beneficial outcomes to that of drug therapies, in terms of rehabilitation after stroke and secondary disease prevention (128, 129). Increased cardiorespiratory fitness from aerobic exercise has been shown to be effective at reducing cardiovascular risk factors of stroke, specifically hypertension, hyperlipidaemia and type-2 diabetes mellitus (130). How this occurs, is a result of aerobic exercise-induced adaptations in respiratory (131, 132), vascular (133-135) and muscular functions (136-138). Increases in VO_2 are significantly correlated with improved heart rate, cardiac output and arterial-venous oxygen difference, which in turn contribute to an improved overall health status (139).

To date, there are a number of systematic reviews involving stroke survivors that explore the effects of aerobic exercise training on cardiorespiratory fitness (65, 96, 140). Overall, reviews have reported aerobic exercise to be effective in improving cardiorespiratory fitness (VO_2). For example, Lee et al. (140) found a 12% increase in cardiorespiratory fitness (mean effect size = 0.41, CI = 0.25 to 0.56) from pooled data from 10 studies (602 stroke survivors). It was found that interventions greater than 12 weeks in duration resulted in greater increases in cardiorespiratory fitness, when compared to aerobic exercise interventions that were less than 12 weeks (140). The mode of aerobic exercise reported in previous studies varied, including cycling, stepping, arm ergometry and treadmill walking (9, 96, 141). Exercise intensity appears to be sporadically reported within studies and ranged from 30% to 80% of either maximum heart rate, heart rate reserve, maximal effort; by watts, walking speed or by RPE.

However, in Lee et al. (140), only one study in the meta-analysis was a randomised controlled trial (142). Other studies appeared to be preliminary, pilot or feasibility work, which has implications for interpreting the strength and quality of the evidence, since there may be a greater risk of bias from other study designs (143).

2.7 Cardiopulmonary exercise testing

As previously noted, cardiopulmonary exercise testing (CPET) is the gold standard method of measuring cardiorespiratory fitness, as quantified by maximal aerobic capacity (VO_{2max}) (60-62). Maximal aerobic capacity represents the greatest amount of oxygen one can utilize during dynamic exercise (144, 145). Testing in this way is a safe procedure, with the risk of death for patients between two and five per 100,000 exercise tests performed (146). It has been shown to be safe and feasible for use in clinical practice and in research studies involving stroke survivors (147).

To determine values of cardiorespiratory fitness, i.e. VO_{2max}, individuals are expected to exercise, incrementally, usually on a treadmill or cycle ergometer, while open circuit spirometry is used to measure oxygen uptake. For open circuit spirometry, participants wear a mask over their mouth and nose and are asked to breathe normally. Pulmonary ventilation and expired fractions of oxygen and carbon dioxide during dynamic exercise is quantified. The workload, i.e. the resistance on a cycle ergometer (watts) or the speed on a treadmill (metres per second), is gradually increased until there is a '*levelling off*' or a '*plateau*' in oxygen consumption is observed, despite a continual increase in workload (148). The '*plateau*' in oxygen consumption is described schematically in figure 3 and defines the maximal exercise effort one can achieve. It is expected that individuals would achieve maximal effort and therefore a plateau in oxygen uptake, within 8 to 12 minutes of incremental exercise (149).

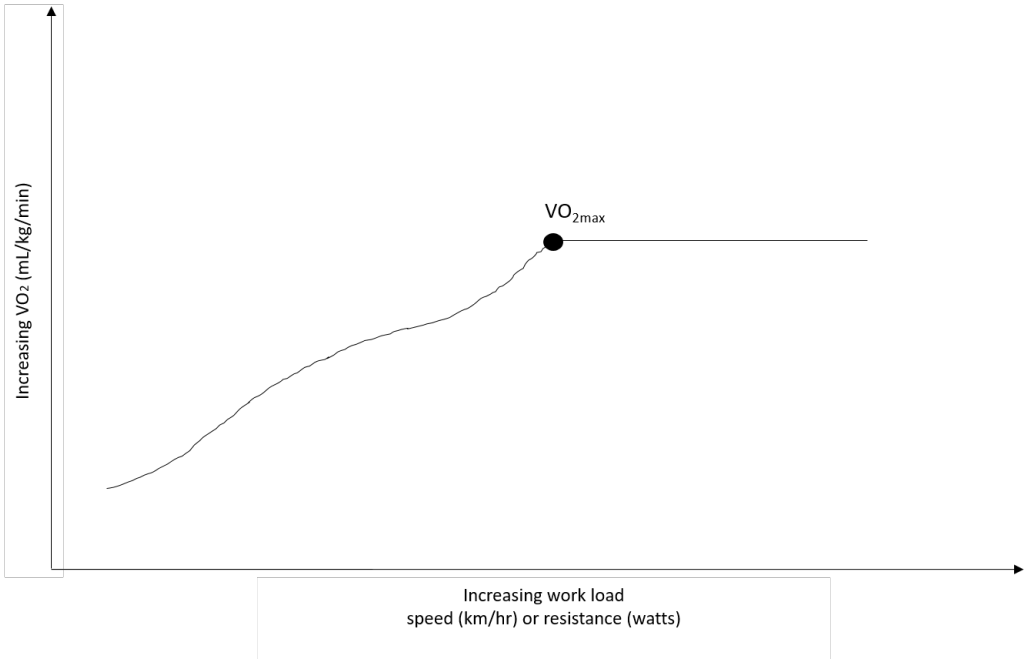

Figure 3: An illustration of a plateau in oxygen consumption, despite an increase in workload

However, one key debate within the literature is the ability of individuals to achieve a plateau in oxygen consumption and therefore VO_{2max} (150). This is further debated among those with stroke (151). Following stroke, people may experience changes in cellular metabolism and musculoskeletal impairments. These may reduce the utility of oxygen during exhaustive exercise precluding a plateau in oxygen consumption (152-156). Non-cardiopulmonary factors, such as hemi-paresis, fatigue, poor balance, spasticity, lack of motivation and depressive symptoms may also compromise a stroke survivor's ability to achieve VO_{2max} during CPET (67, 105, 155, 157). For example, a study evaluating the correlation between exercise test performance and cognitive and motor impairments suggested that stroke survivors with greater post-stroke cognitive and motor impairment are less able to achieve either a plateau in oxygen consumption or secondary criteria (158). In a systematic review of 60 studies (159), one study reported only 34% of 35 participants reaching this plateau (158).

In the absence of a plateau of oxygen consumption, several other secondary criteria have been proposed to determine maximal effort (152). Most commonly used is a respiratory exchange ratio of more than one (160-163). Respiratory exchange ratio is the ratio between the amount of carbon dioxide produced and oxygen utilized. Other criteria used with the stroke population includes reaching 85% of an individual's age-predicted maximum heart rate (152).

As it is unlikely that stroke survivors will be able to reach VO_{2max}, and in some cases even a secondary criteria, it may be more appropriate for studies involving participants with stroke to report peak VO_2 values (VO_{2peak}) (164). Peak VO_2 is defined as the highest point of oxygen consumption during CPET (159). The stopping criteria, or maximal effort, is therefore defined by factors such as volitional fatigue or the inability to maintain a pre-determined pace or workload on a cycle ergometer or treadmill.

To my knowledge, there is only one CPET protocol that is validated for stroke survivors to determine VO_{2peak} (164). A total body recumbent stepper CPET protocol was developed specifically for stroke survivors who are living with hemiparesis and/or balance deficits, thus are unable to tolerate CPET undertaken on a treadmill or cycle ergometer. However, the use of a total body recumbent stepper may be problematic for use outside of the research community, as this is specialist equipment. Research into adapting CPET modes that may be more readily available in community settings, such as a cycle ergometer or a treadmill with body-weight support (BWS), is warranted.

2.7.1 Purpose of cardiopulmonary exercise testing

Cardiopulmonary exercise testing is recommended for stroke survivors as a method of screening to ensure safety to participate in exercise training (14). Testing in this way is also beneficial for exercise prescription (165).

For safety screening

As suggested, one purpose of CPET is to screen for any adverse events and ensuring safe participation in exercise training (90). It is advised that, where feasible, and for any exercise at an intensity greater than 50% of age-predicted maximum heart rate, CPET should be a component of pre-participation screening for aerobic exercise training after stroke (90). Interventional studies have used CPET to determine suitability to exercise, in that individuals who complete CPET with no contraindications, are eligible to participate in an exercise intervention (166, 167). Eligibility to exercise is based on an observation of key variables such as electrocardiography (ECG), blood pressure, RPE, and clinical signs and symptoms (159). Observations are in accordance with the American College of Sports Medicine (ACSM) (14) contraindications to exercise training (described in chapter 5, section 5.6.2 and 5.7.4). Despite these recommendations, based on findings of a

systematic review of the use of CPET among stroke survivors, it appears that few studies reported pre-exercise screening procedures (159).

For exercise prescription

Cardiopulmonary exercise testing determines the maximal tolerable amount and intensity of exercise one can achieve. It can be therefore be used to prescribe exercise (168). Exercise prescription based on VO_2 values is subject to achieving sufficient intensities during CPET, which as previously described, is challenging for stroke survivors (159, 164, 168). With the lack of CPET undertaken as a component of exercise after stroke programmes, there is little data to substantiate the feasibility of CPET to develop exercise prescription (113). However, one study by Marzolini et al. (149) concluded that participants were in fact, able to achieve sufficient exercise intensities to inform the prescription of exercise. The study aimed to examine the feasibility of CPET for developing exercise prescription among people who experienced a stroke more than three months ago. At baseline, the proportion of tests providing sufficient information to prescribe exercise intensity was 68.4%. After six-months of an adapted cardiac rehabilitation exercise programme, the proportion of sufficient information available from CPET was 84.7%. This difference in proportions may be a result of participants having a greater cardiorespiratory fitness and therefore being able to undertake CPET for longer. However, the findings of this study are limited to those who are within one year of stroke onset and were able to ambulate independently. Understanding the appropriateness of CPET for exercise prescription among those who are have moderate to severe stroke-movement impairments and are up to several years post-stroke, therefore needs to be explored.

2.7.2 Clinical guidelines for cardiopulmonary exercise testing

There are several published clinical guidelines for the conduct and interpretation of CPET involving clinical populations' (63, 165, 169). Specific guidance has been developed for preoperative (170), cancer (171), respiratory (172) and cardiovascular disease (146) populations. For the stroke population, there is currently no consensus on clinical guidance for CPET procedures. As a result, a systematic review (159) collated CPET procedures implemented across 60 studies (2,104 stroke

survivors) and produced a set of recommendations for CPET with stroke survivors. This is replicated in table 3.

Table 3: Recommendations for conducting and reporting cardiopulmonary exercise testing after stroke[1]

Conducting CPET	Reporting CPET outcomes
Participants	
Instruct the patient to refrain from ingesting food, alcohol or caffeine or using tobacco products 3 hours before testing, to avoid significant exercise on the day of the assessment, to wear loose-fitting clothes and suitable shoes, to use or stop using the medication (depending on the purpose of the test), to bring a list of medications, to drink ample fluids during 24 hours preceding the test	• Age • Gender • Time since stroke • Severity of the stroke • Use of medication • Co-morbidities • Patient-related risk factors to conduct CPET
Safety	
Include pre-test screening by physical examination, according to the ACSM criteria (14) Have the patient complete the Physical Activity Readiness Questionnaire or get approval from a physician Check contraindications as described by ACSM guidelines During the test, monitor the following variables continuously or at the end of each stage: ECG, HR, BP, RPE and gas exchange. Clinical signs and symptoms also need to be closely monitored by the test supervisor Have the test supervised by an experienced and trained person under supervision of a physician Skills needed to supervise an exercise test are described by the ACSM guidelines based on the ACC and AHA guidelines	• Definition of serious adverse events • Number of serious adverse events occurring during CPET • Nature of serious adverse events occurring during CPET
Equipment	
Use a proper test modality depending on the aim of the assessment and the patient's characteristics, e.g. treadmill (with/without BWS), cycle ergometer (recumbent or non-recumbent) or stepper (recumbent or non-recumbent) Cycle ergometry is recommended as is less influenced by sensorimotor deficits, when a patient is unable to pedal, treadmill is a valid alternative Include a test session to familiarize the patient with the equipment Calibrate all equipment as recommended before use	• Type of equipment used • Brand (version) of the equipment used • Safety and quality label
Protocol	
Use a reliable and valid incremental test protocol Incremental steps can be individualized or standard steps. Steps need to be small. Aim for test duration of 8–12 min. Make termination criteria clear to test supervisor and patient Instruct the patient to exercise until exhaustion	• Reliability and/or validity values • Information about warming up/cooling down period • Incremental scheme • Termination criteria for safety (e.g. ACSM) • Reasons for test termination • Test duration (mean, range)
Outcomes	
Record VO_{2peak} RER, BP and HR continuously during testing Average VO_{2peak} over the last 20-30 secs, preferably during the plateau phase Define criteria and cut-off points to determine maximum effort, such as VO_{2peak} plateau, RER ≥ 1.0, according to the population being studied	• Absolute mean (range) VO_{2peak} and RER values for total population, divided by sex and age • Criteria and cut-off points to judge maximum effort • Number (& %) of patients who met the criteria
Abbreviations **ACSM** American College of Sports Medicine **RPE** Rating of perceived exertion **RER R**espiratory exchange ratio **HR** Heart rate **BP** Blood pressure	

[1] This table has been replicated from van de Port (156). These recommendations for CPET were formulated based on the findings of 60 studies reporting CPET procedures and outcomes among stroke survivors.

van de Port et al. (159) found reporting of CPET procedures were inconsistent and did not always comply with national and international guidance across the 60 included studies. This finding is similar to reviews summarising the quality of reporting for CPET in cancer (173), healthy (174) and older adults' (162). The research described in van de Port et al. (159) mainly consisted of mild stroke survivors. Much like exercise after stroke guidance, there was limited inclusion of stroke survivors with moderate to severe movement impairments. Research involving a broader range of stroke survivors is required to explore the applicability of CPET procedures and guidelines for best practice with stroke survivors with moderate to severe movement impairments.

Although no study has specially addressed the implementation of CPET in exercise after stroke services in the UK, it is expected that its application is limited. There appears to be limited availability and accessibility to CPET in most acute and community stroke settings (12). This is in contrast to the use of CPET as part of the standard care pathway for cardiac rehabilitation programmes (175-177). There are similarities in risk factors and some rehabilitation goals (i.e. vascular risk reduction, return to pre-morbid functional status) among cardiac and stroke populations' (178-181). Therefore, the purpose of using CPET for screening for potential adverse events to exercise and for exercise prescription may be transferable to the stroke population.

The expected lack of CPET within exercise after stroke services in the UK may also be attributed to the perceived lack of safety for CPET among those with more complex medical status or severe movement impairments (113). An increased amount of high-quality evidence demonstrating the safety and feasibility of stroke survivors of this nature is therefore warranted.

2.7.3 Summary of cardiopulmonary exercise testing in stroke survivors

There appears to be limited research to support the use of CPET in exercise after stroke services for both safety screening and for exercise prescription. There is therefore the need to explore appropriate CPET modes for stroke survivors, particularly for those who have more severe movement impairments (159).

2.8 Aerobic exercise and cognitive health

In older adults, exercise training has been found to have a favourable effect of on global cognitive health (182). Benefits appear to be greatest in cognitive speed, auditory and visual attention (183) and executive control (182). Similar findings have been demonstrated in studies involving stroke survivors, whereby several systematic reviews have identified benefits in cognitive health as a result of aerobic exercise (43, 184-190). For example, a systematic review (14 studies, 736 stroke survivors) found that 12-weeks or more of combined aerobic exercise and strength training produced greatest cognitive benefits among those who had experienced a stroke (189). This was supported by studies involving heathy adults aged 50 years and above (191). Here, an interventios of combined aerobic exercise and strength training, at a moderate to vigorous intensity exercise for a minimum duration of 45 minutes, showed greater improvements in cognitive function, compared with other doses of exercise prescription (191).

In previous systematic reviews exploring aerobic exercise to improve cognitive health among stroke survivors, authors reported variation in the dose of exercise prescribed (43, 184-190). There also appears to be a lack of consistency in the general definition of the exercise interventions (43, 185, 189). The terms 'physical activity' and 'exercise' have been used interchangeably. However, by definition, they refer to distinct behaviours (14). Examples of physical activity include household chores, gardening or walking, thus is defined as,

> '*any bodily movement produced by skeletal muscles that results in energy expenditure*' (192) pg. 127.

Whereas exercise, a subcategory of physical activity, is defined as,

> '*planned, structured, repetitive, and aims to improve or maintain one or more components of physical fitness'* (192) pg. 127.

Some reviews also included studies that implemented tai chi, yoga and stretching practice, under the definition of 'aerobic exercise' (43, 193, 194). Conclusions may therefore be misleading as exercise trials of a different nature have been synthesised. Evidence has suggested that low intensity physical activity, i.e. less than 40% of age-predicted maximum heart rate (usually noted in yoga, tai chi and physiotherapy practice), is not great enough to induce cardiorespiratory

adaptations (195). Thus, for this reason, low intensity exercise such as balance or stretching activities, are often chosen as a control condition in controlled trials (43, 196, 197). The difference between aerobic exercise and physical activity as an intervention, may result in different cardiovascular or cognitive health outcomes (184). Balance or stretching activities may produce different physiological mechanisms that promote gains in cognitive health.

Although much of the data relies on animal studies, several physiological adaptations are known to occur with aerobic exercise, which appear to impact cognitive health (198). These include the upregulation of neurotrophins (e.g. brain-derived neurotrophic factor), neurotransmitters (e.g. epinephrine) and hormones (e.g. cortisol and dopamine) and increased cerebral blood flow (199). Adaptations have been associated with improvements in cognitive outcomes; specifically, spatial learning, motor learning and memory function, in animal models (200, 201).

Consistent with animal models, aerobic exercise has also been shown to increase levels of brain-derived neurotropic factor in studies involving healthy older adults, acquired brain injury and spinal cord injury populations (202). Exercise promotes cerebral blood flow, therefore enriches oxygen saturation and consumption, glucose transportation, oxidant capability and cerebral perfusion (203). With exercise, adaptations in cerebral structures and in cerebral blood flow have also been observed in older adults, including grey and white matter size and hippocampal hypertrophy (204). In ageing populations, aerobic exercise increased the size of the anterior hippocampus which was found to translate to improvements in spatial memory (204, 205).

Cardiorespiratory fitness has also been proposed as a mechanism by which cognitive health is improved (206). Measures of VO_{2max} have been found to be positively associated with cognitive health in healthy young adults' (207), older adults' (73) and in those living with mild cognitive impairment (208).

However, in a review that examined the relationship between cardiorespiratory fitness (VO_2) and cognitive performance, no significant relationship between effect sizes of VO_2 and cognitive performance were found (209). The reported lack of evidence to support the relationship between VO_2 and cognitive performance may be attributed to the variability in participant populations examined in the review. The review included studies that involved healthy individuals, those with

depression and those with chronic obstructive pulmonary disease. Pooling data from such heterogeneous populations limits the interpretation of these findings. Symptoms of depression may confound the relationship between cardiorespiratory fitness and cognitive health, as already, depression is known to have some association with cognitive impairment and dementia (210). Similarly, individuals living with chronic obstructive pulmonary disease may experience impaired cardiorespiratory function, therefore limit the measurement of VO_{2max}. As a result of the combined patient population in this review, the nature of the relationship between cardiorespiratory fitness (VO_2) and cognitive performance is still largely unknown.

Research exploring mechanisms that underpin cognitive changes among stroke survivors is ongoing. Preliminary research involving stroke survivors has found that gains in cardiorespiratory fitness, lead to increases in brain-derived neurotrophic factor, which in turn, is associated with improved global cognition scores (197, 199). Pilot studies involving stroke survivors have also demonstrated positive associations between measures of cardiorespiratory fitness and executive function (211) and attention (212) domains of cognition. However, the magnitude of this relationship is yet to be quantified among stroke survivors.

The use of a variety of tools to measure cognitive outcomes across exercise trials has prevented previous pooled meta-analyses of data (43, 184-190). Across previous studies, tools used include Mini-Mental State Examination (MMSE) (167, 196, 211, 213, 214), variations of the Addenbrooke's Cognitive Assessment (ACE) (167) and the Montreal Cognitive Assessment (MoCA) (215). Furthermore, there are also studies that have used sub-scales of tools such as the Functional Independence Measure (216, 217) and the Stroke Impact Scale (11, 218) to measure cognition. The use of different measures across studies makes meta-analyses challenging and therefore a synthesis of various study findings tends to be less robust (219). Previous systematic reviews have highlighted the need for researchers to form a consensus regarding measurement tools for cognitive function (184, 188, 220). Authors suggest that the use of standardised measures of cognitive function would offer a wider prospective of the impact exercise-based interventions may have on cognitive function and the risk of developing vascular dementia (187, 188). Researchers

should attempt to implement consistent valid and reliable measurement tools, aiming to optimally reflect all aspects of cognitive health most likely to be affected by stroke.

There has been some suggestion that although most commonly affected by stroke; memory, attention and executive function domains of cognition may be most amenable to change with exercise training (221, 222). In support of this, studies have reported improvements memory (10, 223), attention (166, 224) and executive function (10), in response to exercise-based interventions after stroke. However, findings of these studies should be interpreted with caution as a result of their pilot of feasibility study design. There are few definitive randomised controlled trials that report the effectiveness of exercise training for cognitive health (11, 167, 217, 225, 226). A recent Cochrane review of physical fitness training for stroke survivors and a review of research priorities for stroke both reported cognitive function is under-investigated, despite being a key outcome for stroke survivors and a priority in stroke research (9, 88). The need for this research has also been articulated in a previous systematic review, whereby authors stated that more rigorously designed and standardised training protocols with a view to improve cognition are required for stroke survivors (43). Thus, the lack of high-quality evidence calls for further research to define optimal feasibility parameters, to inform the design of future definitive trials, exploring exercise after stroke to benefit cognitive health.

An evidence-base exists in support of combining aerobic exercise and strengthening activities for optimal outcomes in cognitive health (186, 189). However, the majority of the aforementioned evidence was based upon data from mild stroke survivors. Stroke survivors who are living with moderate to severe movement impairments have been considerably underrepresented in the literature (11, 12), thus knowledge regarding the effectiveness of adapted exercise programmes for cognitive health is not yet known. Though methodological insights from previous studies have been useful in informing the design of future studies, there is a gap in the knowledge as to the transferability to those who are living with the long-term consequences of a severe stroke.

Overall, there are several gaps in the evidence-base exploring the impact of aerobic exercise on cognitive health among stroke survivors. There are limited high-quality randomised controlled

trials; there is a lack of inconsistency in tools and methods used, to measure both cardiorespiratory fitness and cognitive health; the magnitude of the relationship between cardiorespiratory fitness and cognitive health is unknown; and there are issues around the inclusion of stroke survivors who are living with the moderate to severe movement impairments. Future research is therefore warranted to address these gaps.

2.9 Summary of chapter

In this chapter, I have introduced and defined the key concepts addressed in this thesis, including cardiorespiratory fitness, cognitive health and their methods of measurement. A number of gaps have been identified within the evidence-base, justifying the research presented in this thesis.

In summary, there is variation in clinical guidance for the dose of exercise after stroke and there is limited clinical guidance for administering CPET with stroke survivors. Those living with the long-term consequences of a severe stroke and thus have moderate to severe movement impairments are underrepresented in most aspects of the literature reported in this chapter. Therefore, the feasibility of CPET and exercise interventions for stroke survivors with moderate to severe movement impairments needs to be addressed. Research regarding the impact of aerobic exercise on cognitive health among stroke survivors appears to be underdeveloped. The extent to which outcomes of aerobic exercise, for example cardiorespiratory fitness, mediates improvements in cognitive health, is yet to be established among stroke survivors.

Chapter 3

Statement of aims

The background and literature review in the preceding chapter established that:

- Exercise after stroke is recommended for improving cardiorespiratory fitness and reducing the risk of a recurrent stroke (90). However, there is variation in the training parameters (*dose*) of exercise (i.e. the FITT principle) across clinical guidelines.
- Stroke survivors with moderate to severe movement impairments are underrepresented in the literature (11, 12).
- There appears to be limited research to support the use of CPET in exercise after stroke services for both safety screening and for exercise prescription.
- There is some evidence in support of aerobic exercise after stroke to benefit cognitive health (43, 184-190). The extent to which outcomes of aerobic exercise, for example cardiorespiratory fitness, mediates improvements in cognitive health, is yet to be established among stroke survivors.

From this I have therefore extrapolated the need to explore the following:

- The feasibility of exercise interventions, with a view to maintain cognitive health, for stroke survivors with moderate to severe movement impairments;
- The feasibility of CPET and exercise training for stroke survivors with moderate to severe movement impairments;
- The nature of the association between cardiorespiratory fitness and cognitive health among stroke survivors;
- Optimal feasibility parameters of studies exploring the optimal dose of aerobic exercise to maintain cognitive health.

Accordingly, the overall aim of this thesis is,

To explore the influence of exercise after stroke on cardiorespiratory fitness, with a view to maintain cognitive health.

To address this overall aim, I undertook a systematic review of the literature and conducted a mixed methods feasibility study.

Chapter 4 is a systematic review that aimed to explore the specific research question:

What is the nature of the relationship between cardiorespiratory fitness and cognitive health, among stroke survivors?

Objectives included:

- To systematically identify relevant literature to be included in this systematic review,
- To quantify an estimate of the association, if any, between cardiorespiratory fitness and cognitive functioning among stroke survivors, by means of a meta-analysis where appropriate.

Chapters 5, 6 and 7 present the EXERCISES study, which aimed to explore the research question:

Is it feasible for stroke survivors with moderate to severe movement impairments post-stroke undertake CPET and adhere to a six-week exercise intervention?

Objectives included:

- To undertake a small proof-of-concept study of CPET procedures with healthy volunteers, aiming to explore the research question, *what barriers of CPET procedures may stroke survivors encounter?* Specifically,
    - To record reasons for test termination,
    - To create the optimal environment for CPET protocols,
    - To refine the delivery of CPET.
- To investigate the safety and feasibility of delivering two methods of CPET modes: treadmill with BWS and cycle ergometry; specifically,
    - The ability of participants with moderate to severe movement impairments as a result of stroke, to undertake CPET;
    - The acceptability of random allocation to CPET order;
    - Participant feedback of their experience of CPET, including aspects of acceptability and satisfaction.

- To investigate the safety and feasibility of delivering exercise-based interventions to people with moderate-severe movement impairments as a result of stroke; specifically,
    - Adherence to study protocol;
    - Participant feedback of their experience of the exercise intervention, including acceptability and satisfaction;
    - An evaluation of outcome measure tools, including their responsiveness to change and the potential for floor and ceiling effects;
    - An estimate of recruitment rate and attrition to a subsequent definitive trial.

Chapter 4

The association between cardiorespiratory fitness and cognitive function in stroke survivors: a systematic review

4.1 Introduction

This chapter presents a systematic review of the current evidence base, aiming to investigate the relationship between cardiorespiratory fitness and cognitive function. This chapter includes the background and rationale for the review and a description of the methodology used. Findings are reported and then discussed within the context of current literature.

4.2 Background

It is estimated that up to 83% of stroke survivors are living with some level of cognitive impairment (4). Post-stroke cognitive impairment is associated with increased disability (227), and a worse quality of life (228). Approximately 10% of stroke survivors will develop dementia within the first year of a first event stroke (6). This risk is estimated to increase by 20% with a recurrent stroke (6). It was established in the previous chapter that aerobic exercise may be a promising intervention for the maintenance of cognitive health (167, 212). In healthy adults, it has been suggested that as a result of aerobic exercise, gains in cardiorespiratory fitness lead to improved cognitive performance (229, 230). Specifically, measures of VO_{2max} have been found to be positively associated with cognitive health in healthy young adults' (231), older adults' (73) and in those living with mild cognitive impairment (208). However, to my knowledge, the extent to which this association exists among stroke survivors is yet to be reviewed.

To explore the nature of the relationship between cardiorespiratory fitness (VO_{2max}) and cognitive functioning in those with stroke, a systematic review of the literature was undertaken. Knowledge of this relationship has implications for predicting longitudinal cognitive function trajectories for those living with the long-term consequences of stroke. It also has implications for the design and prescription of exercise-based interventions. For example, an increase of cardiorespiratory fitness by approximately 3 mL/kg/min from stroke-specific normative values, can enable stroke survivors

to sustain light activities of living (58). It may be anticipated that a similar premise may be proposed, describing how much cardiorespiratory fitness needs to be increased to expose cognitive benefit. Consequently, exercise after stroke interventions may be tailored specifically to maintaining cognitive health.

4.3 Aims and objectives

To undertake a systematic review of the literature, to explore the research question:

What is the nature of the relationship between cardiorespiratory fitness and cognitive health, among stroke survivors?

The objectives of this review are as follows:

Objective 1 – To systematically identify relevant literature to be included in this systematic review.

Objective 2 – To quantify an estimate of the association, if any, between cardiorespiratory fitness and cognitive functioning among stroke survivors:

- **Objective 2a** – To quantify an estimate of the association at one time-point, i.e. at baseline.
- **Objective 2b –** To quantify an estimate of a temporal association between changes in VO_2 and changes in cognitive function.

4.4 Methodology

The aim of a systematic review is to synthesise the best available evidence and contribute to clinical decisions and guidelines (232, 233). The Medical Research Council (MRC) framework for developing complex interventions recommends systematic reviews for identifying the evidence base and developing theory (234). Key characteristics of systematic reviews include pre-determined inclusion criteria, a critical appraisal of the methodological quality and a qualitative or quantitative synthesis (meta-analysis) of available data (235). A critical appraisal of the literature alongside an evidence synthesis can highlight methodological rigor and flaws within the evidence-base, therefore judging the trustworthiness, value and relevance in a given context (236). Clinical and research implications derived from systematic reviews encourages improved evidence-based practice and can help inform the design of future studies (237-239).

4.4.1 Initial scoping exercise

Prior to the systematic review, a scoping exercise of the literature was undertaken. The purpose of the scoping exercise was to ensure no other review of this nature had previously been conducted and to confirm the availability of primary research for potential inclusion to my systematic review. The methodology used for the scoping exercise was informed by procedures outlined by Arksey and O'Malley (240). A search was conducted in common databases used within healthcare research: AMED; MEDLINE and MEDLINE Complete; PsychARTICLES and PsychINFO; SportDiscuss; CINAHL; using the search terms: '*systematic review OR meta-analysis'* AND '*stroke'* AND '*cognitive function*' AND '*exercise OR physical activity'* AND '*association OR correlation OR relationship*'.

Searches were undertaken in May 2018 and were updated in October 2019. Of 151 articles retrieved, nine reviews were found to be of relevance (43, 184-190). The scoping exercise found no existing review that examined the nature of the association between cardiorespiratory fitness and cognitive functioning among stroke survivors; yet revealed sufficient evidence of primary research that could be included in my review.

4.4.2 Inclusion and exclusion criteria

In order to guide this systematic review, an inclusion criteria was set in which studies must adhere to in order to be included. It is common for review questions to follow the PICOS formula, defined by the Cochrane Collaboration (233), which defines **P**articipants, **I**ntervention, **C**omparators, **O**utcomes and **S**tudy designs of included studies. However, for this review, the aim was not to compare types of interventions or investigate the effect of an intervention, thus **I**ntervention and **C**omparator items were removed. In their place, an **E**xposure was added, as the focus of this review was to predict a relationship between two variables.

Box 1 is a summary of the inclusion and exclusion criteria of this review.

Box 1.

Summary of review inclusion criteria

- Diagnosis of stroke;
- A direct measure of cardiorespiratory fitness, quantified by aerobic capacity (VO_2);
- Any measure of cognitive function;
- Published primary research (English language).

Summary of review exclusion criteria

- Study participants who had a diagnosis of a transient ischemic attack, any other neurological cognition or where stroke is only a subset of participants;
- Study protocols, qualitative projects or reviews.

Inclusion criteria

- ***Participants****: Diagnosis of stroke*

Study samples including adults (18 years and older) diagnosed with stroke were included.

- ***Exposure****: Cardiorespiratory fitness, quantified by aerobic capacity (VO_2)*

Studies were included if they provided a measure of VO_{2max}, determined by CPET, the gold standard method of measurement (60-62). Cardiorespiratory fitness is treated as the exposure in this review due to its established impact and association with other physical health outcomes (241).

- ***Outcome Measure****: Any measure of cognitive function*

Studies were included if they reported at least one measure of cognitive function; e.g. global, memory, attention.

The scoping exercise revealed common neuropsychological tests within the literature measuring global cognitive function including the Montreal Cognitive Assessment (MoCA) (242), Mini-Mental State Examination (MMSE) (243), and different versions of the Addenbrooke's Cognitive Examination (ACE) (244, 245). Specific cognitive domains that were identified from the initial scoping exercise, include, but are not limited to memory (working, episodic, procedural, and semantic); attention (processing speed); executive function (problem-solving, organisation) and language (verbal fluency).

- ***Study Design**: Published primary research*

Any study that had available numerical data to predict a relationship (e.g. randomised controlled trial, cohort, pretest-posttest, observational) were included. There were no restrictions of country, journal of publication or publication date. Studies were limited to English as there was no access to translation services for the purpose of this review.

It is suggested that the most reliable forms of evidence derive from well-designed randomised controlled trials and that these should form the basis of a systematic review (233). However, the initial scoping exercise revealed a relative scarcity of post-stroke exercise and cognition literature and therefore, observational studies were also included.

Exclusion criteria

- *Diagnosis of a transient ischemic attack, other neurological condition or stroke survivors as a subset*

Studies where the predominant focus was towards those who had experienced a transient ischemic attack, rather than a stroke, were excluded. This is based upon the rationale that by definition, a transient ischemic attack elicits no lasting symptoms (246). There is some discrepancy in diagnostic accuracy also, with misinterpretations of an embolism or spasm (247).

Studies that included stroke survivors as a subset of participants or participants diagnosed with any other neurological disorder such as a traumatic brain injury, dementia or Alzheimer's, Parkinson's disease, or multiple sclerosis were also excluded, unless data were reported separately for stroke survivors and could be adequately extracted.

- *Study protocols, qualitative studies or reviews*

Study protocols and qualitative projects were excluded, as data required to estimate associations between variables would not be available. Case studies were excluded as no statistical inferences can be made from such reports. Studies involving animal models were excluded, as the interest of this review lies within the translation of findings to future clinical practice.

4.4.3 Search methods

To identify relevant literature, searches were conducted using the following databases: AMED; MEDLINE and MEDLINE Complete; PsychARTICLES and PsychINFO; SportDiscuss; CINAHL; Database of Research in Stroke (DORIS); Physiotherapy Evidence Database (PEDro); National Rehabilitation Information Centre (NARIC Rehabdata); Trip Medical Database and Occupational Therapy (OT) Seeker Database. Databases were chosen based on their relevance to stroke and exercise and were within the scope of medicine, nursing, physiotherapy and occupational therapy, community health care and rehabilitation. Literature alluded to in national guidance documents and reference lists of reviews and studies researching exercise and cognition post-stroke, were also hand-searched for relevant articles.

Searches using terms associated with "**stroke**", "**cognitive function**" and "**cardiorespiratory fitness**" were executed. Box 2 is an example of the search strategy used in MEDLINE. Appendix 2 includes the full search strategy for each selected database.

Box 2.
Search strategy for MEDLINE.

(MM "Stroke+") OR "Stroke" OR (MM "Stroke Rehabilitation")
AND
(MM "Cognition+") OR "cognitive function"
AND
(MM "Cardiorespiratory Fitness") OR "cardiorespiratory fitness" OR (MM "Physical Fitness+") OR (MM "Exercise Test+")

4.4.4 Screening

I conducted all electronic database searches. Searches were conducted in August 2018 and were updated in October 2019. References were managed with Microsoft Excel and reference management software, EndNote. Duplicates and titles that were clearly irrelevant were removed. Abstracts of the remaining papers were screened and either removed or potentially included. Full texts of the remaining articles were obtained and screened against the predetermined inclusion criteria (box 1) by myself and a second reviewer (RH).

It is good practice to employ a second reviewer when undertaking a systematic review (248, 249). Their role is to verify inclusion and exclusion decisions, as there may be differences in interpretation and the way in which the inclusion criteria was applied. It is also beneficial at data extraction stages to reduce possible errors in data misinterpretation or data entry (250). Any disagreement in including articles was resolved by discussion and consensus with an additional, third reviewer (KMa). A third reviewer involved in the systematic review facilitated a consensus-based discussion for any issues regarding study eligibility (251).

4.4.5 Data extraction

A data extraction sheet was developed, piloted and refined. Data extraction of included studies was performed independently by RH and I. Extracted data from each study included:

- Study characteristics – including study design, country where the study was conducted, aims and objectives, sample size and randomisation, study strengths and limitations;
- Participant characteristics – including age, gender, time since and severity of stroke;
- Measures of cardiorespiratory fitness (exposure) – including method of measurement and numerical data;
- Measures of cognitive function (outcome measures) – including method of measurement and numerical data;
- Correlation coefficients between cardiorespiratory fitness and measures of cognitive function.

4.4.6 Methodological quality and risk of bias within studies

Quality appraisal of the included studies was undertaken independently by RH and I, using the Quality Assessment Tool for Quantitative Studies, developed by the Effective Public Health Practice Project (EPHPP) (252). The EPHPP has been demonstrated to be reliable, have content and construct validity, and have good test-retest reliability (i.e. Cohen's Kappa of 0.74) (253, 254). Assessing the methodological quality is a strength of a systematic review, compared to narrative reviews (143). Providing clear information regarding evidence quality allows interpretations to be made about the appropriateness of study design and conduct, as well as internal and external

validity. Through an assessment of methodological quality, the presence of any biases or confounders influencing the study outcomes may be identified. This is particularly important for this review in order to understand how the relationship between exposure and outcome may be formed. The quality of the research can, therefore, be summarised, providing a basis for future research recommendations.

A number of appraisal tools, including the Downs and Black checklist for randomised and non-randomised studies (255), Joanna Briggs Institute Critical Appraisal Tools (256), and Cochrane (143, 257), were piloted in order to investigate which tool would be most appropriate for this review. The EPHPP tool was chosen to assess the methodological quality of the included studies due to its ability to account for design-specific biases in randomised and non-randomised studies.

The tool provides a checklist and a qualitative summary score of complete descriptions of what researchers did or did not do, therefore allowing for transparent interpretations and appropriate recommendations for future research. Based on a study's selection bias, study design, confounders, blinding, data collection methods, withdrawals and dropouts, intervention integrity and analysis, an overall methodological rating of strong, moderate or weak, can be concluded (257). This checklist has also been used in previous stroke rehabilitation-based systematic reviews (258-260).

4.4.7 Data synthesis

In order to describe the nature of the relationship between VO_{2max} and cognitive function among stroke survivors, two meta-analyses were proposed in line with the following objectives:

- Objective 2a was to quantify an estimate of the association at one time-point. To perform a meta-analysis in this way, studies that included at minimum, one measurement of VO_{2max} and global cognitive function, for example at baseline, were required.
- Objective 2b was to quantify an estimate of a temporal association between changes in VO_2 and changes in cognitive function. To perform a meta-analysis in this way, studies that provided pre-exposure and post-exposure data were required.

The ability to perform these meta-analyses was subject to homogenous outcome measures and appropriate study designs. In the absence of this, I planned to perform a narrative synthesis. The

narrative synthesis in this review broadly conforms to the framework outlined by Popay et al. (261). From the text, I was able to identify influencing factors within included studies that relate to or explain the nature of the relationship between cardiorespiratory fitness and cognitive function. Influencing factors were reviewed and discussed within the research team and formulate headings of the discussion section (section 4.7).

4.5 Findings

The electronic database search yielded 198 potential references. With duplicates and irrelevant titles removed (n = 124), 74 records were assessed for eligibility. Twenty-seven required full-text assessment. Of the remaining 27 articles, eight studies met the inclusion criteria. Figure 4 is a PRISMA flow chart detailing the number of studies identified by the searches. Appendix 3 includes a list of excluded studies at the full-text stage and their reason for exclusion.

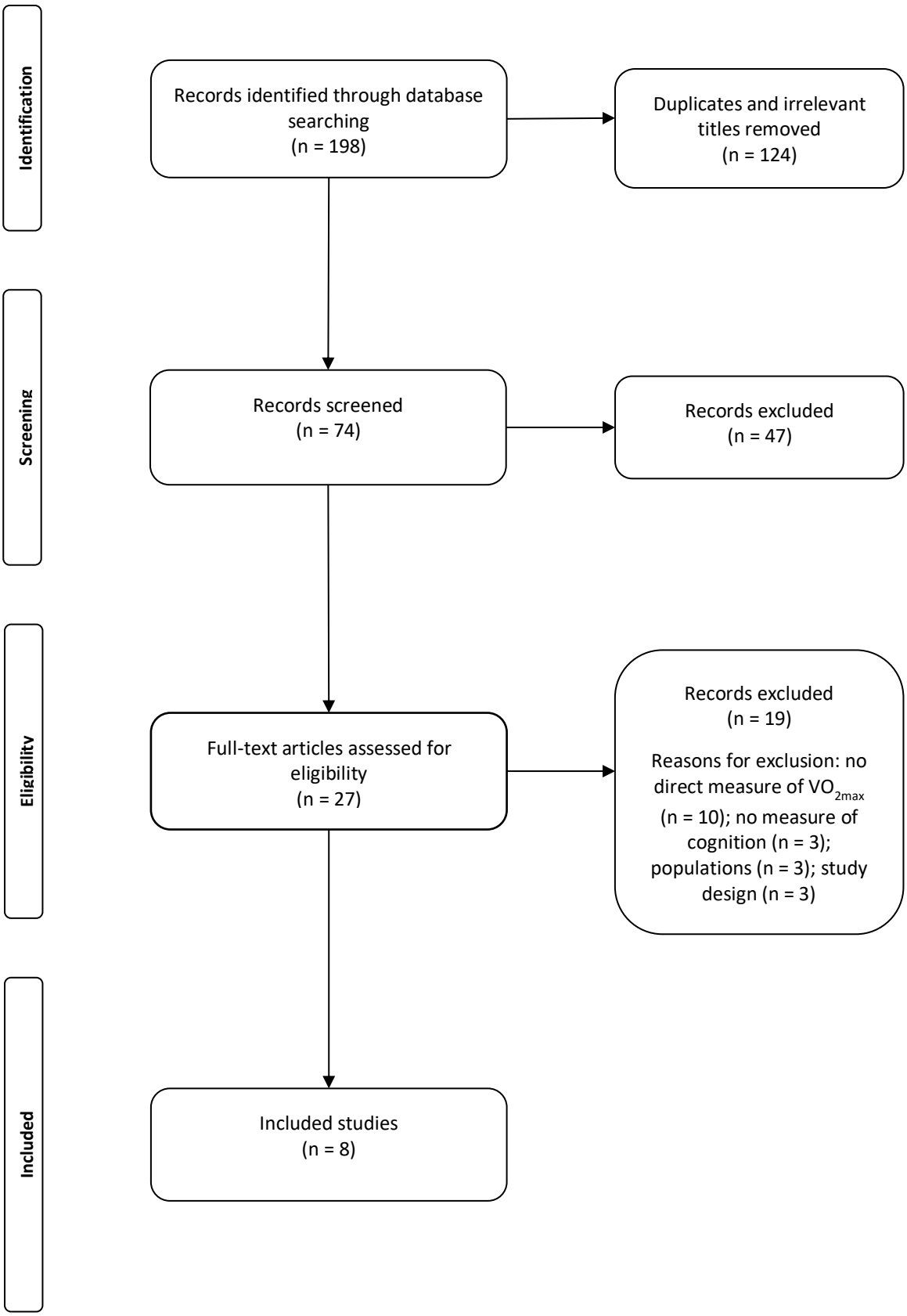

Figure 4: Flow diagram of the identification of studies

Data extraction of included studies was performed independently by RH and I. The characteristics of included studies are presented in table 4.

All included studies were conducted between 2011 and 2019 and were undertaken across three countries: Canada (n = 4), USA (n = 2), Hungary (n = 1) and the UK (n = 1). There was variation in the study designs of included studies: two randomised controlled trials (214, 262), two pilot randomised controlled trials (167, 196), three one-group, pretest-posttest designs (166, 211, 212) and one secondary analysis of a larger randomised controlled trial (263, 264).

Sample sizes ranged from nine participants (211) to 52 participants (262). For this review, summary data of exposure (VO_2) and outcome (cognitive health) was available for 279 participants.

Table 4: Characteristics of included studies

Author (year)	Study design	Sample	Exposure	Cognitive outcomes
Blanchet et al. (166) Canada	Quasi-experimental, one-group pretest-posttest design	Chronic community-dwelling stroke survivors with cognitive impairment (n=14)	VO_{2peak}	• Episodic memory • Working memory • Attention
Debreceni-Nagy et al. (214) Hungary	Rater-blinded, randomised and controlled clinical study	Subacute and chronic stroke patients (n=37)	VO_{2max}	• Global cognition • Working memory • Processing Speed
Kluding et al. (211) USA	Pilot, pretest-posttest design	Chronic community-dwelling stroke survivors (n=9)	VO_{2peak}	• Working memory • Attention • Executive function • Memory
Marzolini et al. (212) Canada	Pretest-posttest design	Chronic community-dwelling stroke survivors with mild movement impairments (n=41)	VO_{2peak}	• Global cognition
Moore et al. (167) UK	Single-centre, single-blind, parallel, pilot randomised controlled trial	Chronic community-dwelling stroke survivors with mild to moderate movement impairments (n=40)	VO_{2peak}	• Global cognition
Ploughman et al. (262) Canada	Randomised controlled trial	Chronic stroke survivors with concerns about cognitive impairment (n=52)	VO_{2peak}	• Global cognition • Fluid intelligence (problem solving)
Quaney et al. (196) USA	Randomised clinical pilot study	Chronic community-dwelling stroke survivors (n=38)	VO_{2max}	• Learning • Attention • Working memory • Motor learning • Reaction time
Tang et al. (263) Canada	Randomised controlled trial	Chronic community-dwelling stroke survivors with mild movement impairments (n=47)	VO_{2peak}	• Global cognition • Working memory • Attention

Abbreviations
NR Not reported VO_{2peak} peak aerobic capacity VO_{2max} maximal aerobic capacity

4.5.1 Description of included studies

A brief summary of the eight included studies is provided below.

Blanchet et al. (166)

Blanchet et al. (166) conducted a single group, pretest–posttest study of 14 community-dwelling stroke survivors with residual cognitive deficits. The study aimed to evaluate the short- and long-term effects of aerobic exercise interventions, either alone or combined with cognitive training, on cardiorespiratory fitness and cognitive function (memory and attention). Exercise (walking or cycling) was performed twice a week, for eight weeks, at an intensity of 60 to 70% of heart rate reserve for up to 30 minutes. Immediately following the intervention, a statistically significant improvement in attention, as measured by the Continuous Performance Test (265) was found. Changes in attention were not matched by changes in VO_{2peak}.

Debreceni-Nagy et al. (214)

Debreceni-Nagy et al. (214) assessed the impact of low-intensity aerobic training on cognitive functions via a single-blinded randomised controlled trial. Participants were severely deconditioned and within either the sub-acute or chronic time period following stroke. Thirty-five stroke survivors completed conventional physiotherapy practice for 20 consecutive days. Those randomised to the study group also completed an additional 30 minutes of cycling, at an intensity of 40 to 60% of heart rate reserve. Authors reported statistically significant improvements in processing speed, as measured by the Coding Sub-Test and Symbol Search Sub-Test on the Wechsler Adult Intelligence Scale (266). With 20 consecutive days of cycling, authors found no statistically significant improvement in working memory, nor in the cognition domain of the Functional Independence Measure (267).

Kluding et al. (211)

Kluding et al. (211) undertook a single group, pretest–posttest pilot study, involving nine stroke survivors. Participants had mild movement impairments and were in the chronic phases of stroke. The study aimed to describe the changes in cognitive and executive function following a combined aerobic and strengthening exercise training programme. A secondary aim was to explore the

relationship between changes in aerobic fitness and changes in cognitive function. Aerobic exercise was performed three times a week for 12 weeks at an intensity of 50% of VO_{2max} for up to 20 minutes, before progressive strength training, performed at the same intensity. Post-intervention, working memory (Digit-Span Backwards Test (266)) and motor control (Fugl-Meyer test (268)) were statistically significantly improved. Strong trends towards improvements of cardiorespiratory fitness and attention, as measured by the Flanker Test (269) were indicated. A statistically significant association between improved cardiorespiratory fitness and improved attention was reported.

Marzolini et al. (212)

Marzolini et al. (212) undertook a pretest–posttest design involving 45 mild stroke survivors that aimed to evaluate changes in cognition and cardiovascular fitness, following a six-month home-based exercise intervention. The intervention was modelled from an existing cardiac rehabilitation programme, Toronto Rehabilitation Institute's Risk Factor Modification and Exercise Program following Stroke (TRI-REPS). Five sessions of aerobic and strength training per week for 20 to 60 minutes, at a progressive intensity of 40 to 70% of heart rate reserve or VO_{2max} were performed. Statistically significant improvements were noted in both global cognition and VO_{2max}. There was a statistically significant positive association between change in attention and concentration domains of the MoCA and changes in oxygen uptake at anaerobic threshold (ATge). There was also a 44.5% reduction in the proportion of participants meeting the threshold criteria for mild cognitive impairment, determined by the MoCA.

Moore et al. (167)

Moore et al. (167) conducted a single-centre, single-blind, parallel randomised controlled trial of 40 mild to moderate stroke survivors that aimed to explore the effects of structured community exercise on metabolic risk factors and brain, physical and cognitive function. The exercise intervention followed the Fitness and Mobility Exercise (FAME) programme (91), in which participants completed three, 45 to 60-minute sessions of strength and aerobic exercises each week for 19 weeks, at a maximum intensity of 70 to 80% of predicted maximum heart rate (270). Authors reported statistically significant within-group changes in VO_{2peak}. Significant differences between

groups were reported in favour of the exercise intervention in walking ability (6- and 10-minute walk tests (271, 272)), balance (Berg Balance Test (273)), cognition (ACE-R), mood and overall stroke recovery (Stroke Impact Scale (274)).

Ploughman et al. (262)

Ploughman et al. (262) undertook a block-randomised, single-blinded pilot trial. Authors were interested in whether aerobic exercise, combined with cognitive training, would improve fluid intelligence, compared with each intervention alone and compared with an active control group. Fluid intelligence was measured by the Raven's Progressive Matrices Test (275). Fifty-two individuals who were at least six-months post-stroke were recruited. Interventions lasted for 10 weeks, in which participants would complete three sessions each week for a duration of 50 to 70 minutes. The primary mode of aerobic exercise training was performed on a treadmill with a body-weight supported harness at an intensity ranging from 60 to 80% of VO_{2peak}. Ploughman et al. (262) concluded that fluid intelligence scores statistically significantly improved at 12 weeks post combined aerobic and cognitive training, when compared to baseline.

Quaney et al. (196)

Quaney et al. (196) conducted a randomised pilot study of 38 chronic stroke survivors to determine whether eight weeks of aerobic exercise could produce changes in cognitive function and motor learning. Participants practised stationary cycling three times a week, at an intensity progressing from 40% to 70% of predicted maximum heart rate (270). Maximal aerobic capacity was statistically significantly improved immediately after the intervention; however, levels of fitness were not sustained at an eight-week follow-up. For cognition, statistically significant between-group comparisons were found in favour of the aerobic exercise group, for motor learning, (measured by the Serial Reaction Timed Task (276), post-intervention. No statistically significant changes in attention were reported.

Tang et al. (263)

Tang et al. (263) conducted a secondary analysis of data from a randomised controlled trial of 50 chronic stroke survivors to compare the effects of high or low-intensity community exercise on

specific domains of cognition. The exercise intervention lasted for six-months, where participants undertook combined aerobic and strength training three times a week at intensities ranging from 40% to 80% of heart rate reserve. There were no statistically significant improvements in measures of cognition with the exception of working memory over time. Cardiorespiratory fitness was only measured at baseline. This study found no evidence that high or low-intensity exercise improved cognitive function.

4.5.2 Participants

Overall, there were 184 (66%) men and 95 (34%) women (total n=279). Mean ages ranged from 59 years to 69 years. The mean time since stroke onset ranged from 3.5 months to 58 months.

Two studies did not report the type of stroke experienced by participants (166, 211). Of the other six studies, 71% (n=183) of participants experienced an ischaemic stroke, 21% (n=54) a haemorrhagic stroke, 8% (n=19) were reported to be unknown.

In four of the included studies, the severity of post-stroke impairments was reported to be 'mild to moderate' as assessed by the National Institute of Health Stroke Scale (NIHSS) (167, 214, 262, 263). Both Blanchet et al. (166) and Marzolini et al. (212) described their participants as having '*modified dependence, with supervision*', as depicted by the Chedoke–McMaster Stroke Assessment. Quaney et al. (196) and Kluding et al. (211) did not describe the severity of impairments of their sample.

Five studies included stroke survivors who had some level of cognitive impairment. Blanchet et al. (166) recruited those with clearly defined cognitive deficits, in which the severity was defined as,

> *'scoring 1.5 standard deviations or more, below age- and education-corrected norms on at least one test in a standardised neuropsychological test battery*'' (277).

In Marzolini et al. (212), 45 participants (65.9%) were considered to have mild cognitive impairment, but do not state how this was defined. In Tang et al. (263), around half of participants were considered to have mild cognitive impairment, based on the MoCA scores of less than 26 (out of a total of 30). The sample included in Ploughman et al. (262) self-reported cognitive problems that interfered with their daily functioning. Of the 33 participants who completed the MoCA at baseline, 45% (n=15) scored below the cut-off point for normal cognition (26 out of 30).

Kludling et al. (211), Moore et al. (167) and Quaney et al. (196) excluded stroke survivors who presented with a mild cognitive impairment. Debreceni-Nagy et al. (214) also excluded those who exceeded the cut-off for dementia on the MMSE (23 out of 30).

Of the 279 participants included in this review, 124 (44%) were reported as living with additional co-morbidities. These included: 34 participants (27%) with (undefined) cardiovascular disease (210, 208, 259), 26 participants (20%) with hypertension (259), 29 participants (23%) living with diabetes (207, 208, 259) and three participants (2%) who were reportedly living with kidney disease (259). Twenty-eight participants (23%) were reported to have mental health disorders, either at the time of the study or previously (162, 208, 210, 260).

Table 5 provides a summary of the participants' characteristics in the included studies.

Table 5: Characteristics of Included participants

	Total Sample (n) (Male/Female)	**Age** (years)	**Type of stroke**	**Side of stroke**	**Time since stroke** (months)	**Severity of stroke**	**Cognitive impairment**	**Indication of co-morbidity**
Blanchet et al. (166) Canada	14* (9/5)	61.9 ± 9.9	NR	NR	51.5 ± 38.2	Modified dependence, with supervision (CMSA)	Yes - Defined as >1.5 SD below NINDS test norms (277)	Antidepressant medication n=6
Debreceni-Nagy et al. (214) Hungary	35 (24/11)	59 (50-65)[a]	Ischemic = 22 Haemorrhagic = 13	Dominant side paresis = 10	10 (4.5-13.5) [a]	Mild-moderate (NIHSS)	Yes - (self-reported)	CVD n=14 Mental health disorders n=13
Kluding et al. (211) USA	9 (5/4)	63.7 ± 9.1	NR	Left = 6 Right = 3	50.4 ± 37.9	NR	No -Defined as MMSE score of >23	Diabetes n=4
Marzolini et al. (212) Canada	41 (30/11)	63.6 ± 13.5	Ischemic = 27 Haemorrhagic = 13 Unknown = 1	Left = 21 Right = 20	18.5 ± 33.6	Modified dependence, with supervision (CMSA)	Yes (n = 27) - Defined as MMSE score of <25	CVD n=8 Diabetes n=12 Atrial fibrillation n=8 History of depression n=9
Moore et al. (167) UK	40 (34/6)	69.5 ± 9.6	Ischemic = 37 Unknown = 3	Left = 16 Right = 21 Bilateral = 3	18.5 ± 25.2	Mild-moderate (NIHSS)	No - Defined as MMSE <24	NR
Ploughman et al. (262) Canada	52 (36/16)	63.4 ± 11.3	Ischemic = 40 Haemorrhagic = 12	Left = 24 Right = 25 Bilateral = 3	41.0 ± 39.8	Mild-moderate (NIHSS)	Yes – Self-reported cognitive problems related to stroke, interfering with daily functioning	Hypertension n=26 Diabetes n=13 CVD=12 Kidney disease n=3
Quaney et al. (196) USA	38 (17/21)	61.5 ± 13.6	Ischemic = 38	NR	58.3 ± 40.0	NR	Yes - Defined as MMSE <23	NR
Tang et al. (263) Canada	50 (29/21)	66 (62 – 71)[a]	Ischemic = 19 Haemorrhagic = 16 Lacunar = 7 Unknown = 8	Left = 18 Right = 31 Bilateral = 1	3.5 (2.2-6.7) [a]	Mild (NIHSS)	No - Defined as MMSE >26	NR

Values expressed as mean ± standard deviation, unless stated otherwise

[a] Values expressed as median (IQR)

*AE and AE & RT groups only – control group data not reported.

Abbreviations AE Aerobic exercise **C** Control group **CMSA** Chedoke–McMaster Stroke Assessment **CVD** Cardiovascular disease **MMSE** Mini Mental State Examination **NIHSS** National Institute of Health Stroke Scale **NINDS** National Institute of Neurological Disorders and Stroke **NR** Not reported **RT** Resistance training **SD** Standard deviation

4.5.3 Interventions

All studies included in the review examined the effects of an exercise intervention on cardiorespiratory fitness outcomes and various domains of cognitive function.

Interventions included aerobic exercise only (166, 196, 214, 263); a combination of aerobic and resistance exercise training (167, 212, 213) or a combination of aerobic exercise with cognitive training or cognitive games, or physical activity with cognitive training or cognitive games (262). The duration of intervention length ranged from 20 consecutive days (262) to six-months (263). The frequency of intervention delivery was consistent across six studies, typically two to three times per week. Marzolini et al. (212) offered one supervised session per week, with an additional four aerobic exercise sessions and one or two additional resistance training sessions to be completed at home. Debreceni-Nagy et al. (214) expected participants in the intervention group to undertake 20 consecutive weekdays of exercise training. Exercise time ranged from twenty minutes to sixty minutes; with a mean time of forty minutes. Modes of aerobic exercise were common across studies and included walking on a treadmill and stationary cycling. Types of resistance training included task-specific activities using dumbbells, exercise bands or the participants' body weight. Types of functional activities included sit to stands, step-ups on to a platform and marching. Table 6 is a summary of the interventions each study implemented.

Control groups

Four studies compared interventions to low intensity, stretching exercise interventions (167, 196, 214, 263). Ploughman et al. (262) reported findings from four intervention groups: aerobic exercise plus cognitive training, aerobic exercise plus computer-based games; physical activity plus cognitive training, and physical activity plus computer-based games.

Kludling et al. (211) and Marzolini et al. (212) only had one exercise intervention group. Blanchet et al. (166) had a control group of relaxation activities but the results from this group were not reported.

Adverse events

Six included studies did not report any adverse events, serious or otherwise (166, 167, 196, 212, 262, 263). Kluding et al. (211) reported one participant experiencing a fall at home, unrelated to the study. Debreceni-Nagy et al. (214) reported one death because of a pulmonary embolism during a resting, weekend day, perceived to be unrelated to the study.

Table 6: Description of interventions tested in included studies

	Type	Frequency	Intensity	Time	Supervision	Setting
Blanchet et al. (166) Canada	AE (walking, cycling)	2 x week for 8 weeks	60-70% of HRR	30 mins	Exercise physiologist	Research centre
Debreceni-Nagy et al. (214) Hungary	AE (cycling)	20 consecutive weekdays	40-60% HRR	30 mins	NR	Rehabilitation centre
Kluding et al. (211) USA	AE (TBRS) RT (seated knee & ankle exercises with resistance bands)	3 x week for 12 weeks	50% of $VO_{2max,}$ or 11-14 RPE	20 minutes AE, 20 minutes RT	NR	Academic medical centre
Marzolini et al. (212) Canada	AE (walking, cycling)	1 x supervised session per week for 6 months.	AE: 40-70% of VO_{2max} or 11-16 RPE	20-60 mins	NR	Rehabilitation centre with additional home-based elements
	RT (task-specific)	Recommended 4 additional AE session and 1-2 RT sessions per week	RT: >50% of 1RM or 13-14 RPE			
Moore et al. (167) UK	Combined programme of stretching, functional strength, balance, agility and fitness training	3 x week for 19 weeks	40-80% of HR_{max}	45-60 mins	PT & exercise instructor	Community leisure centre
Ploughman et al. (262) Canada	AE (treadmill with BWS)	3 x weeks for 10 weeks	60-80% of VO_{2peak}	50-70 mins	Laboratory supervised	NR
Quaney et al. (196) USA	AE (cycling)	3 x week for 8 weeks	70% of HR_{max}	45 mins	PT & exercise physiologist	NR
Tang et al. (263) Canada	AE (walking, cycling and functional movements)	3 x week for 6 months	40-80% HRR	30-40 mins	PT, OT & exercise instructor	Research centre

Abbreviations
1RM one repetition maximum **AE** Aerobic exercise **BWS** Body weight support **HR_{max}** Maximum heart rate **HRR** Heart rate reserve **Mins** Minutes **NR** Not reported **OT** occupational therapist **PT** Physiotherapist **RM** Maximum repetitions **RPE** Rating of perceived exhaustion **RT** Resistance exercise **TBRS** Total body recumbent stepper **VO_{2max}** Maximal aerobic capacity

4.5.4 Exposure

Cardiorespiratory fitness data from included studies were reported at baseline (time-point one) and percentage change in scores at time-point two (referring to values reported immediately after the intervention); and time-point three (referring to values reported at a follow-up, specifically three months for Blanchet et al. (166) and Ploughman et al. (262) and eight weeks for Quaney et al. (196)). Debreceni-Nagy et al. (214), Tang et al. (263) and Ploughman (262) collected VO_{2max} data at baseline only. Five studies measured cardiorespiratory fitness pre- and post-intervention; three of which observed a statistically significant increase (167, 196, 212).

For those studies that reported VO_{2max} pre- and post-intervention, I have reported the change scores in cardiorespiratory fitness from aerobic exercise interventions only, in line with objective 2b of this review (table 7, figure 5). Other data, e.g. pre- and post-intervention findings, and control groups are reported in appendix 4.

Table 7: Summary of cardiorespiratory fitness at time-point-one and % change scores at time-point two and three, where appropriate, for aerobic exercise intervention groups only

	Baseline VO_2 (time-point 1) (mL/kg/min)	**% change in VO_2 at time-point 2 (mL/kg/min)**	**% change in VO_2 at time-point 3 (mL/kg/min)**
Blanchet et al. (166)	18.1 ± 6.6	+6%	+8%
Debreceni-Nagy et al. (214)	11.9 (9.85 – 16.70)[a]	-	-
Kluding et al. (211)	13.9 ±4 .5	+9%	-
Marzolini et al. (212)	15.3 ± 4.9	+17% *	-
Moore et al. (167)	18.0 ± 5.0	+17% *	-
Ploughman et al. (262)	15.4 ± 3.6	+11% *	-7%
Quaney et al. (196)	14.76 ± 4.23	+5% *	
Tang et al. (263)	14.0 (12.9 – 19.8)[a]	-	-

Values expressed as mean ± standard deviation, unless stated otherwise
* denotes significant findings
[a] Values expressed as median (Q1 – Q3)
+ is percentage increase in VO_{2max}, - is a percentage decrease in VO_{2max}
Abbreviations
VO_2 Maximal aerobic capacity **mL/kg/min** millilitres per kilogram of body weight

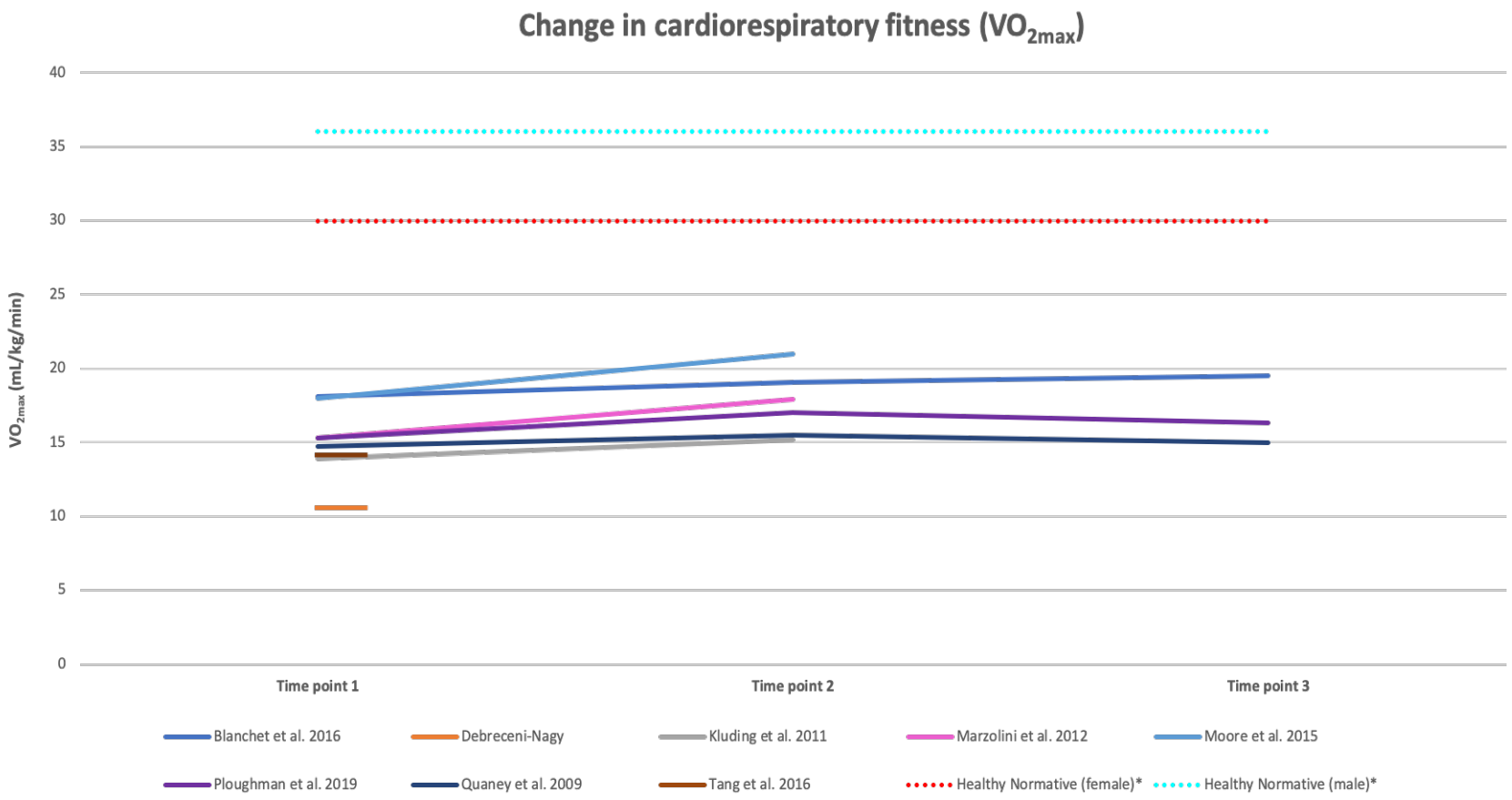

Figure 5: A line graph to show the change in cardiorespiratory fitness over time from the included studies.
Where time-point 1 refers to baseline values of VO_{2max}, time-point 2 refers to values reported immediately after the intervention and time-point 3 refers to values recorded at a follow-up.
The red dotted line denotes normative VO_{2max} values for healthy females, aged 60 to 65 years, and the turquoise dotted line, males aged 60 to 65 years.

4.5.5 Outcome measures

For this review, studies needed have at least one measure of cognitive function (global or other domain) at a minimum of a one-time-point.

In this section, I report the findings from the aerobic exercise intervention groups only. This is based on the rationale that the interest of this review lies within how cognition may be changed in conjunction with changes in cardiorespiratory fitness, which is achieved through sustained aerobic exercise training (Objective 2b).

Cognitive function data from included studies were reported at baseline and percentage change in scores at time-point two (referring to values reported immediately after the intervention); and time-point three (referring to values report at a follow-up, specifically three months for Blanchet et al. (166) and Ploughman et al. (262) and eight weeks for Quaney et al. (196)).

Global cognition

Four studies used global cognitive tools to describe the characteristics of their sample and measured at baseline only (167, 196, 213, 263).

Two included studies assessed change in global cognitive function post-intervention using the MoCA and the revised-ACE (ACE-R) (167, 212).

Table 8: Summary of global cognition scores at time-point one and % change scores at time-point two and three, where appropriate, for aerobic exercise intervention groups only

Study Reference	Assessment Tool	Baseline (time-point 1)	% change in global cognition at time-point 2
Debreceni-Nagy et al. (214)	*MMSE*	28 (27 – 29) [a]	-
	FIM	35 (33.5 – 35) [a]	0
Kluding et al. (211)	*MMSE*	27.8 ± 2.2	-
Marzolini et al. (212)	*MoCA*	22.5 ± 4.5	+7%
Moore et al. (167)	*MMSE*	28.0 ± 2.0	-
	ACE-R	86.0 ± 8.0	+7%*
Ploughman et al. (262)	*MoCA*	23.8 ± 5.6	-
Quaney et al. (196)	*MMSE*	28.17 ± 2.15	-
Tang et al. (263)	*MoCA*	26 (23 – 28) [a]	-

Values expressed as mean ± standard deviation, unless stated otherwise
* denotes significant findings
[a] Value expressed as median
+ is percentage increase in global cognition scores, meaning the likelihood of MCI or dementia is reduced; - is a percentage decrease in global cognition score, meaning the likelihood of MCI or dementia is greater (278, 279)
Abbreviations:
ACE-R Addenbrooke's Cognitive Assessment-Revised **MoCA** Montreal Cognitive Assessment **MMSE** Mini Mental State Examination

Domains of cognition

Attention

Four studies measured the attention domain of cognition. Blanchet et al. (166) used the Continuous Performance Test (CPT) and Kluding et al. (211) reported results of the Flanker Test. Both Quaney et al. (196) and Tang et al. (263) used the Stroop Test and the Trail Making Test (TMT).

Table 9: Summary of attention scores at time-point-one and % change scores at time-point two and three, where appropriate, for aerobic exercise intervention groups only

Study Reference	Assessment Tool	Baseline (time-point 1)	% change in attention at time-point 2	% change in attention at time-point 3
Blanchet et al. (166)	*CPT (omission errors)*	14.6 ± 21.5	-45%	-77%
	CPT (commission errors)	16.4 ± 6.3	-34%*	-20%
Kluding et al. (211)	*Flanker (congruent)*	92.4 ± 3.7	+2%	-
	Flanker (incongruent)	71.8 ± 18.2	+16%	-
	Flanker (reaction time)	29 ± 35.9	-7%	-
Quaney et al. (196)	*Stroop test*	-25.42 ± 9.11	0	+2%
	TMT (B-A)	75.63 ± 47.77	-11%	-32%
Tang et al. (263)	*TMT (B)*	127.2 [a]	+3%	-
	Stroop Test	111.7 [a]	+9%	-

Values expressed as mean ± standard deviation, unless stated otherwise
* denotes significant findings
[a] Value expressed as median
'+' is percentage increase in attention scores, whereby higher scores are indicative of greater cognitive functioning for the Flanker Test and the Stroop Test
'–' is a percentage decrease in attention scores, whereby lower scores are indicative of greater cognitive functioning for CPT, Flanker (reaction time) and the Trail Making Test
Abbreviations
AE Aerobic exercise **CPT** Continuous Performance Test **TMT** Trial Making Test

Memory

Kluding et al. (211) completed the Stroke Impact Scale (SIS) with participants, with a particular interest in the self-reported memory function domain. Working memory may briefly be defined as the use of attention to manage short-term memory (280). Blanchet et al. (166) reported findings from the Brown-Peterson Paradigm (BPP). Kluding et al. (211) and Tang et al. (263) used the Digit Span Backward Test (DSBT) to measure working memory.

Episodic memory, referring to long-term, contextual memories (281); was measured using the Hopkins Verbal Learning Test-Revised (HVLT-r) (166).

Table 10: Summary of memory scores at time-point-one and % change scores at time-point two and three, where appropriate, for aerobic exercise intervention groups only

Study Reference	Assessment Tool	Baseline (time-point 1)	% change in attention at time-point 2	% change in attention at time-point 3
Self-Reported Memory Function				
Kluding et al. (211)	*SIS: Self-reported memory score*	73.3 ± 18.7	+5%	-
Working Memory				
Blanchet et al. (166)	*BPP (short delays)*	13.6 ± 3.5	-5%	+1%
	BPP (long delays)	10.3 ± 2.7	+17%*	+7%
Debreceni-Nagy et al. (214)	*DST (subtest sum score)*	23 (21.5 – 25.5) [a]	+13%	-
Blanchet et al. (166)	*DST (backwards)*	3.22 ± 0.7	+17%*	-
Tang et al. (263)	*DST (forwards)*	8.0 [a]	0	-
	DST (backwards)	3.0 [a]	-17%	-
Episodic Memory				
Blanchet et al. (166)	*HVLT-r*	23.2 ± 4.7	+5%	+5%

Values expressed as mean ± standard deviation, unless stated otherwise
* denotes significant findings
[a] Value expressed as median (IQR)
'+' is percentage increase in memory scores , whereby higher scores are indicative of greater cognitive functioning for SIS, BPP and HVLT-r
'–' is a percentage decrease in memory scores , whereby higher scores are indicative of greater cognitive functioning for DST
Abbreviations:
BPP Brown-Peterson Paradigm **DST** Digit Span Test **HVLT-r** Hopkins Verbal Learning Test-Revised

Learning

One study measured learning as a cognitive outcome using the Wisconsin Card Sorting Task (WCST) (196).

Table 11: Summary of learning scores at time-point-one and % change scores at time-point two and three, where appropriate, for aerobic exercise intervention groups only

Study Reference	Assessment Tool	Baseline (time-point 1)	% change in learning at time-point 2	% change in learning at time-point 3
Quaney et al. (196)	*WCST*	1.74 ± 1.66	0	+12%

Values expressed as mean ± standard deviation
'+' is percentage increase in learning scores whereby higher scores are indicative of greater cognitive functioning for WCST
Abbreviations:
WCST Wisconsin Card Sorting Task

Fluid Intelligence

One study measured fluid intelligence as a cognitive outcome using the Raven's Progressive Matrices Test (RPMT) (262). Fluid intelligence is defined as using reasoning to arrive at understanding relations among stimuli, comprehend implications, and draw conclusions (282).

Table 12: Summary of fluid intelligence scores at time-point-one and % change scores at time-point two and three, where appropriate, for aerobic exercise intervention groups only

Study Reference	Assessment Tool	Baseline (time-point 1)	% change in fluid intelligence at time-point 2	% change in fluid intelligence at time-point 3
Ploughman et al. (262)	*RPMT*	28.5 ± 16.94	+8%	+20%

Values expressed as mean ± standard deviation
'+' is percentage increase in learning scores whereby higher scores are indicative of greater cognitive functioning for RPMT
Abbreviations:
RPMT Raven's Progressive Matrices Test

Processing Speed

One study measured processing speed as a cognitive outcome using the Symbol Search and Coding subtests of the Wechsler Adult Intelligence Scale (WAIS) (214). No included study appeared to have tested for an association between processing speed and cardiorespiratory fitness.

Table 13: Summary of processing speed scores at time-point-one and % change scores at time-point two and three, where appropriate, for aerobic exercise intervention groups only

Study Reference	Assessment Tool	Baseline (time-point 1)	% change in processing speed at time-point 2
Debreceni-Nagy et al. (214)	*WAIS: Coding subtest*	32 (27.5 – 38.5)	+13%*
	WAIS: Symbol search subtest	17 (14 – 20.5)	+12%

Values expressed as median (IQR)
* denotes significant findings
'+' is percentage increase in learning scores whereby higher scores are indicative of greater cognitive functioning for WAIS
Abbreviations
WAIS Wechsler Adult Intelligence Scale

4.5.6 Associations between cardiorespiratory fitness and cognition

Of the eight included studies, only two tested for an association between VO_{2max} and domains of cognition (211, 212).

In nine participants, Kluding et al. (211) tested for an association between change in VO_{2max} and change attention scores. Authors reported a statistically significant correlation between changes in VO_{2max} and the incongruent component of the Flanker Test. Congruent scores of the Flanker Test

presented a moderately strong relationship but did not achieve statistical significance. Kluding et al. (211) also tested for an association between change in VO_{2max} and change in self-reported memory function on the Stroke Impact Scale subscale scores. However, this relationship did not achieve statistical significance, nor for Digit Span Backwards Test scores as a test of working memory.

Marzolini et al. (212) found a positive correlation between change in VO_{2max} and change in attention. In 41 stroke survivors, attention domains of the MoCA were statistically significantly associated with oxygen uptake at the anaerobic threshold.

Table 14: Correlation between change in aerobic fitness and cognitive measures

Study Reference	Assessment tool	Correlation coefficient	*p* value
Kluding et al. (211) [a] (n = 9)	Change in SIS-memory score	*r* = 0.567	0.11
	Change in Flanker (congruent)	*r* =0.588	0.1
	Change in Flanker (incongruent)	*r* =0.74	0.02*
	Change in Flanker RT cost	*r* =-0.231	0.55
	Change in digit span backwards	*r* =-0.485	0.19
Marzolini et al. (212)[b] (n = 45)	Change in attention/concentration domains of the MoCA	β = 0.383	≤0.001*

*denotes statistically significant findings
[a] Pearson correlation coefficient with change in VO_{2max}
[b] Pearson correlation coefficient with change in oxygen uptake at the ATge
Abbreviations
ATge Gas exchange anaerobic threshold **MoCA** Montreal cognitive assessment **RT** Reaction time **VO_{2max}** Maximal aerobic capacity

4.5.7 Data Synthesis

Given the available data, it was not possible to carry out meta-analyses at one time-point (objective 2a), nor over time (objective 2b).

Although at baseline, four studies administered the MMSE (167, 196, 211, 214), and three studies administered the MoCA (212, 262, 263), these data could not be pooled, in order to meet Objective 2a. This was because no study reported correlation coefficients for cardiorespiratory fitness and cognitive function at baseline.

Another reason is due to the fact there was diversity in the purpose or concept of why the cognitive functions are measured. Baseline measures of both cognitive and cardiorespiratory health were

used as a description of the study's sample and of the prevalence of cognitive impairments and cardiovascular deconditioning. The MMSE was used as an eligibility screening tool for entry into the study (167, 196, 211, 214). Differences in the theoretical justification for measurement makes it challenging to synthesise studies, with regard to their association with cardiorespiratory fitness.

With the available literature, it also was not possible to meet Objective 2b: to quantify an estimate of a temporal association between changes in VO_2 and changes in cognitive function. Only two of the eight included studies in my review explored the relationship between change in cardiorespiratory fitness and change scores of attention variables of cognitive health (211, 212). However, one study reported a Pearson correlation (r) (211) and the other, beta coefficient (β) (212), thus could not be pooled.

Of the three studies that provided global cognitive function data at more than one time-point, three different measurement tools were administered (167, 212, 214). Debreceni-Nagy et al. (214) used the cognitive sub-scale of the Functional Independence Measure; Moore et al. (167) administered the ACE-R and Marzolini et al. (212) used the MoCA. Although the difference in assessment tools may have been accounted for statistically, methodological heterogeneity in the time-points for data collection (20 days, 6 months and 19 weeks, respectively) precluded a meta-synthesis of the three studies. In addition, if data was to be combined, the pooled sample size would also be too small to formulate meaningful conclusions as to how changes in cardiorespiratory fitness (VO_2) and changes in cognitive function are associated (283).

4.6 Methodological quality

RH and I independently reviewed the included studies for their methodological quality, using the EPHPP quality assessment tool (252) (appendices 5 and 6). We discussed quality rating and established consensus. As with study inclusion, any disagreement was resolved by discussion and consensus with the third reviewer (KMa). The Kappa coefficient for the interrater agreement of global ratings for methodological quality was 0.77, indicating a substantial agreement between the two reviewers (284). Scores of methodological quality are presented in table 15. S

Table 15: Quality assessment of included studies using the EPHPP tool

Author (Year)	Selection bias	Study design	Confounders	Blinding	Data collection methods	Withdrawals and dropouts	Global rating
Blanchet et al. (166)							
Debreceni-Nagy et al. (214)							
Kluding et al. (211)							
Marzolini et al. (212)							
Moore et al. (167)							
Ploughman et al. (262)							
Quaney et al. (196)							
Tang et al. (263)							

Key: **Strong** **Moderate** **Weak**
For global rating: **Strong** (no weak rating) **Moderate** (one weak rating) **Weak** (two or more weak rating)

4.6.1 Global quality rating

In terms of global rating, two studies were rated as strong (262, 263), three moderate (166, 212, 214) and three weak (167, 196, 213). Studies received a weak rating of methodological quality as they presented a high risk of bias in two or more components, as per the EPHPP quality assessment tool.

4.6.2 Selection bias

Five studies were rated to have a moderate risk of selection bias (166, 212, 214, 262, 263). The remaining three were rated as 'weak'. Selection bias refers to the extent to which the sample reflects the target population and can occur if there are differences between those included in the study and those who are not (285).

Convenience sampling and self-selection were used in two studies (167, 213). Selection bias and the use of convenience sampling affects the study's internal validity and the generalisability of findings to the wider population (286).

4.6.3 Study design

Five studies were randomised controlled trials, resulting in a strong rating for methodological quality (167, 196, 214, 262, 263). The remaining three studies were also pretest–posttest designs and have moderate quality rating (166, 211, 212).

4.6.4 Confounders

A confounder can be defined as a third variable which influences both the exposure and outcome variable; therefore 'blurring' or 'mixing' effects (287).

For the presence of confounders, two studies were rated as weak (167, 196). Studies were rated as weak as there were high drop-out rates (167) and there was greater variation in participant demographics that were not accounted for statistically (196). The remaining six included studies had a moderate quality rating (166, 212-214, 262, 263).

In this review, it is important to consider the impact of additional confounders, as it may be that VO_{2max} is not the only exposure that has the ability to moderate change in cognitive outcomes.

Participant characteristics, such as diagnostic features (i.e. type of stroke, time since stroke) and co-morbidities (i.e. cardiovascular disease, mental health disorders) are important to quantify and report, as they may have the potential to confound both the nature and extent of the association between exposure (or intervention) and outcome, as well as the effect of an intervention (9).

4.6.5 Blinding

One study was rated as weak (211) and the remaining seven were rated as moderate. Blinding is used to conceal group allocation from those involved in the research process, for example those who deliver an intervention or the outcome assessors (288). The blinding of study personnel reduces the risk of performance bias, referred to differences between the treatment and control groups resulting from the care that was provided, or exposure to factors other than the interventions of interest (289). Blinding of outcome assessors is also important in reducing the risk of potentially over or underestimating of the size of effect (288).

Participants may be blinded to their group allocation and also to the research question which aims to protect again performance biases (288). However, due to active participation of stroke survivors and those delivering the exercise interventions, it is usually not possible for participants and those delivering an intervention to be blinded (290, 291).

4.6.6 Data collection methods

Five studies were rated as strong (166, 167, 213, 262, 263) and three studies received a moderate rating for the quality of data collection methods (196, 212, 214). On average, seven outcome assessments for cognitive, functional and physical measures were conducted per participant. Selected outcome measures used should be valid and reliable for use with the target population. This is particularly important for the objective of this review, as methods of data collection need to be precise and sensitive enough to provide sufficient data for estimating associations between an exposure and outcome measures.

Cardiorespiratory fitness

Four studies undertook CPET on a stationary cycle ergometer (166, 167, 214, 263), each with previously validated protocols (292-295).

Marzolini et al. (212) chose the mode of CPET based on each participants' ability to balance and their level of control of the lower limb. Options included: recumbent cycle ergometer, upright cycle ergometer or treadmill. Authors do not make reference to validated protocols for any of these modes.

Kluding et al. (211) completed four exercise tests, two at baseline and two at 12 weeks. Protocols for cycle ergometer and total body recumbent stepper protocol were based on previous protocols (164, 295). The validation of the total-body recumbent stepper CPET protocol was a secondary aim of the study. Table 16 provides a description of CPET modes and protocols undertaken in the included studies.

Ploughman et al. (262) implemented CPET on either a treadmill, using a protocol adapted from a previous study (296) or on a total-body recumbent stepper, using the same protocol as Kluding et al. (164, 211).

Table 16: A description of cardiopulmonary exercise testing method, implemented in included studies

	Mode	Protocol	Supervision	Criteria for Reaching VO_{2max}	Test Termination Criteria	Adverse Events
Blanchet et al. (166)	Semi-recumbent ergometer	2 mins warmup 10W /1 min, 60 rpm	Cardiologist & exercise physiologist	NR	Inability to maintain cadence or items from ACSM test termination criteria (2010)	NR
Debreceni-Nagy et al. (214)	Cycle ergometer	10W /1 min, 60 rpm	NR	NR	Symptom limited or RER of $\geq$1.1	None related to CPET
Kluding et al. (211)	Bicycle ergometer TBRS	10W /1 min, 60 rpm 25 W, 40 W, 55 W, 70 W, 85 W, 100 W, 115 W, 130 W /2 min, 80 steps/min	Exercise physiologist & physician	Maximal effort: defined as 90% of predicted maximum heart rate	Angina, dyspnea, fatigue (voluntary exhaustion or inability to maintain cadence), hypertension, hypotension or ECG abnormalities	None
Marzolini et al. (212)	Recumbent bicycle ergometer	8.3 or 16.7 W /1 min	NR	NR	NR	NR
Moore et al. (167)	Recumbent bicycle ergometer	3 mins warm up at 20W 10W /1 min, 50 rpm	NR	NR	Volitional exhaustion	NR
Ploughman et al. (262)	Treadmill with 10-15% BWS or TBRS	2.5% incline /1 min, then 0.05m/s /2 min 20W /2 mins	Physiotherapist or exercise physiologist & physician	NR	Volitional exhaustion	None
Quaney et al. (196)	NR	NR	NR	NR	NR	NR
Tang et al. (263)	Cycle ergometer	10W or 20W /1 min, 60 rpm	Physician	NR	Volitional exhaustion	NR

Abbreviations:
ACSM American College of Sports Medicine **ECG** Electrocardiogram **min** Minute **NR** Not reported **RER** Respiratory exchange ratio **RPM** Revolutions per minute **TBRS** Total body recumbent stepper **W** Watts

Cognitive function

Global

Global cognition was reported in all but one study (166). Assessment tools included the MMSE (167, 196, 213, 214), the MoCA (212, 262, 263) and the ACE-R (167). They have all been shown to be feasible for use with stroke survivors, demonstrating high sensitivity and specificity (297).

Attention

Attention was measured by the Continuous Performance Test (166) and the Flanker Test (211). The Continuous Performance Test has demonstrated satisfactory test re-test reliability in people with chronic stroke (298). The Flanker task appears to be feasible, and a reliable and valid measure of selective attention in those with dementia (299), thus may be transferable to those with post-stroke cognitive impairment, due to some similarities in population characteristics.

Memory

Blanchet et al. (166) used the Brown Peterson Paradigm and Hopkins-revised Verbal Learning Test to measure working memory and episodic memory, respectively. Findings from Geurten et al. (300) appear to confirm the validity of the Brown Peterson Paradigm for use with those who have sustained traumatic brain injury. The Hopkins-revised Verbal Learning Test is also found to be a valid test of memory for use with older patients with possible dementia (301), the Digit Span Test used by Kluding et al. (211) is also a test of working memory. It has previously been shown to be responsive to change with exercise in older adults with mild cognitive impairment (302, 303). Although each of these memory assessments have not demonstrated validity in the stroke population, given some similarities in populations, transferability may be assumed.

Learning

The Wisconsin Card Sorting Task, used in Quaney et al. (196), has been found to have poor to adequate ecological validity, acceptable discriminative validity and acceptable convergent validity in patients with stroke (304).

Fluid Intelligence

The primary outcome for Ploughman et al. (262) study was fluid intelligence, as measured by Raven's Progressive Matrices Test. It is reliability has been found to be satisfactory (305).

Processing Speed

To measure processing speed, Debreceni-Nagy et al. (214) administered Symbol Search and Coding sub-tests of the Wechsler Adult Intelligence Scale (265). In studies involving stroke survivors, this assessment has been demonstrated to have high construct validity (306).

4.6.7 Withdrawals and dropouts

All studies were given a strong rating for this component, each reporting withdrawal and drop-out rates and reasons. Reporting withdrawals and drop-outs is important for reducing biases related to missing data (307).

Three included studies had full adherence to the protocol, in that there were no withdrawals (167, 196, 263). Collectively, the other studies reported withdrawals were due to: recurrent stroke (n = 2), time commitments (n = 4), transportation and schedule conflicts (n = 5), fall at home (n = 1), death of spouse (n = 1), instance of cancer (n = 1), group assignment refusal (n = 3), considered amount of remuneration insufficient (n = 1), withdrew consent (n = 1) and adverse event (n = 1). Reporting reasons for withdrawals provides information regarding the safety of an intervention and the acceptability of study procedures.

4.7 Discussion

The overall aim of my systematic review was to explore the nature of the association between cardiorespiratory fitness and cognitive health, among stroke survivors. The main finding was that there was a lack of evidence available to quantify the nature of the association between cardiorespiratory fitness and cognitive function. Eight studies were identified from the evidence-base, with varying methodological quality: three studies were rated as weak, three as moderate and two had strong methodological quality.

4.7.1 Key findings

As described in the findings of this review (section 4.5), a meta-analysis, aiming to describe the nature of the relationship between cardiorespiratory fitness and cognitive function, could not be undertaken at one time-point (objective 2a), nor over time (objective 2b). Overall, this was a result of a lack of, or insufficient data; differences in concepts of measuring cognition; variation in outcome measures and methodological heterogeneity in the length of exercise interventions. My findings are similar to those of previous reviews, who were also unable to quantify such relationship in older adults without stroke, in that there was insufficient data to pool and estimate the nature of the association between cardiorespiratory fitness and cognitive function (183, 209).

Only two of the eight included studies in my review explored the relationship between change in cardiorespiratory fitness and change scores of attention variables of cognitive health, specifically attention (211, 212). However, these data could not be pooled due to differences in the data that was reported. Despite no fixed minimum number of data points required for a meta-analysis, the limited number of data points available from the included studies, may also limit the precision of pooled estimates as well as the power to detect effects, particularly among studies with small sample sizes (283). Thus, findings reported by Kluding et al. (211) and Marzolini et al. (212) should be interpreted with caution, as sample sizes are small.

In the remainder of this chapter, factors that relate to the nature of the relationship between cardiorespiratory fitness and cognitive function are discussed.

4.7.2 Outcome measures

Tools used to measure global cognition post-intervention differed between studies, thus limiting the ability to infer the nature of the association over time. Variation in outcome measures is a common challenge encountered across stroke rehabilitation trials, making summarising and analysing data problematic in a systematic review (308). A lack of consistency in measurement tools for cognitive function is in line with findings from Zheng et al. (43), in that authors also found there was no standardised tool to measure domains of cognition.

Debreceni-Nagy et al. (214) used the cognitive sub-scale of the Functional Independence Measure to determine global cognitive health. Other published work have also used the cognitive sub-scales of the Functional Independence Measure (216, 217) and of the Stroke Impact Scale (11, 218) to measure cognition. The use of different tools to determine cognitive health challenges the opportunity to undertake a synthesis of multiple study findings (219). This may be further emphasised when pooling findings based on cognitive sub-scales, as tools may not be sensitive enough to detect cognitive impairments. Much like other reviews, the findings of my systematic review highlights the need for researchers to form a consensus regarding measurement tools for cognitive function (184, 188, 220).

My review builds on previous work by Etnier et al. (209), as I only included studies that recorded direct measures of VO_2 via CPET. This provides a more accurate measure of cardiorespiratory fitness (60-62). Similar to van de Port et al. (159), I found the reporting of CPET and methods defining cardiorespiratory fitness to be inconsistent across the included studies. A combination of VO_{2max} (196, 214) and VO_{2peak} (166, 167, 211, 212, 262) was reported. I found that the mode of CPET used to determine cardiorespiratory fitness differed across studies. Modes included recumbent cycle ergometers, upright cycle ergometers or treadmills (with and without BWS) and a total-body recumbent stepper.

Despite CPET being the gold standard to determine VO_2, having no direct measure of VO_2 (maximal or peak) was the most common reason for exclusion at both the abstract and full-text stage (60-62). Studies have suggested that post-stroke cognitive and motor impairment (158) preclude stroke survivors' from undertaking CPET, therefore estimated values of VO_2 or composite measures of cardiorespiratory fitness may be more appropriate for stroke survivors (157). Field-based submaximal tests, such as the six-minute walk test (309, 310) are common (311-313). Such tests provide an estimate of submaximal VO_2 and composite measures of cardiorespiratory fitness; such as heart rate, blood pressure and body composition. With studies reporting composite measures, how each of these may be associated with cognitive function may be an important area for future investigation. In addition, the relationship between estimated VO_2 and cognition may be more reflective of clinical practice, thus warrants future exploration.

4.7.3 Interventions

Although not the focus of this review, it is important to consider the characteristics of exercise interventions implemented within included studies. In line with previous work, my review found variety in the dose of exercise prescribed (43, 185, 189). Heterogeneity in exercise prescription prevents the opportunity to provide an overall estimate of the optimal dose of exercise required to benefit cognitive health.

Should the nature of the relationship between cardiorespiratory fitness and cognitive health be confirmed, intervention parameters such as the length of an exercise programme and exercise intensity could have implications for the magnitude of the relationship between cardiorespiratory fitness and cognitive health. For example, a previous meta-analytic study of stroke survivors found that longer-term interventions (three months or more in length) provided greater cognitive benefit, compared with shorter-term exercise training (189). With longer durations of an intervention, the capacity to improve cardiorespiratory fitness and cognitive health may be greater (189).

My review found a range of intensities and types of exercise were prescribed across the included studies. In the present review, exercise intensity ranged from 40% to 80% and was reported as either maximum heart rate (167, 196), heart rate reserve (166, 214, 263) or VO_{2max} (211, 212, 262). Diversity in reporting intensity via different parameters leads to challenges in comparing studies. Exercise at higher intensities has shown to improve neuroplastic outcomes that are associated with cognitive health (182). Therefore, studies that prescribe exercise at an increased intensity may result in greater improvements in cardiorespiratory fitness, thus potentially influencing the relationship with cognitive health.

Intensity is a critical component of the dose of exercise prescription, in which manipulation may influence the extent to which an aerobic exercise intervention is effective at improving cognitive health or not (182). Studies included in my review revealed modest, or non-significant changes in VO_2, post-intervention (166, 211). Authors attributed a lack of findings to the characteristics of the intervention. In two studies (166, 211), improvements in cognitive health were therefore absent of any changes in VO_2, suggesting that there may be other mechanisms, aside from physiological adaptations, that are responsible for improvements in cognitive performance. For example, the

effects of socialisation have been hypothesised to promote cognitive health (166, 190, 314). Group exercise is associated with increased participant motivation and self-esteem (315, 316). From research with older adults, it is known that social participation plays an important role in cognitive functioning (314). However, the extent to which this is true among stroke survivors is yet to be robustly established.

4.7.4 Population characteristics

Earlier in this chapter potential confounders were identified (Section 4.6.4), which may impact both the nature of the relationship between cardiorespiratory fitness and cognitive health, and the effect of an intervention. The following section discusses participant characteristics, including co-morbidities that may produce an unaccounted-for influence on the association between exposure and outcome.

The heterogeneity of stroke itself, for example type, severity and/or level of post-stroke impairment, may affect both the exposure (cardiorespiratory fitness) and the outcome (cognitive function), differently; in that more severe strokes are known to result in poorer outcomes (11). Greater levels of cognitive impairment and symptoms of post-stroke depression have been observed in individuals who experienced a partial anterior circulation infarction, compared to those with a lacunar circulation infarction (12).

In this review, five studies included participants who were living with post-stroke mild cognitive impairment (1, 2, 4, 6, 7). The presence and severity of post-stroke cognitive impairment may influence the specificity of changes in cognitive health, as a result of aerobic exercise. Memory, attention and executive function are the specific domains of cognitive function that are known to be most affected by a stroke event (13, 14). However, they are also likely to be those most amenable to change with aerobic exercise (15, 16). The extent to which cognitive physiological adaptations take place in response to exercise among stroke survivors is currently unknown.

Differences in baseline cognitive health across the population may also influence an individual's ability to engage with, and adhere to, exercise prescription. There is evidence to suggest those with mild-cognitive impairment face challenges related to exercise participation (17). For example, individuals may experience low intrinsic motivation, memory deficits and confusion and variability

in their cognitive health on a day-to-day basis (17). Such factors may diminish accessibility to exercise interventions or programmes, thus reducing opportunities to increase cardiorespiratory fitness and in turn, cognitive health.

Additionally, time since the onset of stroke may impact on the findings of this review. Stroke survivors included in my review were approximately one to four years post-stroke. In a review of physical activity interventions implemented approximately 2.5 years after stroke, a moderate positive treatment effect was found (18). Within the chronic phases of stroke, it is known that individuals spend are more sedentary (19) and are at a greater risk of cognitive decline (20-22).

Etnier et al. (23) found that the age of participants was statistically significantly associated with the relationship between cardiorespiratory fitness and cognitive performance in a review including healthy adults, those living with chronic pulmonary obstructive disease and those living with depression. For adults aged 60 years and over, there were gains in cardiorespiratory fitness predictive of larger gains in cognitive performance. In my review, the mean age of study samples ranged from 59 years to 69 years, thus findings from Etnier et al. (23) may be comparable. Around three-quarters of stroke events occur over the age of 65 years (24), thus age should be considered as a confounder in future studies, that aim to explore the nature of the relationship between cardiorespiratory fitness and cognitive health.

The presence of comorbidities may affect the extent to which an outcome is responsive to the proposed exposure; in this case, the extent to which cognitive health is affected by cardiorespiratory fitness. Seventy-two percent of included participants were living with co-morbid cardiovascular disease, including hypertension and diabetes. One study reported half of the participants were diagnosed with type-II diabetes mellitus (3). Already, it is known that low cardiorespiratory fitness is a risk factor for diabetes mellitus (25). Furthermore, evidence suggests diabetes mellitus is associated with a decline in cognitive health, specifically cerebral atrophy, translating to deficits in memory and learning (26). The estimated prevalence of diabetes among stroke survivors is 28%, and thus should be an important consideration for future work exploring the nature of the association between cardiorespiratory fitness and cognitive health (27).

As previously identified, there is an evidence-base supporting the association between cardiovascular disease and low cardiorespiratory fitness (28, 29). Among participants living with cardiovascular disease, measures of cardiorespiratory fitness are already up to 45% lower than those without (30). The phenomena by which individuals with initially low cardiorespiratory fitness demonstrate the largest gains, is referred to as the 'law of initial values' (28). This pattern is well-documented within the exercise physiology literature and has been demonstrated among patients undergoing cardiac rehabilitation (31, 32). Consequently, the effect of an exercise intervention may be greater among those living with co-morbid cardiovascular disease, compared to those without, due to an already lower cardiorespiratory fitness. It will be important for future studies that intend to explore the association between cardiorespiratory fitness and cognitive health to consider this theory.

In this review, there is a mixed sample of participants who are living with, without or whom have a history of depression. Previous research has found an association between depression and cognitive impairment in older adults' (33). Depression is also known to predict cognitive decline and the onset of dementia (33, 34). It is therefore important to acknowledge depression as a potential confounder to the association between cardiorespiratory fitness and cognitive health.

Participant characteristics, in particular co-morbidities, should be considered within the design of future studies. In studies that aim to define the nature of the relationship between cardiorespiratory fitness and cognitive health, researchers should ensure methodological design, specifically data analyses, are adjusted and appropriate to account for such confounders.

4.7.5 Limitations of this review

There are a number of methodological shortcomings of my review. Only one reviewer, due to resource constraints, was able to screen the retrieved titles and abstracts, leading to potential bias in study inclusion. However, the fact a second review was employed to independently screen full texts, extract data and appraise the quality of each included study, is a strength of this study.

The search strategy used in this review may be criticised, in particular the search terms used. For example, only terms related to *'cognition'* and *'cognitive functio*n' were searched for. A previous

review hand-searched relevant studies for cognitive outcomes (188). This may be a more robust way of identifying relevant citations as trials that assessed cognition as a secondary measure may have been missed, particularly when they referred to specific sub-domains of cognition. Or, if studies were assessing cognitive domains as one component of a questionnaire, such as the Functional Independence Measure, as noted in a Cochrane review of physical fitness post-stroke (9).

Terms related to intervention description, for example *'aerobic exercise'* or *'strength training'* were not explored, as this review was interested in the associations between exposure and outcome, not the effect of an intervention. As a result of this, some potentially relevant studies may have been missed when searching for articles for inclusion. In addition, all included studies were conducted in high income countries.

4.7.6 Strengths of review

To my knowledge, this is the first systematic review aiming to quantify the nature of the relationship between cardiovascular fitness and cognitive health among stroke survivors. The strengths of this review lie within the focus on direct measures of cardiorespiratory fitness, by means of CPET. Here, the most accurate values of cardiorespiratory fitness (VO_2) were obtained with a view to explore their association with cognitive health.

4.8 Learnings informing The EXERCISES Study

Summarising CPET protocols used in included studies was useful in informing CPET methodology for The EXERCISES Study. Section 4.6.6 provides an overview of the CPET modes and intensity increments that were used with participants. Included studies demonstrated the feasibility of different modes of CPET (e.g., cycle ergometer, treadmill with BWS) among stroke survivors, which supported my decision to use these modes in The EXERCISES Study. Although participants included in this review were living with mild post-stroke movement impairments, the included studies described some adaptations that were made to equipment and/or protocols to account for this. This provided me with the opportunity to further modify CPET methodology to accommodate the

target population of The EXERCISES Study (stroke survivors with moderate to severe movement impairments).

Across the included studies, there was variation in the CPET protocols utilised with stroke survivors. The studies provided evidence of safe exercise modes and protocols for increasing intensity. The different protocols informed the design of the exploratory CPET work undertaken with healthy individuals (Chapter 5, section 5.13.2). I was able to trial and adapt the existing protocols and explore different methods of increasing exercise intensity; for example, via speed (as in Ploughman et al. (6)) or via resistance (as in Kluding et al. (3)).

CPET safety procedures used in The EXERCISES Study were also informed by studies included in the review. Expected values of CPET variables, including heart rate, blood pressure, RPE and VO_{2max} were vital in the formulation of CPET stopping criteria. Studies also provided evidence of the acceptability of the ACSM Test Termination Criteria for use with stroke survivors (37). Furthermore, previous findings gave an indication of what physiological responses to exercise we may expect, for example peak heart rate. Findings of previous studies suggested that stroke survivors, although living with mild movement impairments, found it challenging to achieve a true VO_{2max}. Thus, when it came to the data collection and analysis phases of The EXERCISES Study, submaximal values of aerobic capacity were expected.

Where studies included measures of global cognition, the most frequently used tools were considered for use in The EXERCISES Study. These were the MMSE (2, 5, 7, 10) and the MoCA (4, 6, 8). The suitability of such outcome measures for the target population of The EXERCISES Study was considered, taking into account cognitive and dexterous ability. Although it was found that most of the included studies implemented a battery of cognitive assessments (up to seven measures), I felt that this approach, in addition to secondary outcome measures and CPET, would be too burdensome for participants.

4.9 Summary of chapter

The main finding of this review was a lack of primary evidence available to quantify the nature of the relationship between cardiovascular fitness and cognitive health among stroke survivors.

Overall, this was a result of a lack of, or insufficient data, differences in concepts of measuring cognition, variation in outcome measures and methodological heterogeneity in the length and type of exercise interventions.

As previously stated, an increase in cardiorespiratory fitness by approximately 3 mL/kg/min has been shown to enable stroke survivors to sustain light activities of living (58). It was anticipated that this present review would be able to provide evidence, building towards a similar statement with regards to a dose-response relationship for maintaining cognitive health. More well-designed studies, with consistent measures of cardiorespiratory fitness and cognitive health, are warranted to confirm the nature of such relationship exists among the wider stroke population. Studies should also account for confounders, including the impact of exercise intervention components (i.e. the FITT principle) and population characteristics (i.e. age, time since, or severity of stroke), when defining the magnitude of this relationship.

Chapter 5

The EXERCISES Study: Methodology

5.1 Introduction

This chapter presents the methodological approach and the methods of data collection chosen to address the aims and objectives of the feasibility study, entitled Exercise and Cognition in Stroke Survivors (the EXERCISES study). A full description of the methodology used to undertake this study is provided, detailing decision making, and the justification of procedures used. This chapter then provides a description of the study's epistemological stance to justify the use of a mixed methods feasibility study design. I have chosen to provide the reader with a full description of the study, followed by the process of development, including the proof-of-concept study undertaken with healthy volunteers. I chose to report the methodology in this order, so that these more theoretical aspects of the study can be understood in light of how the EXERCISES study was undertaken.

5.2 Background

In the Chapter 2 (background and literature review), it was established that exercise after stroke is recommended for improving cardiorespiratory fitness and in turn, potentially benefits cognitive health (43, 184-190). However, it was found that stroke survivors with moderate to severe movement impairments are underrepresented in the literature (11, 12) and there appears to be limited research to support the use of CPET in exercise after stroke services, for both safety screening and for exercise prescription (159). The feasibility and acceptability of exercise-based interventions and CPET for this population is still largely unknown, thus warrants investigation.

5.2 Aims and objectives

Aim 1 – To investigate the safety and feasibility of delivering two methods of CPET modes: treadmill with BWS and cycle ergometry; specifically,

- The ability of participants with moderate to severe movement impairments as a result of stroke, to undertake CPET;
- The acceptability of random allocation to CPET order;
- Participant feedback of their experience of CPET, including aspects of acceptability and satisfaction.

Aim 2 – To investigate the safety and feasibility of delivering exercise-based interventions to people with moderate-severe movement impairments as a result of stroke; specifically,

- Adherence to study protocol;
- Participant feedback of their experience of the exercise intervention, including acceptability and satisfaction;
- An evaluation of outcome measure tools, including their responsiveness to change and the potential for floor and ceiling effects;
- An estimate of recruitment rate and attrition to a subsequent definitive trial.

5.3 Overview of study design

A mixed methods feasibility study design was used to address the limited knowledge around the acceptability of CPET and exercise training for those living with the long-term consequences of a severe stroke. The methodological approach when designing a study must reflect the most appropriate means of addressing both the type and the nature of the proposed research question (330). The feasibility design of this study was informed by the MRC framework (234) and guidance from Bowen et al. (331) in how to design feasibility studies.

This mixed methods study combines and integrates qualitative and quantitative research methods of data collection and analysis. An embedded approach was adopted, in which a qualitative study

was embedded within a larger quantitative experimental pretest–posttest study design. The central premise for mixed methods research is that the triangulation of approaches provides a better understanding than a singular approach (330). In my study, quantitative data was used to estimate feasibility parameters and the potential for change in cardiovascular and cognitive function; whereas qualitative data collected sequentially, explored participants' experiences and perceptions of the intervention they participated in and of CPET procedures.

To provide an overview of the EXERCISES study, individuals who were more than six-months post-stroke and living with moderate to severe movement impairments were invited by the local community health and care NHS trust or through community stroke survivor support groups to take part. Each participant underwent a rigorous screening process by me and a stroke consultant, to ensure their safety to participate in exercise. Participants were randomised to order of CPET (treadmill with BWS at baseline and cycle ergometer at follow up, or vice versa). Baseline measures of cardiovascular fitness were recorded, in addition to cognitive health, quality of life and activities of daily living. Participants were sequentially allocated to one of three intervention groups: (i) aerobic exercise only, (ii) strength training only or (iii) a combination of aerobic exercise and strength training. Participants were expected to take part in two, one-hour sessions of individually tailored exercise training for six-weeks. Measures taken at baseline were repeated post-intervention, with the alternative CPET mode to that undertaken at baseline. Following the intervention, six participants were invited to participate in a semi-structured interview with an independent member of the research team, not involved in intervention delivery. Interviews aimed to explore their experiences and perceptions of the intervention they participated in and of CPET procedures. Key events of the EXERCISES study are illustrated in figure 6.

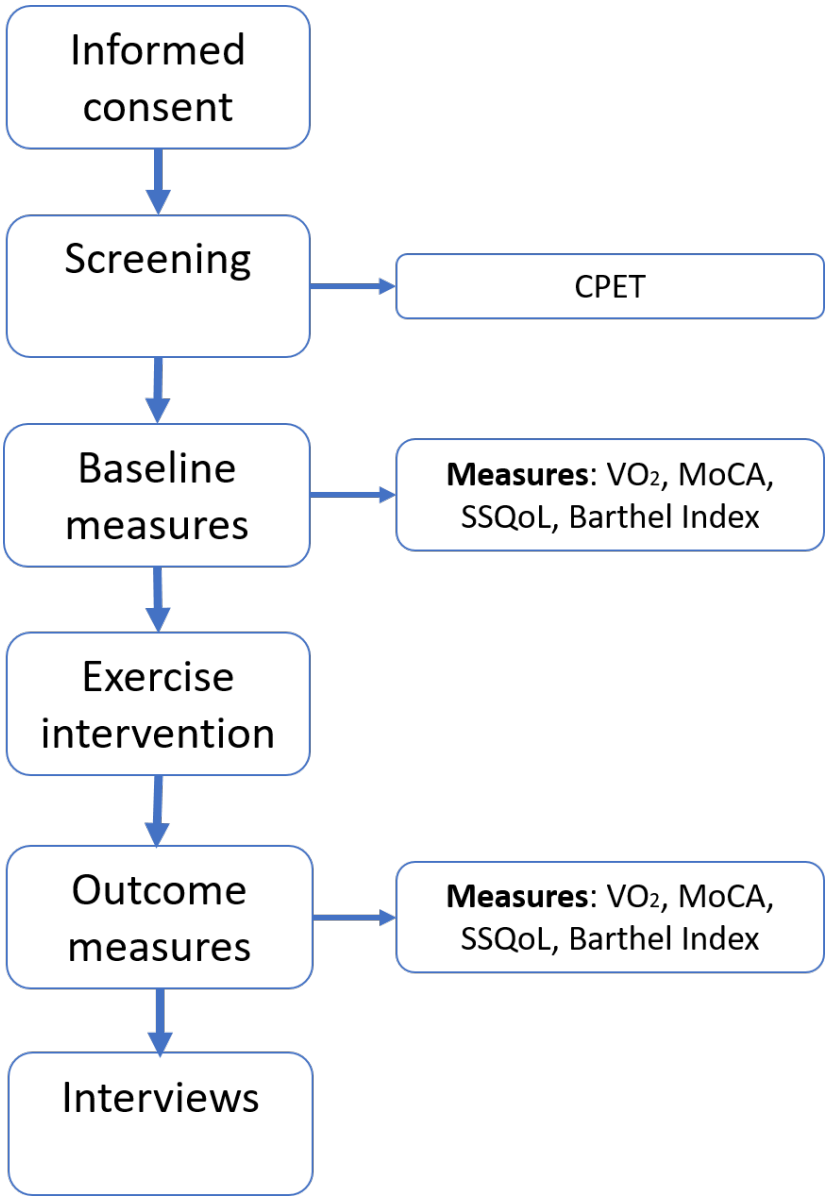

Figure 6: Key events of the EXERCISES study

5.4 Study setting

This study took place in a rural county in England. A population estimate in 2018 was recorded to be 903,680; of which, 219,260 were aged 65 years and over (332). It is estimated that 21.8% of adults are inactive in this region (332). With both age and physical inactivity as risk factors for stroke, it has been predicted that there are approximately 1,345 to 1,603 new stroke cases in this region in one year (333).

5.5 Participants

5.5.1 Inclusion criteria

The study aimed to recruit 24 participants who met the following criteria:

- **Capacity to provide informed consent**: Participants must have had no cognitive disturbance that may have impeded their ability to make autonomous decisions or their capacity to give informed consent.
- **Aged 18 years and over**: The aetiology of paediatric stroke is documented to be different to that of adult, in that there are differences in risk factors and causes for stroke, signs and symptoms of the event (334). Therefore, only adults who had experienced a stroke over the age of 18 were invited to participate.
- **Six-months or more post-stroke** (at the time of recruitment): For those six-months or more post-stroke, anecdotal evidence from clinicians and service users suggests that exercise participation is an unmet need for those with chronic stroke. There also appears to be a focus within existing literature upon acute, mild stroke and the early implementation of aerobic exercise training (335, 336). Some literature suggests that at approximately six-months post-stroke, there is a plateau in recovery and no further functional gain is noted (115). As a result of this, rehabilitation services are often discontinued, leaving stroke survivors unsupported in maintaining health outcomes. One of the long-term consequences of stroke is increased sedentary behaviour (53). The impact of sedentary behaviour contributes to a higher risk of a second stroke, cardiovascular and muscular deconditioning and the development of additional comorbidities (69).
- **A score of two or three on the Functional Ambulation Category (FAC)** (appendix 1): The FAC is a validated, six-point scale that assesses the ambulation status of a person by determining how much additional human support is required when walking (13). Categories two and three were chosen to capture participants who had moderate to severe lower-limb movement impairments.

  A score of two is defined as,

'Subject requires manual contact of no more than one person during ambulation on level surfaces to prevent falling. Manual contact consists of continuous or intermittent light tough to assist balance of coordination'.

A score of three is defined as,

'Subject can physically ambulate on level surfaces without manual contact of another person, but for safety reasons, requires standby guarding by no more than one person. This is because of poor judgement, questionable cardiac status, or the need for verbal cuing to complete the task'.

- **Sufficient communication and orientation:** Sufficient communication and orientation was defined as the ability to follow one-stage commands, for example: '*step here'.* Some instructions administered during CPET are complex, thus participants must have had sufficient communication and orientation to understand these.

5.5.2 Exclusion criteria

Participants were excluded from the study if they presented with any of the following:

- **Meeting any listed 'absolute' contraindications to exercise** (American College of Sports Medicine Contraindications to Exercise, 2014) (14) (table 17): These are well-established guidelines for ensuring safe participation in exercise. Absolute contraindications to exercise are classified as 'absolute' as the risk of injury or death outweighs the benefit of exercise. Where a relative contraindication to exercise existed (table 17), participants were included in the study at the consultant's discretion.
- **A previous diagnosis of dementia or any other significant cognitive decline:** At this feasibility stage of what is anticipated to be a programme of research, it was decided for practical and ethical reasons, to exclude those with cognitive impairment that were considered 'significant' or had a diagnosis of dementia.
- **Any other significant musculoskeletal or physiological disorder, not related to stroke, preventing participation in exercise**: This may have hindered performance of exercise training and compromised safety.

- **Body weight over 250lbs (113kgs)**: Weight restrictions were implemented in line with manufacturer guidelines for the use of the BWS harness (LiteGait, LG1 250E, USA).
- **Attending any other community exercise class, gym or rehabilitation class**: Participants may become fatigued or develop overuse injuries if additional structured exercise is being executed. Attendance and adherence to the intervention may have also suffered due to increased time commitments.

Box 3.

Summary of inclusion criteria

- Capacity to provide informed consent,
- Aged 18 years and over,
- Six-months or more post-stroke,
- A score of two or three on the Functional Ambulation Category,
- Sufficient communication and orientation.

Summary of exclusion criteria

- Meeting any listed 'absolute' contraindications to exercise (American College of Sports Medicine Contraindications to Exercise, 2014),
- A previous diagnosis of dementia or any other significant cognitive decline,
- Any musculoskeletal or physiological disorder preventing participation in exercise,
- Weigh over 250lbs (113kgs),
- Attending any other community exercise class, gym, or rehabilitation class.

Table 17: American College of Sports Medicine Contraindications to Exercise (14)

ACSM <u>Absolute</u> Contraindications to Exercise	ACSM <u>Relative</u> Contraindications to Exercise
• A recent significant change in the resting ECG suggesting significant ischaemia, recent myocardial infarction (within 2 days) or another acute cardiac event, • Unstable angina, • Uncontrolled cardiac dysrhythmias causing symptoms or hemodynamic compromise, • Symptomatic severe aortic stenosis, • Uncontrolled symptomatic heart failure, • Acute pulmonary embolus or pulmonary infarction, • Acute myocarditis or pericarditis, • Suspected or know dissecting aneurysm, • Acute systematic infection, accompanied by fever, body aches or swollen lymph glands.	• Left main coronary stenosis, • Moderate stenotic valvular heart disease, • Electrolyte abnormalities e.g. hypokalaemia, hypo-magnesia, • Severe arterial hypertensions i.e. systolic BP of >200mmHg and/or diastolic BP of >110mmHg at rest, • Tachydysrthythmia or bradydsrhythmia, • Hypertrophic cardiomyopathy and other forms of outflow tract obstruction, • Neuromuscular, musculoskeletal or rheumatoid disorders that are exacerbated by exercise, • High-degree atrioventricular block, • Ventricular aneurysm, • Uncontrolled metabolic disease e.g. diabetes, thyrotoxosis or myxoedema, • Chronic infectious diseases e.g. mononucleosis, hepatitis, AIDS, • Mental or physical impairment leading to inability to exercise adequately.

Abbreviations
ACSM American College of Sports Medicine **AIDS** Acquired Immune Deficiency Syndrome **BP** Blood pressure **ECG** Electrocardiogram **mmHg** millimetres of mercury

5.5.3 Participant recruitment

Participants were recruited to this study via the six-month review team, attached to the Early Supported Discharge (ESD) Unit at the local community health and care NHS Trust and via voluntary stroke support group within the community (figure 7).

Six-month review team

Clinical staff members, typically a nurse within the six-month review team identified potentially eligible participants by reviewing relevant medical records alongside the study inclusion criteria (box 3). At a patient's six-month review meetings, verbal information about the study was provided, along with invitation letters and a consent to contact form. If a potential participant agreed, they were contacted by their preferred method of contact (i.e. email, post, home visit, phone, or via their next of kin). Participant information sheets were then shared with potential participants (appendices 7 and 8). Information about the study was also shared as a video: https://www.youtube.com/watch?v=MXonLF21pZ0&feature=youtu.be

Voluntary stroke support groups

With study recruitment slow at the outset of the study, the recruitment strategy was expanded to recruit participants via local stroke survivor support groups. Information was provided to the lead contact of the support group in the format of a poster and a short study summary. The lead contact then disseminated study information and my contact details to group members at meetings and via social media platforms. Following an expression of interest, further study information was provided to potential participants again via their preferred method of contact.

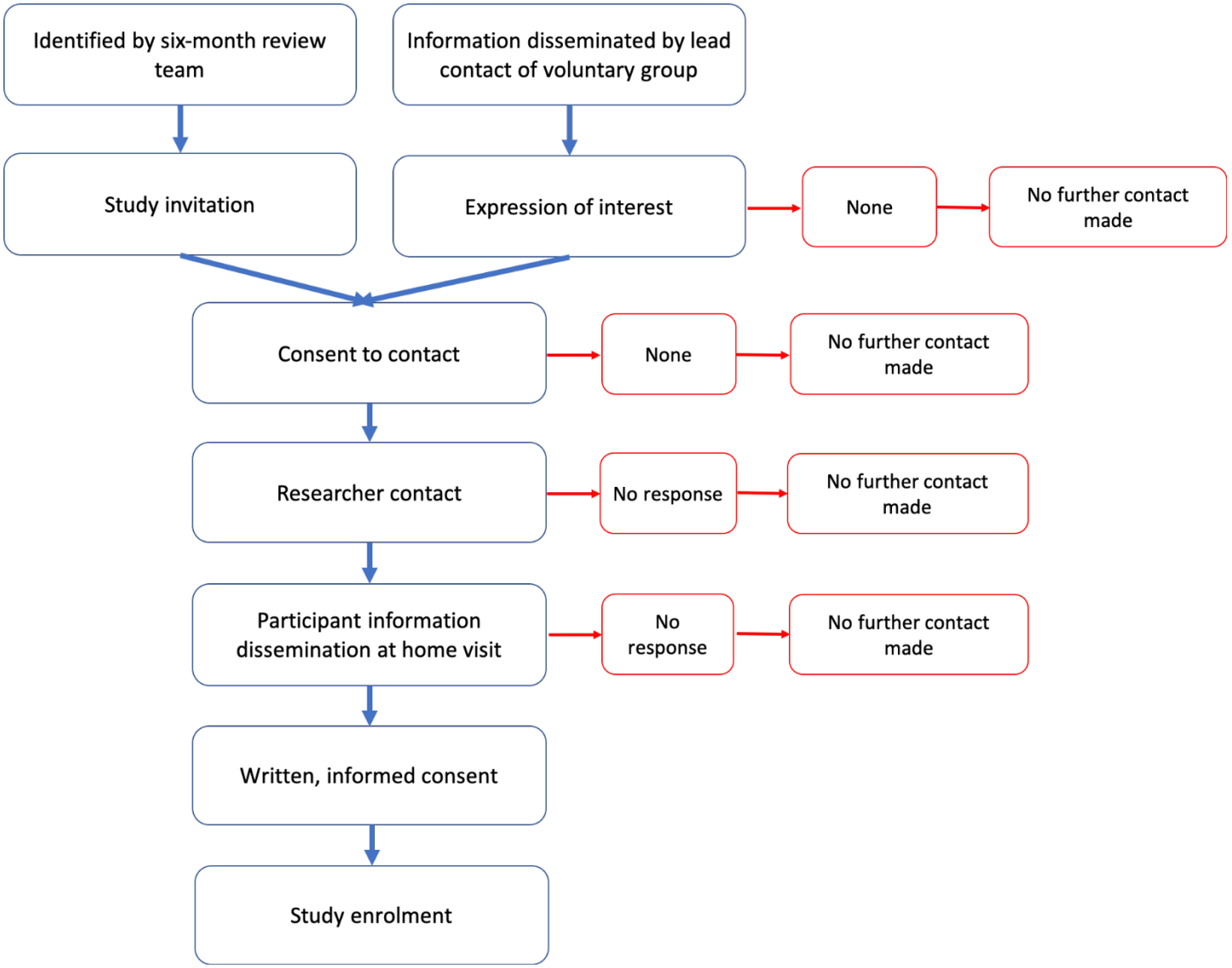

Figure 7: A flow chart of participant recruitment pathways, via the local community health and care NHS trust and via community stroke survivor support groups

5.5.4 Consent

All participants were asked to provide written informed consent (appendix 9). Subsequently six participants also provided written informed consent for their participation in an interview (appendix 10). Participants were given up to seven days to decide whether to take part. Discussion with family, friends and members of the research team about taking part was encouraged, given the time and travel commitment that was required for participation in this study. All individuals, whether they decided to take part in the study or not, were assured that it would not affect the level and quality of health care provided to them at that time or in the future. I wrote a letter to participant's GPs' to inform them that their patient was taking part in the EXERCISES study (appendix 11).

5.5.5 Participant screening

Participants underwent a rigorous screening process to ensure their safety to participate in exercise (figure 8). Screening procedures were informed by best practice guidance for exercise after stroke services (93). This included a multidimensional assessment of the participants medical and functional status, as per the ACSM Contraindications to Exercise (14). This guidance states that screening procedures, i.e. an individual risk assessment, should be used to appropriately adapt and tailor exercise prescription, as well as ensuring the correct provisions (e.g. modified equipment) is available (93).

I developed a brief screening questionnaire (appendix 12) which was usually undertaken during a home visit, after informed consent was provided. The purpose of the questionnaire was to gather information about a participant's most recent stroke, medical history and current health, prescribed medications, exercise history and current levels of physical activity. I also noted through self-report and informal observation post-stroke impairments; for example, walking ability, muscular tone and strength, range of movement, balance, visuospatial deficits and noted pre-stroke function. If I had any concerns or queries related to a participant's movement ability or medical status, I discussed them with the stroke consultant (KM) and the physiotherapist (KMa).

KM undertook a medical screen of participants. They obtained participants' medical records (at the local NHS site) to confirm their current medication prescription and compare their medical records to ACSM Contraindications to Exercise (14) (table 17). I developed a second screening questionnaire for KM to complete with participants face-to-face, in the MoveEx Lab prior to their baseline CPET (appendix 13). This form was in line with the ACSM Contraindications to Exercise (14). KM provided approval for a participant to complete CPET. Following CPET and a review of the electrocardiogram (ECG) findings, KM then made the decision as to whether participants were safe to take part in the exercise intervention.

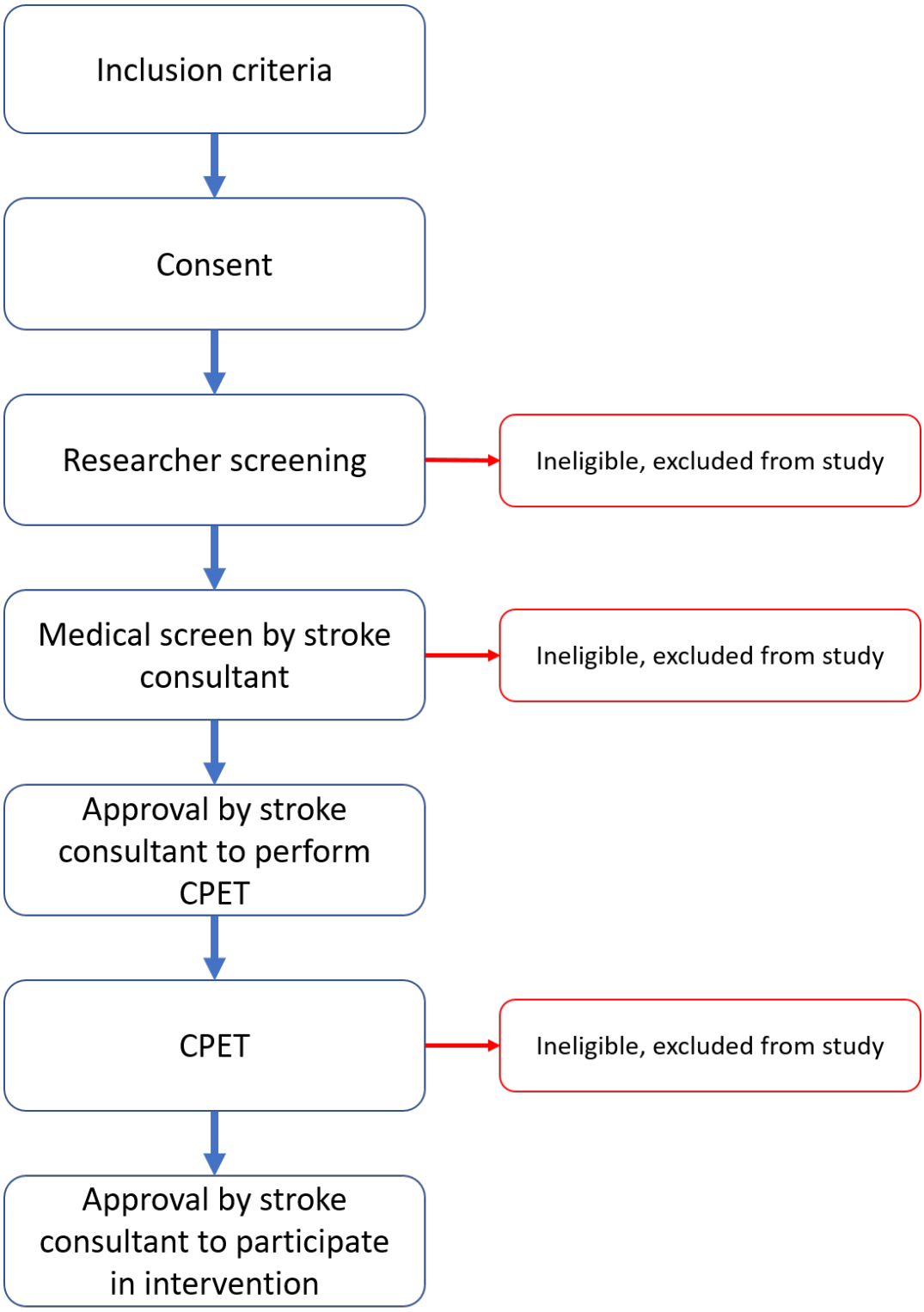

Figure 8: A flow chart summarising participant screening procedures

5.6 Outcome measures

Measures of cardiovascular fitness (VO_{2peak}), cognitive health, quality of life and activities of daily living were taken pre- and post-intervention. Measures of VO_{2peak} were completed in the MoveEx

Lab at the University of East Anglia (UEA). Where needed, I supported participants to complete the questionnaires. This was usually done in their own home to avoid the necessity of travel.

5.6.1 Selection of measures

The selection of appropriate outcome measures is a vital component in the design of a useful and valid trial (337). In the EXERCISES study, feasibility parameters and outcomes related to cardiovascular and cognitive health were chosen to reflect the intended aims of the study. There was an emphasis within recent systematic reviews on the use of consistent outcomes, in order to facilitate robust meta-analyses that evaluate the influence of exercise after stroke, with a view to maintain cognitive health (43, 159). The subsequent sections describe the outcome measures of this study and justifies their use.

5.6.2 Feasibility components

Feasibility studies are used to explore the viability of interventions or outcomes (or both) and to estimate future recruitment rates (92, 234). There are several outcomes that are specific to feasibility study design that were measured in the EXERCISES study, including:

- **Recruitment**: Locally, it is common that health care professionals will refer eligible stroke survivors to community ran, exercise-based rehabilitation schemes, at the point of their six-month review appointment. The six-month review meeting was therefore decided to be the most appropriate time-point to invite patients to take part in my study.
- **Attrition:** Participants' willingness to continue taking part in the EXERCISES study was noted at each meeting. Participants could withdraw from the study at any time. When possible, I aimed to capture participants' reasons for withdrawal. The purpose of requesting reasons for withdrawal was to inform the design of a future trial.
- **Adherence:** For the planning of a future definitive randomised controlled trial, it is important to understand adherence rates to the study's protocol, intervention attendance and engagement (338). This provided useful information on intervention implementation, based upon reasons for non-adherence.

- **Acceptability and satisfaction:** The acceptability and satisfaction of the intervention participants participated in and CPET procedures were explored through semi-structured interviews with six participants. The process for interviews (also referred to as the qualitative sub-study) is explained later in this chapter (section 5.11).

5.6.3 Participant characteristics

Participant characteristics were recorded at baseline. Anthropometric measures (e.g. height and weight) have been shown to be associated with cardiorespiratory fitness (339), thus were important for the conduct of CPET. The time since stroke onset and the classification of stroke was recorded. Data on previous levels of physical activity participation and any additional medical conditions were also collected.

5.6.4 Peak aerobic capacity

Peak aerobic capacity (VO_{2peak}), was determined via CPET, pre- and post- intervention. There were two purposes for conducting CPET in this study: (i) to explore the feasibility of CPET for stroke survivors with moderate to severe movement impairments; (ii) to assess the safety of participants to take part in a six-week exercise intervention.

To explore the feasibility of CPET, two modes were used: (i) treadmill with BWS and (ii) cycle ergometry. These two modes were chosen as they are common modes previously established with stroke survivors (159). Treadmill walking and stationary cycling are also the two main modes of aerobic exercise training advocated in evidence-based guidelines for exercise after stroke (14, 93, 340). As there is no gold standard mode or protocol for CPET with stroke survivors living with moderate to severe movement impairments post-stroke, the feasibility of protocols and procedures need to be investigated prior to validation (159).

To assess the safety of participants to take part in a six-week exercise intervention, KM and I reviewed participant's responses to incremental exercise, including a review of ECG findings. During CPET, participants were screened in line with ACSM Contraindications to Exercise (14).

This study reports values of VO_{2peak}. Peak VO_2 is defined as the highest point of oxygen consumption during CPET (159).

Additional physiological outcomes of interest derived from CPET were as follows:

- Heart rate:
    - To ensure normal cardiovascular responses to exercise,
- Respiratory exchange ratio (RER):
    - To determine maximal effort.

Key feasibility outcomes of interest derived from CPET, were as follows:

- Exercise time:
    - To understand the ability of participants to undertake CPET and to understand the suitability of the CPET mode and protocol,
- Maximal walking speed or maximal cycling resistance achieved:
    - To understand the suitability of the CPET mode and protocol,
- Reasons for stopping the test:
    - To understand the suitability of the CPET mode and protocol, and to define barriers of CPET with stroke survivors living with moderate-severe movement impairments.

Randomisation to CPET order

Participants were randomised to order of CPET mode to be performed at baseline and outcome. To summarise, participants were randomised to either: (order a) treadmill with BWS at baseline, followed by cycle ergometry at outcome; or (order b) cycle ergometer at baseline, followed by treadmill with BWS at outcome. Randomisation to CPET order is described in a flow chart section 5.8.1, in line with intervention group allocation (figure 15).

Randomisation to CPET order was used in this study so that participants' willingness to be randomised could be investigated. The purpose of the crossover in CPET mode was to allow participants to experience both methods of determining VO_2 and ensure that attrition did not adversely affect data available for one of those modes. Participants were also able to discuss their experience of both CPET modes (treadmill with BWS and cycle ergometry) during the interviews.

Randomisation was carried out by a member of the PhD supervisory team (AA) who was not directly involved in delivering outcome assessments or exercise interventions, to minimise the risk of

selection bias. Block randomisation was used to avoid an imbalance between numbers allocated to each CPET order (341). This was performed away from the study site so that the characteristics, medical and exercise history were not known by AA.

CPET procedures

I conducted all exercise tests, with KMa (physiotherapist) and DP (laboratory technician). Tests were supervised by KM (stroke consultant). Testing was conducted in accordance with the UEA School of Health Sciences' standard operating procedures (SOP) for CPET.

Values for age-predicted maximum heart rate ($APHR_{max}$) (111) and estimated VO_{2max} (342) were calculated for each participant:

$$APHR_{max} = 208 - (0.7 \times age\ in\ years)$$

$$or,\ if\ participants\ were\ on\ beta\text{-}blockers,\ APHR_{max} = 164 - (0.7 \times age\ in\ years)$$

$$VO_{2max} = (15.3)\ APHR_{max} / HR_{resting}$$

Predictive equations were used to estimate the timing of CPET termination, i.e. once participants achieved 80% of age-predicted maximum heart rate or 80% of estimated VO_{2max}.

Participants were fitted with a Hans Rudolph face mask, for breath-by-breath analysis through a calibrated metabolic cart (Ultima Cardio, MGC Diagnostics, Minnesota, USA). Heart rate and a 12-lead ECG was recorded continuously throughout the test and for 15 minutes pre- and post-CPET (Montara, T12 ECG, USA). Current recommendations suggest blood pressure be recorded during the last 45 seconds of each CPET protocol stage (14). However, for the purpose of this study, recording blood pressure was at the discretion of the stroke consultant.

During CPET, participants RPE was recorded (343). The Borg 6 to 20 RPE scale (figure 9) is used to determine a subjective rating of effort, muscular fatigue, and breathlessness throughout exercise (344). The scale has been found to be valid and reliable for monitoring and prescribing exercise intensity in a number of clinical populations, including stroke (217, 345, 346). It was explained to participants that they should attempt to describe their level of exertion relative to their feelings of breathlessness. The verbal anchors used for this scale, for example, "very hard", "somewhat hard", "fairly light", are evidenced to be suitable for rating exercise symptoms (347).

Figure 9: Borg 6 to 20 rating of perceived exertion Scale (343)

CPET mode (a) cycle ergometer

Tests were conducted on an electronically braked cycle ergometer (Excalibur Sport, Lode® Netherlands). The seat height and handlebar position were set according to the comfort of the participant. The cycle ergometer was fitted with specialised pedals with heel support to secure feet, preventing the foot from sliding off due to weakness in the ankle joint or the inability to dorsi-flex.

Participants cycled for two minutes with a free wheel at approximately 50 to 60 revolutions per minute (rpm), or a similarly comfortable pace, to 'warm up' and become familiar with the pedalling technique. Every minute, the resistance increased by five watts until test termination (figure 10). A cool down period followed in which participants pedalled at a self-selected speed on a free wheel for two minutes.

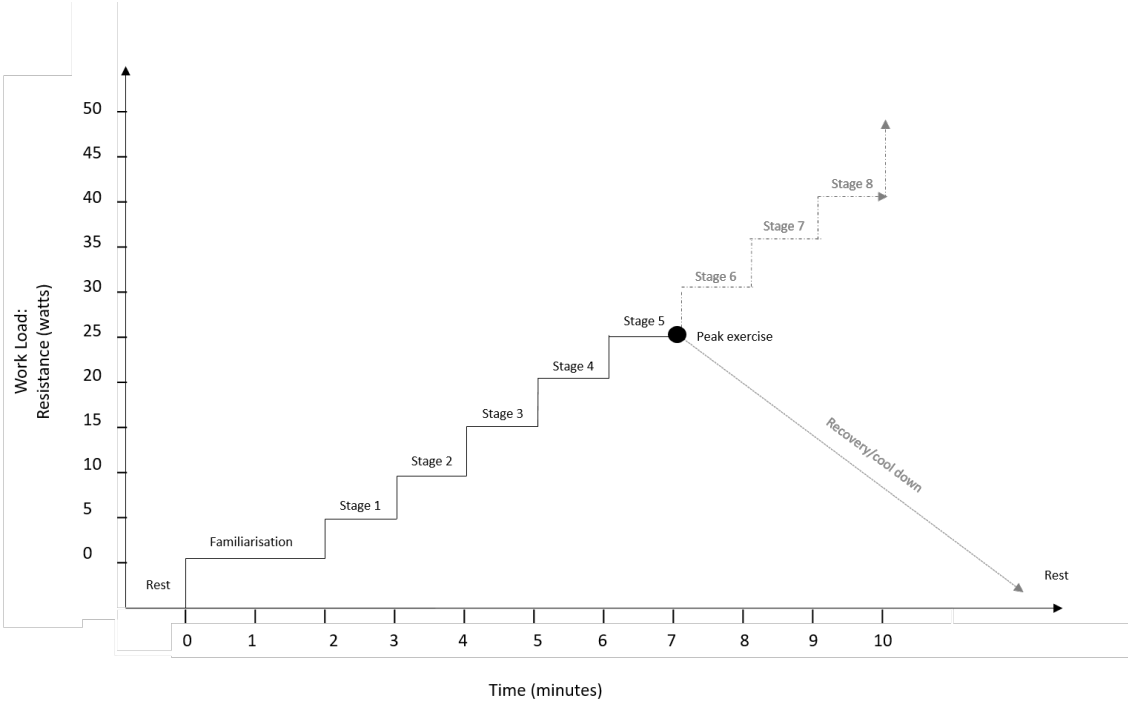

Figure 10: A graphic representation of the cycle ergometer CPET protocol

Figure 11: A proof-of-concept study participant undertaking CPET on a cycle ergometer

CPET Mode (b) treadmill with body weight support

Tests were conducted on a treadmill (HP Cosmos, Mercury Med, Germany), fitted with a BWS harness (LiteGait, LG1 250E, USA). The BWS harness was there to provide postural support for walking and reduce weight bearing load. The harness was worn over the participants' clothes and fastened securely to an overhead suspension system. Within the scope of this study, I did not have the means to quantify the amount of body weight that was displaced with the use of the harness. Participants were suspended to what they deemed comfortable and supportive for walking. I ensured that the normal gait pattern of the participant was not impeded by being suspended and confirmed they were able to execute a heel strike and adequate toe off from the contralateral foot. The treadmill was set at a 1% incline to simulate the energy spent walking outdoors or on regular surfaces (348). Participants walked for two minutes at a self-selected speed (approximately 0.5 km/hr) for both a warm-up and for familiarisation of walking with BWS. Where required, I provided hands on assistance for the weaker leg. Once the warm-up was complete, the speed was increased by 0.5 km/hr every one minute, until test termination (figure 12). A cool-down period followed, in which participants would either walk at a self-selected speed or perform seated marching for one or two minutes.

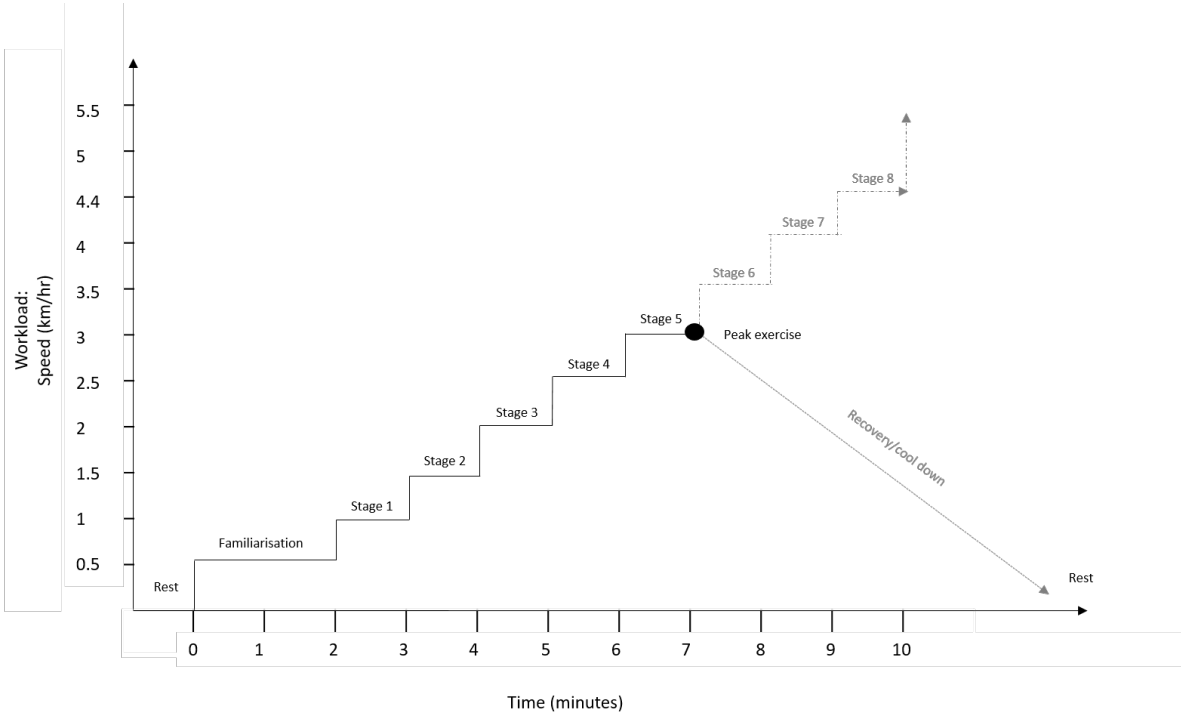

Figure 12: A graphic representation of the treadmill with BWS CPET protocol

Previous CPET protocols would involve increasing the gradient of the treadmill until peak volitional exertion. However, in adapting CPET protocols for a more severe group of stroke survivors, I hypothesized that participants would have impaired abilities to flex adequately at the hip, knee and ankle to ambulate safety on a gradient. Therefore, it was decided that speed would be increased. Furthermore, increasing the gradient on the treadmill was not feasible in this study due to limitations with the BWS harness. As the treadmill would increase in gradient, the harness would need to be manually re-adjusted for support at each increment.

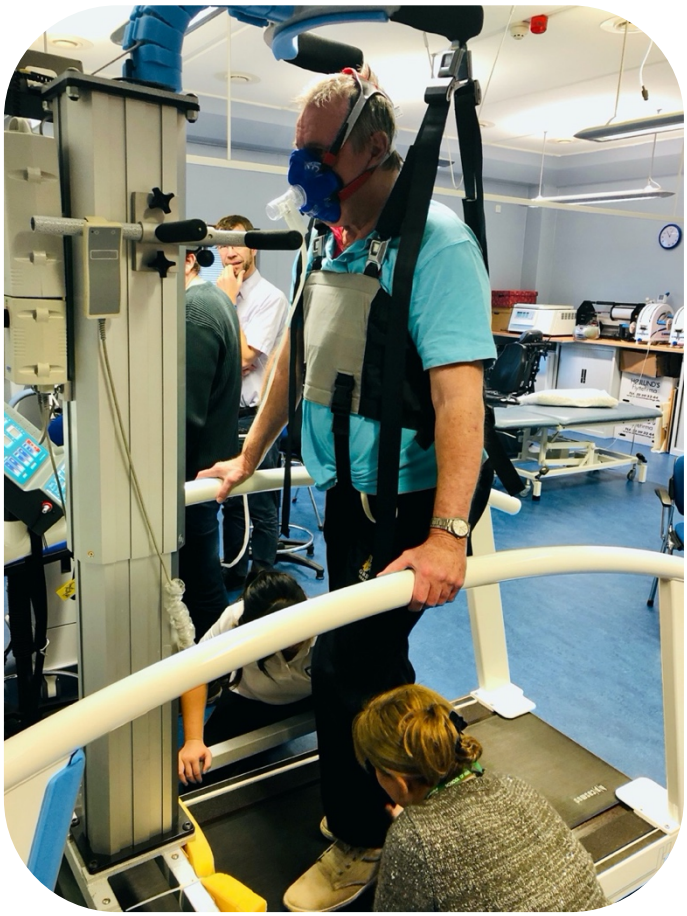

Figure 13: An EXERCISES study participant, undertaking CPET on the treadmill with BWS

Test termination criteria

The ACSM test termination criteria for both CPET protocols was adhered to (table 18) (14). Participants were encouraged to continue exercising until peak volitional effort, i.e. until they were unable to maintain the required pedalling or walking speed. However, it was explained that they were able to stop at any time and for any reason. For example, if they felt they had 'had enough', reported any feelings of discomfort due to mask, ergometer seat and BWS harness, musculoskeletal

pain or discomfort, or significant breathlessness. Test administrators also terminated CPET if a participant's heart rate exceeded 80% of its predicted maximum or they reached 80% of their predicted VO_{2max}.

Table 18: American College of Sports Medicine indications for CPET termination (14)

ACSM <u>Absolute</u> Indications for CPET Termination	ACSM <u>Relative</u> Indications for CPET Termination
• Suspicion of a myocardial infarction or acute myocardial infarction (heart attack), • Onset of moderate-to-severe angina (chest pain), • Drop in systolic BP below standing resting pressure or drop in systolic BP with increasing workload accompanied by signs or symptoms, • Signs of poor perfusion (circulation or blood flow), including pallor (pale appearance to the skin), cyanosis (bluish discoloration), or cold and clammy skin, • Severe or unusual shortness of breath, • CNS symptoms e.g., ataxia (failure of muscular coordination), vertigo (An illusion of dizzying movement), visual or gait (pattern of walking or running) problems, confusion, • Serious arrhythmias (abnormal heart rhythms) e.g.: second / third degree AV block, atrial fibrillation with fast ventricular response, increasing premature ventricular contractions or sustained ventricular tachycardia), • Technical inability to monitor the ECG, • Patient's request (to stop).	• Any chest pain that is increasing, • Physical or verbal manifestations of shortness of breath or severe fatigue, • Wheezing, • Leg cramps or intermittent claudication (grade 3 on a 4-point scale), • Hypertensive response (systolic BP >260 mm Hg; diastolic BP>115 mm Hg), • Pronounced ECG changes from baseline i.e. >2 mm of horizontal or down sloping ST- segment depression, or >2 mm of ST-segment elevation (except in aVR), • Exercise-induced bundle branch block that cannot be distinguished from ventricular tachycardia, • Less serious arrhythmias (abnormal heart rhythms) such as supraventricular tachycardia.

Abbreviations
ACSM American College of Sports Medicine **AIDS** Acquired Immune Deficiency Syndrome **AV** Atrioventricular **aVR** Augmented vector right **BP** Blood pressure **CNS** Central nervous system **CPET** Cardiopulmonary exercise test **ECG** Electrocardiogram **mm** millimetre **mmHg** millimetres of mercury

5.6.5 Cognitive health

The Montreal Cognitive Assessment (MoCA) (appendix 14) is a tool that was originally designed to screen for mild cognitive impairment and dementia in older adults (242). The assessment targets eight sub-domains of cognition: attention and concentration, executive function, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation. The assessment takes approximately 10 to 15 minutes to complete. The sum of all sub-domains create a global score of cognition, with a maximum score of 30, with higher scores indicating better cognitive health. For those who have received less than 12-years of education, one point is added. Global MoCA scores of less than 26 indicate mild cognitive impairment (242).

The MoCA has been recommended for detecting vascular cognitive impairment in stroke (81). Wu et al. (349) demonstrated the MoCA to be responsive to change at six-months or more after stroke onset (effect size = 0.37; standardised response mean = 0.67). In line with Wu et al. (349), Pendlebury et al. (350) also found the MoCA to be valid and reliable for use with stroke survivors and argued it had greater sensitivity to detect the presence of mild cognitive decline post-stroke, in comparison to the MMSE (350).

There is evidence to suggest that specific domains of cognition affected by stroke (including, memory, attention and executive function) may be most amenable to change with exercise training (15, 16) and therefore, outcome measures should be selected to address this. However, in the present study, I chose to explore a global measure of cognitive function only. The rationale for this was three-fold. Firstly, I was mindful of participant burden in undertaking several outcome measures. I therefore wanted to establish whether a global measure of cognitive outcome was feasible and sufficient, as measures of cognitive function needed to be completed alongside complex and potentially burdensome CPET procedures. Secondly, to align with the systematic review reported in chapter 4, a measure of global cognition was chosen over specific domains so that exploratory work could be undertaken to estimate the nature of the relationship between global cognitive health and cardiorespiratory fitness. Finally, the MoCA is currently used by the Early-Support Discharge Team at the local community health and care NHS trust as a measure of

mild cognitive impairment. I therefore had access to training on how to administer the MoCA from an occupational therapist with expertise in cognitive function.

5.6.6 Quality of life

The Stroke Specific Quality of Life (SSQoL) questionnaire was developed in collaboration with stroke survivors and takes approximately ten minutes to complete (351) (appendix 15). The questionnaire has twelve domains, each with a series of statements or questions. Participants choose from a five-point Likert-scale response category, relating to the level of either (i) agreement or disagreement, (ii) degree of help needed, or (iii) trouble or ease in performing task (depending on the nature of the statement or question).

Domains relate to energy, family roles, language, mobility, mood, personality, self-care, social roles, thinking, upper extremity function, vision and productivity. Domain scores are unweighted means of their associated items, while the overall SSQoL questionnaire score is an unweighted mean of all twelve domain scores. The higher the overall score, the greater the individual's perceived functioning and quality of life. The SSQoL questionnaire is advantageous in its ability to assess multiple domains of stroke recovery in one test, reducing patient burden and increasing feasibility for researchers (352). The scale has been shown to have strong internal consistency, excellent test-retest ($r = 0.92$) and inter-rater reliability ($r = 0.93$) (351).

5.6.7 Activities of daily living

The purpose of the Barthel Index is to determine the ability of a participants' ability to complete routine daily tasks (appendix 16). For the present study, the Barthel Index was chosen as no specialist equipment is required and it provides meaningful outcomes of functional independence, specific to stroke. The index consists of 10 items: feeding, bathing, grooming, dressing, bowls, bladder, toilet use, transfers, mobility and stairs. A summary score of the 10 items measures the extent to which one can function independently. It is often used to assess the need for assistance in care. It is valid and reliable, and widely used within the stroke population and takes between two and five minutes to complete (353). The index is known to have excellent inter-rater reliability ($r = 0.93$) and good repeatability (kappa $w = 0.98$) (354, 355).

5.7 Interventions

Participants were sequentially allocated to one of three exercise interventions: (i) aerobic exercise only, (ii) strength training only, or (iii) a combination of aerobic exercise and strength training. The exercise intervention lasted for six-weeks. Participants were expected to attend two, 1-hour exercise sessions each week. Six-weeks is shown to be the minimum period of exercise training known to produce any chronic physiologic adaptations (356). To increase the attractiveness of taking part in the study, if participants missed a scheduled session due to an appointment or were unable to exercise that day, they were offered the opportunity to make up the session at a later date.

The intervention took place in the MoveEx Lab at the UEA (figure 14). The MoveEx Lab is a clinical exercise laboratory which is used to understand the role of exercise testing and training in the prevention, treatment and rehabilitation of chronic disease.

Figure 14: Picture of Movement and Exercise Laboratory

As defined earlier in this thesis, there are several fundamental components of exercise training that should be reported for robust replication and implementation (99). Consistent reporting of exercise interventions encourages transparency, aids in interpretation and the opportunity for replication (357). Reporting of the exercise interventions in this thesis was guided by the Consensus on Exercise Reporting Template (CERT) (357) (appendix 17). The CERT defines minimal standards in which exercise interventions should be described; for example, the dose of the exercise (i.e. the FITT

principle), how it was delivered (i.e. supervision, motivation and format) and tailoring (i.e. progression).

5.7.1 Intervention group allocation

Participants were sequentially allocated to an intervention group: (i) aerobic exercise, (ii) strength training or (iii) a combination of aerobic exercise and strength training. Sequential allocation was chosen as there was a need to avoid waiting times for participants to start that a random allocation would have entailed. Figure 15 provides a description of how participants were allocated to an intervention group, following randomisation to CPET order.

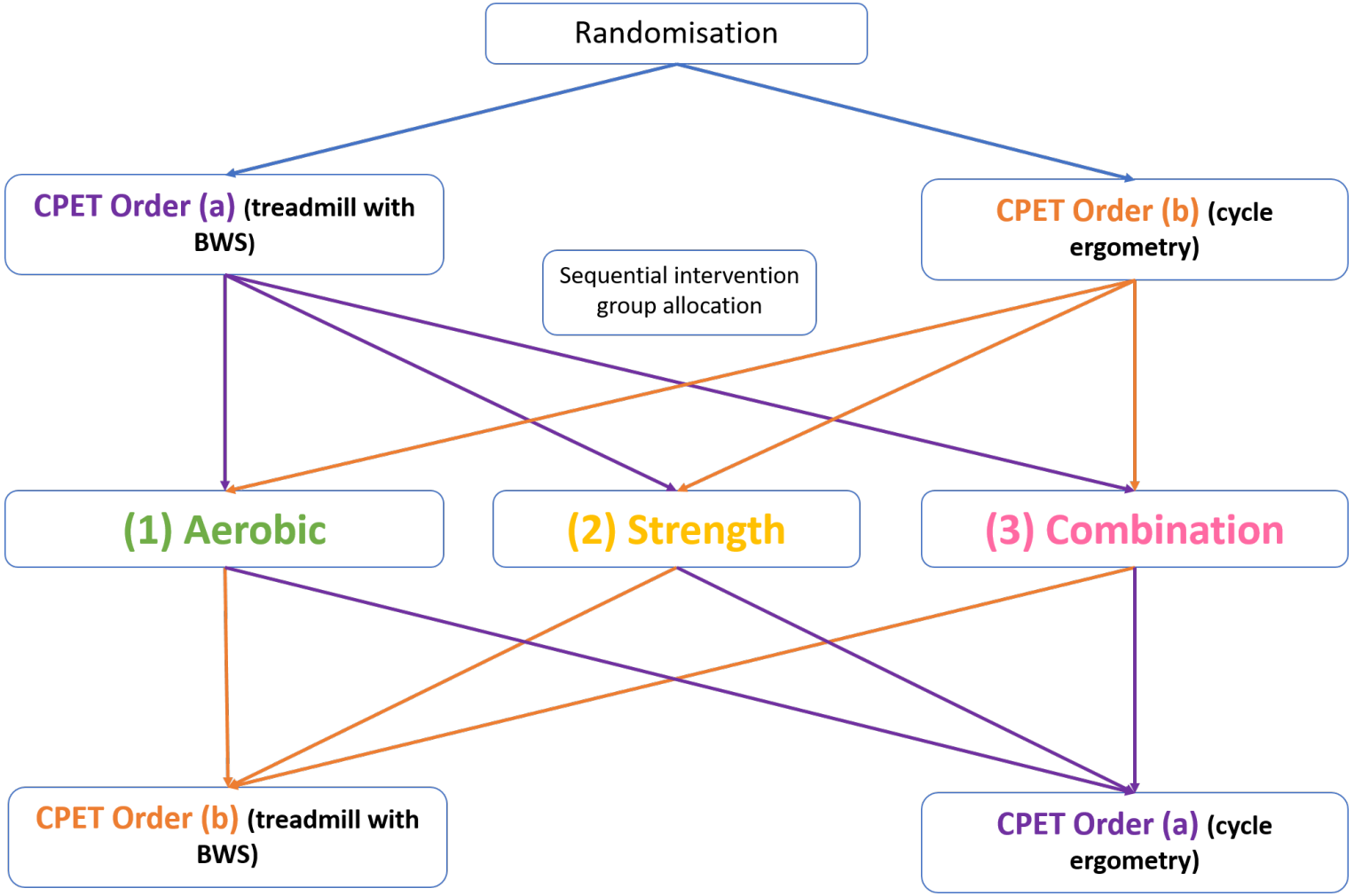

Figure 15: Flow chart to describe randomisation to CPET order and intervention group allocation

5.7.2 Intervention delivery

The intervention was delivered in line with Fitness and Mobility Exercise (FAME) programme, designed for stroke survivors (91). I led all the exercise sessions, supervised by KMa. Students enrolled on the BSc and MSc Physiotherapy volunteered to help facilitate exercise sessions, by providing one-to-one assistance.

To start, participants completed a series of warm-up activities. The warm-up included a light to moderate intensity pulse raiser, usually two to five minutes on the stationary recumbent cycle ergometer. With some participants, passive or active movements of stretching was also required, to reduce the effects of high muscle tone (spasticity), particularly in hands. The aim of a warm-up is to reduce the risk of injury, by increasing blood circulation and body temperature. Specific to stroke survivors, warm-up activities are recommended to facilitate motor recruitment and promote peak range of movement.

The main conditioning period of the exercise session lasted for a duration of approximately 40 to 60 minutes. The exercise session was delivered, if attendance figures permitted, in the format of a group circuit class. A group circuit class was the preferred method of delivery as it is shown to be effective in improving functional outcomes and offers social benefits, such as peer support and social interaction (95, 358, 359). Despite the circuit class format, one-to-one assistance throughout the session was required for almost all participants.

Within the circuit, each bout of 'work' was interspersed with a rest period. The addition of rest periods was designed to mitigate muscular fatigue and increase cardiovascular safety when performing exercises. The time spent on ‘work’ and ‘rest’ stations was individually tailored to the participant. It was intended that the time spent in ‘work’ would increase and time spent in ‘rest’ would decrease over the six-weeks, as cardiovascular conditioning improved. The work to rest ratio was monitored and adjusted where appropriate, according to participants’ status on that day and their reported RPE during exercise.

Participants allocated to the aerobic training group were asked to complete two to four cardiovascular endurance exercises with appropriate rest periods intermittently. For example,

recumbent cycling, rowing and step-ups. Aerobic exercise aimed to commence at an intensity of 40% of peak heart rate (achieved on the CPET) and was increased incrementally by 10% as tolerated, up to a maximum of 80% of peak heart rate (91). Aerobic exercise training was chosen as a specific intervention because of its capacity to improve cardiorespiratory fitness, walking ability, vascular health and the quality of life of stroke survivors (90). The application of aerobic exercise is advocated within current stroke guidelines, leading to many benefits including increasing VO_2 and lowering the energy cost of walking (72).

Those allocated to strength training were prescribed four to six resistance exercises per session. Participants were expected to complete up to a maximum of two sets of 5 to 10 repetitions of two exercises per large muscle group, performed using either body weight, resistance bands, balance balls and/or dumbbells. The intensity aimed to correspond to an exertion rate of 10 to 11 on the Borg 6 to 20 RPE scale, and increased over the weeks to an RPE of 14 to 15 (343). This circuit incorporated strength training around upper limb, lower limb and core muscle groups. Strength training was selected as a training method as there is evidence it can lead to muscle hypertrophy, reduce the risk of falls and promote motor recovery; as well as positive effects on quality of life post-stroke (12). Strength training post-stroke has demonstrated improvements in neural activation, muscle structure and muscle function (360).

For those who were allocated to the combined aerobic exercise and strength training group, participants alternated between cardiovascular endurance and strengthening exercises. Alternating exercises allowed for adequate active rest periods between stations. Current guidelines suggest that a combination of both aerobic and strength training is most beneficial in improving outcomes post-stroke (91).

Table 19 displays examples of activities that participants completed as part of their exercise intervention. Appendix 18 includes an example exercise training programme that was prescribed to a participant in allocated to the combined aerobic exercise and strength training group.

Table 19: Example of specific exercises prescribed for each of the three intervention groups

Aerobic	Strength	Combination
• Seated toe-taps • Seated marching • Step-ups • Recumbent cycling • Upright cycling • Arm ergometry • Treadmill walking with BWS	• Sit-to-stands • Seated wall press • Balance balls • Trunk twists • Heel raises • Seated leg extensions/curls with resistance bands • Chest press with resistance band	• Recumbent cycling • Shoulder shrugs • Shuttle walks • Ball raises/rolls • Sit-to-stands • Arm-ergometry

Exercise sessions finished with a gradual cool-down. This was often performed on a stationary recumbent cycle ergometer or consisted of walking lengths of the room, sometimes with passive or active stretching. There are a multitude of reasons to perform a cool-down following exercise: to safely reduce one's heart rate; to prevent the risk of dizziness from blood pooling in the lower extremities; to dissipate waste products (e.g. lactic acid accumulation); reduce the risk of delayed-onset muscle soreness; safely reduce levels of adrenaline and to allow muscle fibres to return to their normal range of movement (361).

At all sessions, there was allocated time before and after for socialising and light refreshments. Shower and changing facilities were provided if required.

5.7.3 Tailoring

The heterogeneity of stroke calls for the individualisation and tailoring of exercise training (362, 363). *Tailoring* and *adaptation* are additional concepts of exercise training that should also be at the forefront for the prescription and implementation of aerobic exercise for stroke survivors' (12, 90, 126). *Tailoring* refers to production of an exercise training programme based on an individuals' abilities and needs. *Adaptation* refers to changes to movements and/or equipment. For example, foot pedals with a heel sling to prevent the heel from sliding off when cycling, or the addition of a BWS harness to aid treadmill walking. Exercise prescription should be based on comorbidities, participant preference, cardiorespiratory fitness, stroke severity, time since stroke, availability, and treatment goals (90). I worked closely with participants to design their exercise training

programme, which were centred as far as possible, on the goals they wanted to achieve. This promoted motivation and participant autonomy.

5.7.4 Safety

Due to the nature of the EXERCISES study and the physical requirements for participation, monitoring safety was paramount in both the design and conduct of the study. All exercise sessions were supervised by KMa, a HCPC registered physiotherapist, with expertise in neurorehabilitation. All staff involved in the delivery of CPET and the exercise intervention had up-to-date first aid, manual handling and intermediate life support training.

Definitions of adverse events

Definitions of serious adverse events (SAE) and expected stroke-related adverse events were taken from local NHS Foundation Trust and UEA joint Standard Operating Procedures for the Identifying, Recording and Reporting Adverse Events (table 20).

Table 20: Definitions of serious and expected stroke-related adverse events, as defined by the local NHS Foundation Trust and UEA joint standard operating procedures for the identifying, recording and reporting adverse events.

Serious adverse event (SAE)	Expected stroke-related adverse events
• Results in death, • Is life threatening, • Requires hospitalization, or prolonged existed in patients' hospitalization, • Results in persistent or significant disability or incapacity, • Is a congenital anomaly or birth defect, • Is otherwise considered medically significant by the investigator.	• Cardiac, renal or liver problems, • Epileptic seizures, • Revascularisation, • Major bleed, • A fall, • Infections, • Mood disturbances, • Spasticity or contractures, • Deep vein thrombosis.

Treatment-related adverse reactions are broadly defined as unfavourable or unintended event that occurs during the course of the study, caused by the intervention (364). For this study, treatment-related adverse reactions were defined as minor delayed-onset muscular soreness (DOMS), joint pain, and muscular strains. Although exercise training is known to be a safe intervention (9),

adverse reactions may be common in those who are particularly cardiovascularly deconditioned, previously been sedentary or have other existing health conditions.

As with any form of exercise or physical exertion, it was expected that participants could experience minor delayed-onset muscular soreness one to two days following exercise participation. Delayed-onset muscle soreness (DOMS) is a recognised by-product of exercise training and is expected to be relieved in two to three days. Musculoskeletal discomfort was closely monitored to ensure there were no cases of persistent or overuse injury. If the pain was episodic and only occurred during exercise or for up to one hour after, then they were advised to alert a member of the research team, who altered the exercise dose accordingly. If the pain persisted for longer than one hour after the end of the exercise training session and could not be related to any other intervention/experience, then this was recorded as a treatment-related adverse event. If pain persisted for three consecutive days then the participant was removed from the study, but all data was retained with their permission.

Best practice guidelines for Exercise after Stroke (93), states that the most significant risks to stroke survivors when participating in exercise are from cardiac event, falls and fractures. All participants were thoroughly screened on enrolment to the study, (including ECG), by a stroke consultant to ensure the risk of a cardiac event was minimal. If any risk of a cardiac event was detected during the screening process, participants were withdrawn from the study. The risk of falls was reduced by a careful risk assessment of the MoveEx Lab and the presence of supervision at all times.

Pre-exercise session

Prior to each exercise session, each participant underwent a pre-exercise screen to ensure their readiness to exercise that day. Resting measures of blood pressure, (GE Healthcare, CARESCAPE V100, USA), heart rate (Polar, T31, Finland) and oxygen saturation, where appropriate (KZK-302 pulse oximeter, UK) were recorded. Data from the participant's baseline screening and CPET were used as reference for individuals' normative values. If there was a discrepancy or an abnormal measure which would indicate that the participant was not suitable to take part, then participants did not exercise on that day. It was expected that participants would have taken all their medication

as normal prior, during and after the exercise sessions. If participants were prescribed an inhaler, they were expected to have this on their person, if not, they did not exercise that day. Participants were invited back at their earliest convenience to make up for any lost session, provided it was safe to do so.

During exercise session

All participants were required to wear a heart rate monitor (Polar, T31, Finland) throughout the exercise sessions. Continuous heart rate readings were taken to ensure the participant did not exceed their age-predicted maximum heart rate. For each exercise activity, the peak heart rate was recorded. Levels of progression and adaptations to exercise training were monitored and tailored accordingly. For each prescribed exercise, peak RPE was also recorded. Peak RPE helped to gauge levels of effort, monitor any symptoms of pain, and aid in the progression of exercise intensity.

Immediately post-session

Following the cool down, resting measures of heart rate and blood pressure were recorded. Participants were offered refreshments and asked to stay in the MoveEx Lab for a minimum of 20 minutes after the session, so that I was able to monitor heart rate, blood pressure or any other signs that may have indicated an adverse event.

Post- or in-between sessions

To monitor and capture any SAE that occurred outside of the MoveEx Lab, participants were requested to inform the research team at their earliest convenience (page 7, Information Sheet for Exercise, appendix 8). Any non-attendance to a scheduled session was followed-up with a phone call (figure 16). If an SAE was identified, the PhD supervisory team, including the stroke consultant, investigated whether the SAE was related to the study. If it was, the study was stopped immediately and reviewed. Otherwise, the study continued as normal. If the non-attendance follow-up phone call received no response, the participant was re-contacted to establish whether they had been unable to attend or unwilling to attend and preferred to withdraw from the study.

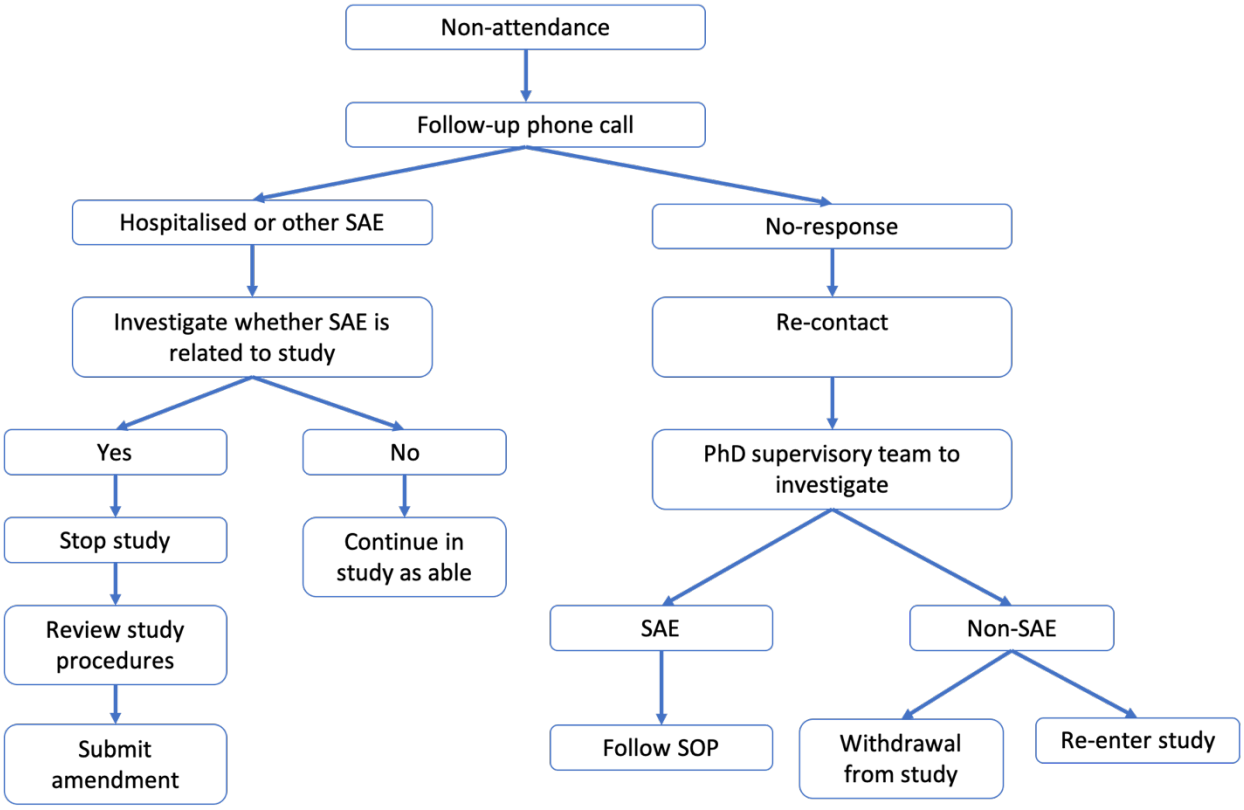

Figure 16: Flow chart describing procedures for monitoring adverse events outside of the MoveEx Lab

Reporting

I was responsible for reporting serious adverse events to the sponsor (the UEA) of the study (figure 17). All reporting followed the SOP for "Identifying, recording and reporting adverse events for healthcare research studies that are not clinical trials of an investigational medicinal product" (SOP 206, version 1.0) (365).

If an adverse event occurred, a reporting form, including study information, participant information, and an evaluation of event, medication information, and outcome of event were reported to the sponsor (the UEA).

If any SAE arose the study was stopped and reviewed immediately. Amendments to the study protocol were made where appropriate. Adverse events were reported to the sponsor (UEA) within 24-hours and followed up with a detailed written report in 48-hours. The SAE was reported to the research ethics committee (REC) within 15-days of becoming aware. If the event affected the health status of a participant, this was reported to the stroke consultant and they were reassessed for their safety to continue participating in exercise. They were either withdrawn or re-entered the study as appropriate. Figure 18 describes the pathway for participants', if they were to experience

an adverse event. The supervising stroke consultant for my study was also the consultant that was responsible for delivering care in and beyond the hospital for participants. I was therefore able to ensure that any impact of the study could be communicated to the clinical care team swiftly and responsibly.

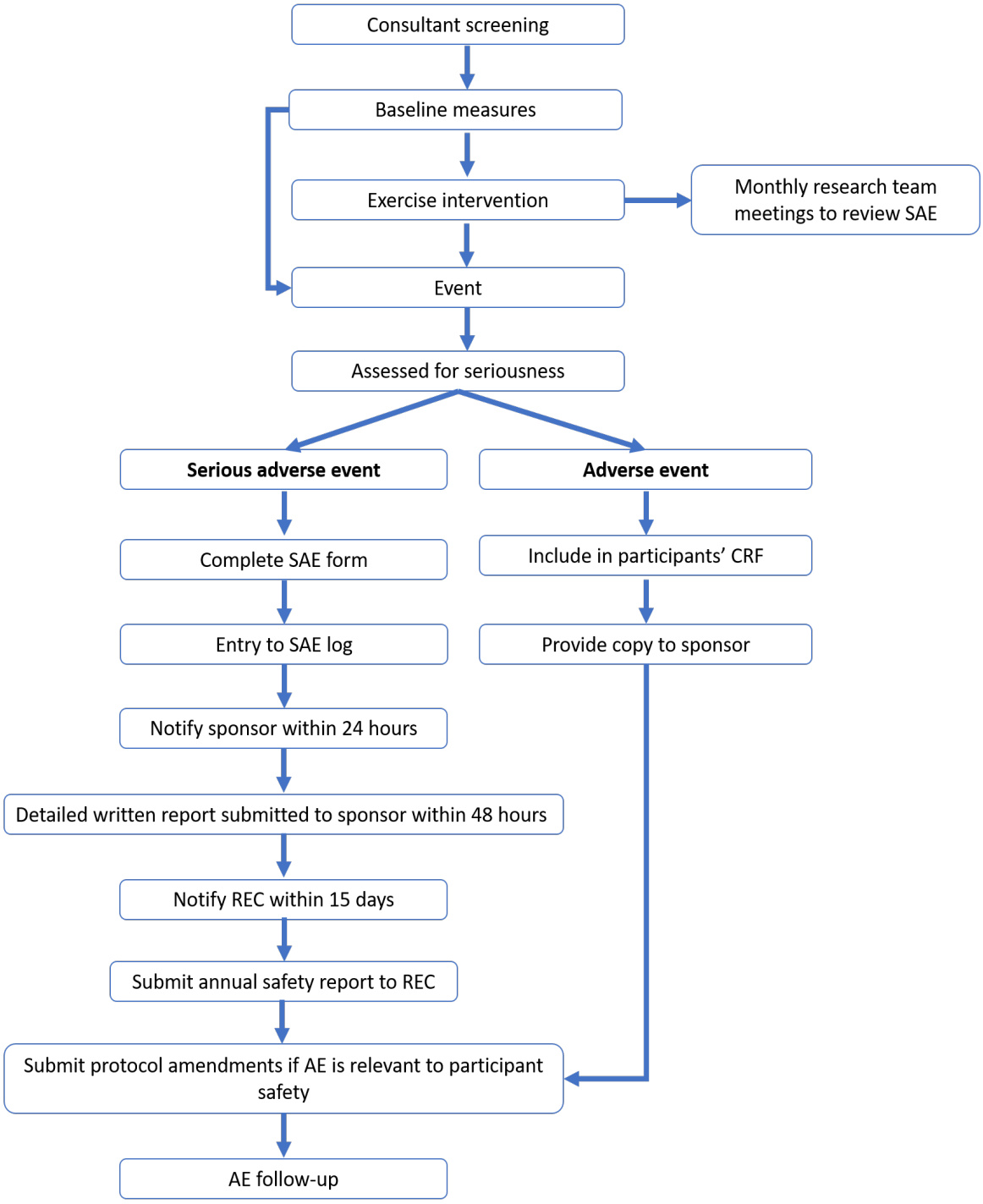

Figure 17: A flow chart summarising the reporting of adverse events

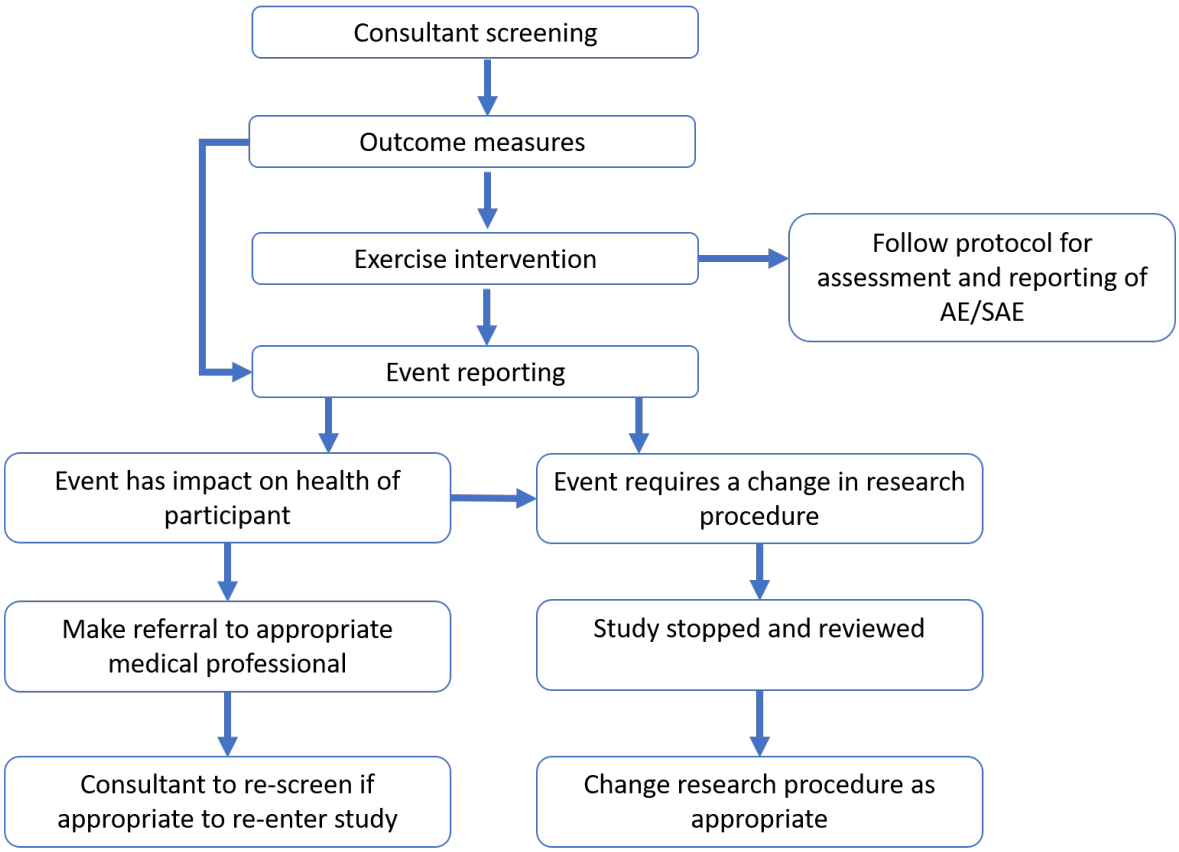

Figure 18: A flow chart summarising the pathway for participants if they experience an adverse event

5.8 Sample size

This study aimed to recruit 24 participants. The sample size was based upon practical considerations of time constraints and expectations of stroke admission numbers, informed by potential gatekeepers and clinical teams. I aimed to recruit eight participants per exercise intervention group. This was in line with best-practice guidelines introduced by Best et al. (93), who recommend a ratio of one staff member to eight stroke survivors.

Unlike definitive randomised controlled trials, which require robust parameter-driven estimates of sample size (263), sample sizes for feasibility studies are based upon an estimation to ensure a sufficient representative cohort is recruited to assess study processes, without unnecessary over-recruitment. Authors have suggested that feasibility studies should have a minimum sample size of 24 to 30 participants (366). Previously published pilot or feasibility studies in this area have recruited numbers ranging from nine to 41 participants (149, 213).

5.9 Quantitative analysis

Quantitative data analysis was undertaken and managed using SPSS version 23. The EXERCISES study was a feasibility study, therefore, inferences about causal relationships were not made. I was interested in the suitability of outcome measures and their potential sensitivity to change following a short-term exercise intervention.

5.9.1 Feasibility outcomes

Recruitment was calculated as the proportion of eligible participants who were approached who consented to participate in the study. The acceptability of randomisation was measured by the number who withdrew from the study, post-randomisation and identified CPET order allocation as a reason for withdrawal. Attrition was calculated as the proportion of participants who consented to take part in the study but subsequently left the study 'actively' (by formally notifying the study team) or passively (by leaving the study without informing the study team). Adherence was calculated individually for each participant who attended at least one study visit (actual visits/expected visits) and also as a mean for the sample of participants who attended at least one study visit.

For measures recorded throughout the exercise intervention, for example, resting heart rate and blood pressure; values are reported descriptively (i.e., mean, standard deviation and range).

5.9.2 Appropriateness of outcomes

The appropriateness of outcome questionnaires (MoCA, SSQoL questionnaire and the Barthel Index) for use with the stroke population, was defined by the proportion of non-completed scales (and any reasons provided by participants for non-completion). For each scale, item non-response was also calculated.

5.9.3 Potential for change in outcome measures

The reporting of outcome measures relative to change before and after the intervention was descriptive and exploratory, given the nature of the feasibility study design (367). Baseline and post-intervention scores of cognitive health, quality of life and activities of daily living were compared using paired sampled *t*-tests for, with significance set at a *p* value of less than 0.05. The relationship

between VO_{2peak} and global of scores achieved in the MoCA determined using Pearson's correlation coefficient.

5.10 Embedded qualitative sub-study

The aim of the qualitative sub-study was to address the acceptability and satisfaction of the EXERCISES study; specifically, (i) to explore participants' participants' experiences and perceptions experiences of intervention they participated in and of CPET procedures; (ii) to identify factors that facilitated or impeded participation; and (iii) to understand participant perspectives to illuminate measures of feasibility and fidelity.

5.10.1 Data collection methods

Semi-structured interviews were chosen as the method of data collection. One-to-one interviews were chosen as they provide the opportunity to generate rich descriptions regarding an individual's perception, feelings and emotion, experiences, motives, attitudes and knowledge (368). The interviews were used to explore individuals' personal experience of CPET and exercise interventions, thereby contributing to the development of a future trial.

5.10.2 Participants

Six participants were purposively sampled to be interviewed. Although the sample size was small, there was an attempt to ensure representation from different sample characteristics. These included: intervention group, randomisation order, gender, age and severity of stroke (369, 370).

At the end of the intervention, participants were approached in person and asked if they were willing to take part in an interview. One participant who was invited to be interviewed declined but gave no reason. Another participant agreed to be interviewed but then was unable as they had other commitments. Those who agreed to be interviewed, signed a second consent form to be audio recorded (appendix 10).

5.10.3 Topic guide

The topic guide was developed with a view to understanding participants' perceptions of the CPET and exercise interventions (appendix 19). Topics were informed by both the research aims of this

study and by previous work looking at the experiences of exercise referral schemes from the perspective of those living with the long-term consequences of stroke (371, 372).

I undertook training in qualitative research methods, including interviewing and data analysis. Working on other research projects as a research associate allowed me build up experience in interviewing and qualitative data analysis. I also piloted the interview procedures and topic guide with colleagues.

Table 21 provides a summary of the topic guide.

Table 21: Summary of topic guide for semi-structured qualitative interviews

Topic	Sub-topics
Exercise behaviour	• Past experience of exercise, before the stroke event • Barriers and facilitators of exercise participation
CPET	• Perceptions of exercise testing before attending • Experience of CPET
Exercise intervention	• Experience of exercise intervention • Factors influencing attendance
Suggestions to improve the suitability and acceptability of exercise testing and training	• Recommendations to improve the exercise intervention
Perceptions of perceived outcomes	• Perceptions of rehabilitation

5.10.4 Interview procedures

For their convenience, participants were either interviewed in their home, over the telephone or at the UEA. Attempts were made to ensure interviews were conducted privately and there was limited external noise. Similarly, it was important to consider participant characteristics; such as mobility, vision or hearing impairments and adapt the interview and environment accordingly.

Prior to the interview starting, I made sure participants were comfortable. Refreshments and the opportunity for comfort breaks were provided during the interview. I read a short introductory statement which detailed the purpose of the interview, the format, how long it was likely to take, and a reminder of the terms of confidentiality which they had previously consented to. Enough time was allowed for the interviewee to ask questions or to seek clarity of information provided.

Interviews were audio recorded. All participants were interviewed in the same manner, following the same questions and prompts. However, interview processes were adapted as appropriate for those participants who presented with communication or mild cognitive difficulties. For example, closed-questions and the use of pen and paper (373). The topic guide was personalised to the participant, taking into account their exercise intervention group and test mode randomisation order.

The topic guide (appendix 19) determined the order of questions, with probes and prompts to facilitate the focus and flow of the interview. At the start of every interview participants were presented with photographs of the two exercise test modalities. This helped avoid confusion and acted as a memory prompt. Notes on any significant observations, such as non-verbal remarks or changes in body language were made. Statements made by participants were paraphrased and summarised to ensure anything said ambiguously had the correct interpretation, before transitioning to the next topic.

At the end of the interview, there was time for the interviewee to add or expand upon anything else that may have not yet been discussed. Following this, closing remarks were made and the interview concluded.

5.10.5 Positioning of the interviewer

Disclosing the 'positioning' of the researcher is an important component of qualitative research in ensuring its dependability (374). I was known to participants and had established a good working relationship over the course of their exercise intervention period. Participants were aware that I was a doctoral student, with experience of working in exercise physiology and in research. They were aware this study would be written up as a thesis. It was originally expected that this would aid rapport and a willingness of participants to share data (375). However, with reflexive practice following the first interview, it was clear that this relationship posed a potential conflict of interest. Reflexivity is used to enhance the rigor and trustworthiness of a study (376). It is a process whereby the researcher,

'*does not simply report 'facts' or 'truths', but actively constructs interpretations of his or her experiences in the field and then questions how those interpretations came about' (376)* (pg. 8).

For the purpose of this study, I reflected on my own involvement of delivering the exercise intervention, in which I was intending to receive feedback from participants. Horsburgh et al. (377) advocated that there should be an evaluation of the extent to which the researcher has a potential or actual effect upon findings, when a researcher is intimately involved in both the processes and products of the research. As a result of reflexive practice, I felt I was 'too close to the data'. I felt as though participants felt they should present themselves in a way they thought I was expecting or said things they thought I wanted to hear. I perceived this to be a result of my direct involvement in the intervention delivery. A member of my PhD supervisory team listened to the audio and read the transcript of the first interview and agreed with the potential bias risks involved. Through discussions with my PhD supervisory team, it was decided that RH, who was not directly involved with the intervention delivery, would undertake the remainder of the interviews. Data collected from the first interview I conducted was still included in the analysis.

5.10.6 Qualitative data analysis

The qualitative analysis was driven by the study aims and objectives, with a specific interest in the acceptability and satisfaction of CPET and exercise intervention. I transcribed all audio-recorded interviews verbatim. Data was managed using NVivo 12 Software.

Thematic analysis was used to analyse the qualitative data (378). The framework emphasizes the identification, examining and the recording of themes across the data set allowing for a qualitative description of the 'phenomena' and contributions to the answering of the given research question (378). The steps of analysis defined by Braun and Clarke (378), have been adapted to the context of this study:

1. **Familiarisation with the data:** I listened to audio recordings and read through the transcripts several times in order to become familiar with the data; enabling a preliminary search for meaning, patterns and potential themes.

2. **Generating initial codes:** According to the main topics defined within the topic guide, initial codes were generated. This process was completed by RH and me independently, to increase the rigor and reliability of the research (379). Initial interpretations of codes were compared and discussed until a consensus was achieved.
3. **Searching for themes:** I searched for themes independently, by considering how the defined codes could be combined to formulate overarching themes, in line with the objectives of the interviews. This was then discussed with RH.
4. **Reviewing themes:** Together RH and I reviewed and refined themes through discussion. Early themes and interpretations were also presented to the PhD supervisory team, also known as 'peer debriefing'. Through collaboration with others, alternative approaches, developing ideas or other interpretations were considered based on the experience and expertise of the research team. Peer review in this way ensured the credibility and internal validity of data (369, 370).
5. **Defining and naming:** I identified the 'essence' of each theme, defined as,

   '*the implicit structure and meaning of such experience'* (380) pg. 470.

   Themes were then described within the context of the research question. At this stage of the analysis, I presented themes to all participants who took part in the EXERCISES study, in the style of a conference presentation, using lay terminology. In an attempt to improve the transferability of the data, participants were invited to challenge and contribute to my interpretations. Although transcripts were not returned to participants, this may be regarded as a form of member checking or respondent validation, which involves the verification from participants as to the appropriateness of my theories, derived from their dialogue (381).
6. **Producing the report:** Findings of the embedded, qualitative sub-study are described within Chapter 6, guided by the Consolidated Checklist for Reporting Qualitative Research (COREQ) (382) (appendix 20). The COREQ is 32-item checklist made to aid researchers in reporting aspects of qualitative research.

5.11 Data triangulation

Data triangulation aimed to capture both the potential to change, and subjective experiences of, the intervention they participated in and of CPET procedures. Triangulation ensured the credibility and internal validity of the data (369, 370).

The nature of the research questions and therefore, the study design, meant the analysis of the embedded qualitative sub-study was treated separately to quantitative outcomes. For this study, the qualitative data was used as a secondary resource to help explain the quantitative findings. To link the two, themes relating to participants' experience of the study's processes, for example recruitment or attendance, were developed. Corroboration of such findings provided a deeper understanding of the feasibility and acceptability of CPET and exercise interventions to participants.

5.12 Ethical considerations

Ethical approval was granted by the East of England - Cambridge Central Research Ethics Committee, reference number 17/EE/0409. Appendices 21 and 22 details research approval documents. The study conformed to Good Clinical Practice (GCP) Guidelines, in which I completed training on 18/01/2017. Accruals were uploaded to the database 'EDGE' in compliance with GCP guidelines and to aid in governance checks. The protocol of this study was peer reviewed by a Professor of Neurorehabilitation at the UEA and a Stroke Consultant at the local NHS Foundation Trust.

5.12.1 Data storage and anonymity

All data was anonymised and stored in a lockable cabinet to comply with the Data Protection Act (2018). Records that included any identifiable information were stored separately to data collection records. Regarding the interview's transcripts, any information relating to the participants, such as names of places, services or other people, were removed. Transcripts and data collection forms were only identifiable by participant numbers.

5.12.2 Managing the inclusion of vulnerable participants

To extend study invitations to as many stroke survivors as possible, supported communication strategies were adopted to improve the dissemination of study information. Resources for this study were developed in collaboration with service users living with aphasia and with a speech and language therapist with expertise in stroke. Key terms were written in bold text or highlighted and pictures to support the text were inserted. There were opportunities for one-to-one conversations about participation and carer involvement. Information about the study was also shared as a video. A link to this is provided in section 5.6.3.

I completed further training in supported communication, which included taking informed consent from those who are living with communication impairments.

The Early Supported Discharge team at the local community health and care NHS trust are research active and regularly promote participation in trials. At the discretion of clinical and research teams, patients are able to participate in more than one trial, as long as dual participation is not listed within the study's exclusion criteria. It was important that throughout the recruitment phase, clinical and research teams liaised to ensure that patients were not being over-burdened with study invitations.

5.12.3 Participant well-being

To ensure the well-being of each participant, a number of steps were taken. Effort was made throughout all exercise sessions to maintain dignity and autonomy of participants. I was mindful that for some, exercising may cause some embarrassment or discomfort, thus when required, screens were used for privacy. A second room was always available for confidential conversations to be had, both for participants and for those who were visiting with them.

For service users who had experience of stroke and who contributed to the study's development, it was important to also consider their well-being. In some cases, discussions were potentially sensitive, especially when referring to experiences of having a stroke and talking about its impact. Although not anticipated in this study, I was aware that if participants were asked to recall an experience of their stroke during an interview, it may have caused some distress or upset.

Participants were made aware that if at any time they felt uncomfortable, they did not have to provide an answer and could terminate the interview at any time. In both cases, individuals were signposted to options of additional support such as attending peer support groups in the local area or to contact their GP for further advice.

15.12.4 Researcher safety

Where possible, I visited participants at home to maximise convenience and reduce their travel and expense. For researcher safety during these home-visits, a risk assessment and SOP were produced (appendix 23). The UEA Faculty of Medicine and Health Lone Worker Policy (383) was adhered too. The details of home visits were left with a member of the PhD supervisory team (KMa) and contact was made to confirm the start and end of each visit.

5.13 Study development

In designing this study, a number of developmental activities were undertaken. Activities included defining the methodological approach and researching the most appropriate epistemological stance for data collection. Other activities were conducted in the operationalisation of the study, including a descriptive proof-of-concept study with healthy volunteers aiming to refine CPET procedures, as well as consultation with service users, as part of Patient and Public Involvement (PPI). The subsequent sections describe and discuss each of these developmental activities.

5.13.1 Theoretical development

The methodological approach when designing a study must reflect the most appropriate means of addressing both the type and the nature of the proposed research question (330). The development of this mixed method, feasibility study has been guided by the underpinning epistemological stance of pragmatism (384).

Epistemological stance

Pragmatism is the primary philosophy of mixed methods research. This epistemological stance of pragmatism focuses on practical consequences of an idea, a theory or proposal (385). Pragmatism applies logic and seeks to incorporate the use of all approaches to understand a research problem

or question (386). The benefit of a pragmatic approach is that it can provide both objective and subjective knowledge.

Traditionally, objective knowledge is gathered through quantitative research. Quantitative research is viewed from a positivist paradigm, in which experimentation and deductive approaches are employed to primarily predict and generalize causal mechanisms of change (384, 387, 388). However, subjective knowledge is shaped by interpretive paradigms. Here, an insight into the experience of a phenomena may be explored (330). Qualitative research is performed inductively, whereby processes and meaning may be deduced, as opposed to affinities with outcomes or causal explanations, as in quantitative research (381, 384, 389). For the purpose of this study, a combination of both positivism and interpretivism, was considered to be most appropriate to address the proposed research questions. A pragmatic approach, with a combination of qualitative and quantitative research paradigms, provided the flexibility and freedom to be explorative in understanding how exercise may be used as an intervention to maintain cognitive health among stroke survivors with moderate to severe movement impairments.

The notion of 'mixed methods' has been referred to as the *'third research paradigm'* (384). It is an increasingly recognised approach for stroke rehabilitation (390), moving beyond intervention efficacy testing, by adding depth to meaning and interpretation. The use of mixed methods is encouraged by the MRC and National Institute for Health Research (NIHR) for use within feasibility study designs (234).

Mixed methods

Mixed methods is defined by Creswell and Clarke (330) as a research design (or methodology) in which the researcher collects, analyses and mixes (integrates or connects) both quantitative and qualitative data in a single study or multi-phase programme of inquiry.

The central premise for using mixed methodology is that the combination of approaches provides an overall better understanding of the research question (330). Furthermore, the use of one method of data collection is often not sufficient in addressing the research aims and objectives. Using a combination of data collection methods is advocated to overcome this. Mixed methods

allows researchers the opportunity to elaborate, enhance and illustrate clarification in results. It is thought that the combination of methodologies is able to overcome limitations posed by a single design (385). The research questions for this study demand descriptive, explanatory and exploratory data to answer them, therefore justifying the use of more than one type of methodology.

This mixed methods study combines and integrates qualitative and quantitative research methods of data collection and analysis. An embedded approach was adopted, in which a qualitative study was embedded within a larger quantitative experimental pretest–posttest design. In this design, quantitative data was firstly collected to explore and estimate feasibility parameters such as recruitment, attrition and outcome measures' potential for change, among stroke survivors with moderate to severe movement impairments. Second in the sequence, a small qualitative sub-study was conducted. Six semi-structured interviews were undertaken to elaborate on the quantitative findings, providing an insight into participants' perceptions and experiences of CPET and exercise interventions.

The collection of qualitative data (participants experiences and perceptions of the intervention they participated in and of CPET procedures), secondary to quantitative data (feasibility, exercise and cognitive outcomes), was necessary for this thesis as findings can enhance the conduct and understanding of such intervention through the incorporation of individual perspectives. The triangulation of data supports the design of future trials, by considering the views and perceptions of participants.

Feasibility study

A feasibility study is defined as a study that formally answers the question, '*can this study be done?*' (330, 391). The purpose of a feasibility study is to determine the viability of key research design elements; including assessing procedures and outcome measures for their acceptability, estimating the likely rates of recruitment and retention of participants, and the calculation of appropriate sample sizes (234). Early development work, particularly in rehabilitation trials, can highlight immediate barriers to implementation whereby analysis and the refining of an intervention can

develop strategies to overcome limitations in a subsequent trial (392). Findings of feasibility studies help deduce whether conclusions are contextually relevant to the research aims, and whether ideas and design elements will be sustainable throughout future definitive trials (331). Feasibility studies are essential to provide sufficient methodological evidence of the design, planning and justification, prior to a large-scale evaluation through a fully powered intervention trial (393).

The design of the EXERCISES study was informed by the research aims and objectives: (i) to investigate the feasibility of delivering two methods of cardiovascular exercise testing modes (treadmill with a BWS harness and cycle ergometry); and (ii) to investigate the feasibility of delivering exercise-based interventions (aerobic exercise, strength training and a combination of aerobic exercise and strength training) to people with moderate-severe movement impairments as a result of stroke. The EXERCISES study broadly conforms to the feasibility and piloting phase of MRC framework (2006) for the development, evaluation and implementation of complex interventions (234). The framework was devised with the rationale that preparatory work would produce meaningful information on the viability of specific interventions or outcomes, thus optimizing the fidelity of each key design element in a future full-scaled trial (234, 394). The cyclical process of this is described in figure 19.

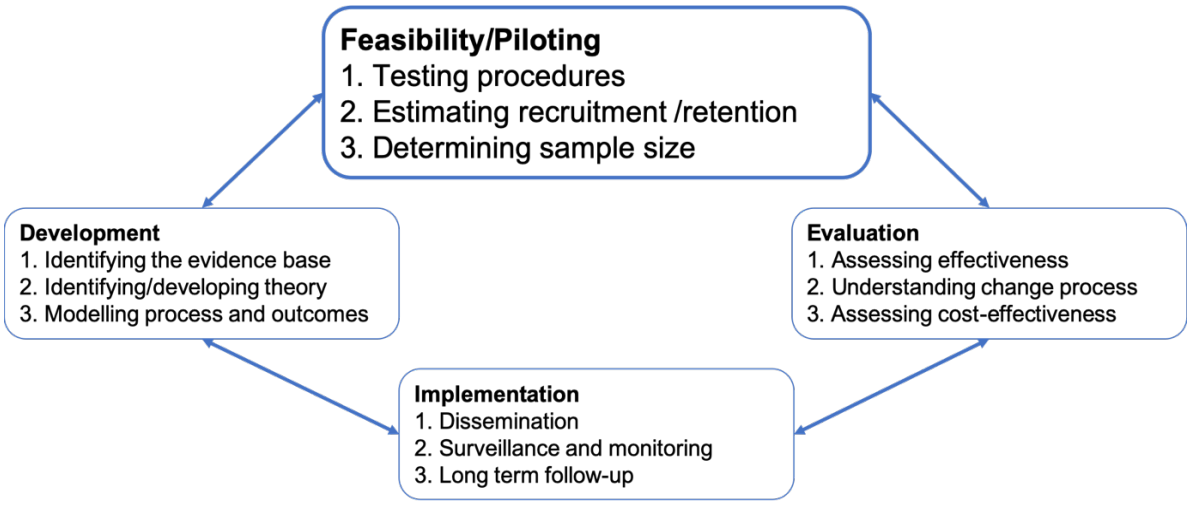

Figure 19: Key elements of the development and evaluation process, reproduced from the Medical Research Council's guidance for developing and evaluating complex interventions (2008) (234)

A feasibility study design was chosen because there are still a number of unknowns regarding this area of inquiry, preventing the implementation of a full-scaled trial. For example, the ability of those who are living with the longer-term consequences of a severe stroke, to undertake CPET safely is yet to be established. With a feasibility study design, I was able to determine whether proposed theories were applicable in a given context, i.e. can those living with moderate to severe movement impairments post-stroke safely participate in exercise training in the community? The flexibility of a feasibility design helped in identifying any 'teething problems' throughout the trial, for example adapting the recruitment strategy for optimal reach of prospective participants. By employing a feasibility study, the demand of a community-based exercise intervention from patients, researchers and clinicians was understood (determined by attrition, adherence and compliance).

5.13.2 Operationalisation

In the development of the EXERCISES study, two important preparatory activities were conducted. This section describes the consultation and collaboration with patient and public involvement (PPI) groups and a small, proof-of-concept study of CPET procedures with healthy volunteers.

Patient and Public Involvement

Patient and Public Involvement (PPI) is an essential component of research, whereby members of the public are actively involved in project identification and prioritisation, design, conduct and dissemination. The benefit of including PPI partnerships in some, or all, aspects of research gives the investigator insights that will make the study more relevant to the target population. As PPI contributors are often experts by experience, this leads to heightened transparency and inclusivity in the research design (395).

I worked in collaboration with service users with experience of stroke to produce participant information documents (appendices 7 to 9). The group also had previous experience of PPI on other research projects. They were familiar with research processes and the principles of capacity and consent. Collaboration in this way was helpful in translating the ethical issues of the study into lay terms. They provided advice on adapting academic language within the participant information sheets, so that it was clear and unambiguous. Members of the group were living with aphasia,

therefore their insights into communication techniques was invaluable. They were able to offer comments on formatting that increased the readability of documents to those who are living with communication or visual impairments. This included a more appropriate font and size (for example, Ariel font, size 14), key words formatted in bold, and the use of images and photographs.

Members of the PPI group also took part in creating the participant information video I shared with potential participants who were living with cognitive, visual or communication deficits post-stroke. A link to this is provided in section 5.6.3.

In addition, members of the PPI group were consulted on the adaptations made to CPET procedures. They trialled getting on and off equipment in order to offer their feedback as an individual living with moderate to severe movement impairments. Table 22 provides a list of the barriers identified and what adaptations I implemented with the operationalisation of the EXERCISES study.

Table 22: Barriers and adaptations identified by service users, when trialling accessing CPET equipment

Barriers Identified	**Adaptation**
Height of step on the treadmill	Place additional step at the foot of the treadmill to reduce height; or if required, use harness as a hoist to facilitate getting participants onto the treadmill - may also be used to facilitate stepping by displacing some body weight
Visibility of harness rig	Addition of brightly coloured foam padding around the edges of the BWS harness rig
Comfort of harness	More padding to be used on the harness around the groin and leg area for increased comfort while walking
Pedals on cycle ergometer (Reduced ability in hip flexion, knee extension and ankle dorsi-flexion on the paretic side made it difficult to hold foot in place on pedal)	The addition of pedals that have a calf/foot shelf to provide support and prevent foot from sliding off
Incline on treadmill (Reduced dorsi-flexion ability on paretic side)	Reduce from 2% to 1% (1% incline was kept, mimicking over-ground walking)
Music and background noise (As a result of potential attention deficits)	No music or radio and reduce additional noise disturbance while explaining, prepping and initiating CPET
Expectations of mask and other equipment/apparatus	Allow participants to try mask on as early as the recruitment stage

Piloting the cardiopulmonary exercise testing process with healthy volunteers

A descriptive proof-of-concept study with healthy volunteers, was designed as a preparatory activity prior to the EXERCISES study. The development of and technical feasibility of CPET protocols and procedures in the MoveEx Lab were required to be trialled and refined, prior to the inclusion of stroke survivors. Additionally, I was interested to explore the responsiveness and tolerability of CPET protocols, by recording individuals' cardiopulmonary responses. Cardiopulmonary responses provided insight to the appropriateness of CPET protocols in attaining maximal exertion.

The specific objectives of this small, proof-of-concept were as follows:

- To record reasons for test termination,
- To create the optimal environment for CPET protocols,
- To refine the delivery of CPET.

Ethical approval was provided by The Faculty of Medicine and Health at the UEA (reference: 2017/18 – 51) (appendix 24). Figure 20 provides an overview of the key events undertaken in this proof-of-concept study.

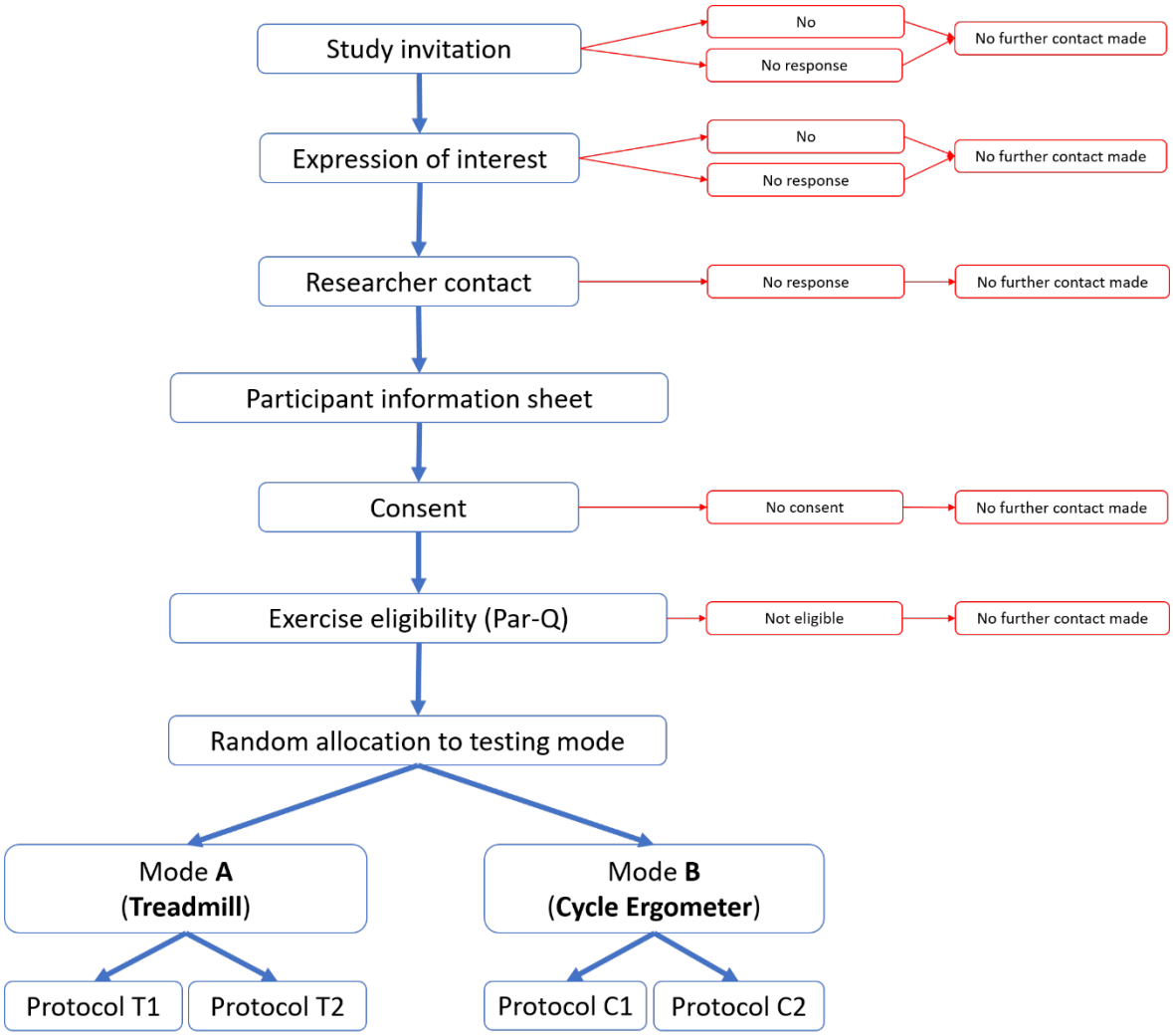

Figure 20: Key events of the proof-of-concept study

Participants

A convenience sample of healthy volunteers from the UEA were recruited via poster advertisement. Potential participants expressed an interest in taking part via email or telephone. I shared participant information with potential participants (appendix 25). Following consent, participants were screened to take part in the study by completing a Physical Activity Readiness Questionnaire (PAR-Q) (396) (appendix 26). Participants were excluded if they self-reported any absolute or relative contraindications to exercise, based upon the American College of Sports Medicine (ACSM) Contraindications to Exercise criteria (2014) (14).

Procedures

Following written informed consent (appendix 27), a member of the research team (AA), who was not directly involved in test administration, randomly allocated participants, via opaque envelopes,

to CPET mode (**T** = treadmill, or **C** = cycle ergometer), and to CPET protocol (**1**) or (**2**). Tests were conducted on an electronically braked cycle ergometer (Excalibur Sport, Lode©, Netherlands), or a treadmill (HP Cosmos, Mercury Med, Germany). A summary of CPET protocols are provided in box 4. The procedures for administering CPET are described earlier in this Chapter (section 5.7.4).

Box 4

Summary of <u>treadmill with BWS</u> CPET protocols
T1. 4% incline, then increase by 2% every 2 mins, self-selected speed, until test termination
T2. 2% incline, the increase by 2% every 2 mins, self-selected speed, until test termination
Summary of <u>cycle ergometer</u> CPET protocols
C1: 10W increase every 1 minute, at 70-80 rpm, until test termination
C2: 20W increase every 1 minute, at 70-80 rpm, until test termination

Findings

Twenty-two individuals expressed an interest to take part in this pilot study. All participants who expressed an interest were eligible to take part, however, ethical approval allowed only 20 volunteers. Over-recruitment was employed in the case of drop-outs. Eleven participants were randomised to a treadmill test and nine were randomised to a cycle ergometer test. No adverse events occurred as a result of any CPET protocols. Technical difficulties with testing equipment was experienced with two participants. Table 23 provides the quantitative findings derived from CPET. Data is reported per mode of CPET.

Table 23: A description of the data and the justification for data collection, derived from CPET undertaken as part of a proof-of-concept study, involving healthy participants

		Treadmill		Cycle Ergometer	
Outcome	**Justification**	**Males (n=6)**	**Females (n=5)**	**Males (n=7)**	**Females (n=2)**
Height (cm)	To describe the demographic of participants.	181.73 ± 9.49	166.70 ± 4.82	175.93 ± 7.30	177.55 ± 5.02
Weight (kg)	To describe the demographic of participants.	73.25 ± 10.86	60.42 ± 3.68	74.61 ± 12.52	67.50 ± 6.79
Relative VO_{2max} (mL/kg/min)	To assess the responsiveness of CPET protocol	56.38 ± 9.31	46.75 ± 3.49	42.95 ± 10.09	34.75 ± 2.89
RER	To assess the responsiveness of CPET protocol	1.21 ± 0.10	1.21 ± 0.4	1.31 ± 0.15	1.26 ± 0.17
Peak heart rate (bpm)	To examine the physiological responses of participants to incremental exercise	185.16 ± 13.73	178.00 ± 14.15	177.28 ± 13.84	180.50 ± 14.84
Peak RPE	To evaluate the tolerability of CPET protocol	18.83 ± 1.47	18.00 ± 1.41	17.42 ± 1.61	19.00
Exercise time (mins)	To evaluate the tolerability of CPET protocol	17.53 ± 4.83	13.02 ± 1.40	13.32 ± 3.02	16.47 ± 6.93
Stage achieved	To evaluate the tolerability of CPET protocol	7.60 ± 1.14	6.50 ± 0.57	21.85 ± 7.03	16.0 ± 7.07
Met criteria for reaching VO_{2max}[a] (*n*)	To evaluate the validity of CPET outcomes	6	5	7	2

Expressed as means ± standard deviations

*Two participants not included: one error in software, one technical issue with hardware.

[a] RER ≥1.0

Abbreviations

bpm beats per minute **CPET** Cardiopulmonary exercise test **HR_{max}** maximum heart rate **km** kilometres **mins** minutes **mL/kg/min** millimetres per kilogram of body weight per minute **RER** respiratory exchange ratio **RPE** rating of perceived exertion

Reasons for CPET termination were recorded (table 24). This was important to understand the technical feasibility of test apparatus and the tolerability of CPET protocols.

Table 24: Reasons for CPET test termination in the proof-of-concept study with healthy volunteers, displayed by CPET mode

		Treadmill		Cycle Ergometer	
	Total (n=20)	**A1** (n=5)	**A2** (n=6)	**B1** (n=6)	**B2** (n=3)
Breathlessness	6	2	1	2	1
Muscular fatigue in legs	4	1	1	1	1
Feelings of nausea	1	-	1	-	-
Stopped by assessor*	2	1	1	-	-
Inability to maintain speed/RPM	4	-	-	3	1
HR exceeded predicted maximum	3	1	2	-	-

Expressed as number of participants
*Two were unable to maintain a safe positioning on the treadmill with that level of incline. One other stated maximum RPE of 20.
Abbreviations
CPET Cardiopulmonary exercise test **HR** Heart rate **RPE** Rating of perceived exertion **RPM** Revolutions per minute

I identified a number of limitations with CPET procedures that those with post-stroke movement impairments may encounter. Limitations are displayed in table 25, along with a recommended adaptation when moving forward into the EXERCISES study.

Table 25: Barriers and adaptations identified to CPET procedures during the descriptive, proof-of-concept study with healthy volunteers

Barriers Identified	**Adaptation**
Discomfort of cycle ergometer seat	A wider, more cushioned seat was fitted
Visual disturbance (Reduced visual feedback from the harness rig over the treadmill and because apparatus was facing wall)	Mirrors were fitted on the walls beyond the treadmill and the cycle ergometer
Risk coming into contact with the harness rig	Soft and visible foam was fitted to the rig to reduce any potential impact
RPE responses (Breathing pattern disturbances when responding to questions of exertion)	Ask participants at the end of the test to recall their perceptions of exertion

Summary of proof-of-concept study

This small, proof-of concept study of CPET procedures was a helpful practice pertaining to development of the EXERCISES study. This study allowed me to define several barriers to CPET participation and trial methods of adapting procedures. Barriers were mainly environmental, such

as the comfort of the cycle ergometer seat and visual disturbances; thus without modification, would have impacted the inclusion of stroke survivors.

5.14 Summary of chapter

This chapter has provided a description and justification of the methodology employed for the EXERCISES study. To summarise, two modes of CPET were explored: treadmill with BWS and cycle ergometry. Participants were allocated to a twice weekly, six-week exercise intervention of either (i) aerobic exercise, (ii) strength training, or (iii) a combination of aerobic exercise and strength training. Outcomes of cognitive health, quality of life and activities of daily living were measured pre- and post-intervention. An embedded qualitative sub-study explored the acceptability and satisfaction of CPET and the exercise intervention from the perspective of participants. The following chapter presents the findings of the EXERCISES study.

Chapter 6

The EXERCISES Study: Results

6.1 Introduction

This chapter presents the results of the EXERCISES study. The rate of recruitment and the characteristics of participants are described. Findings relating to the feasibility of CPET and exercise interventions for stroke survivors with moderate to severe movement impairments are reported. Themes and interpretations generated from qualitative interviews are presented.

6.2 Recruitment

The recruitment process lasted a total of 10 months. Figure 21 is a flow diagram illustrating the study recruitment phases, including patient identification, consent, screening, randomisation and allocation.

6.2.1 Patient identification

Thirty stroke survivors were invited to take part in the EXERCISES study. Of the potential participants identified, 73% (n=22) were identified by the Early Supported Discharge Team and 26% (n=8) identified through local community support groups. At the point of invitation, one potential participant declined to participate. This was because they were unable to fund travel to and from the MoveEx Lab for the duration of the study, as they lived in a rural area. I conducted 29 home-visits to potential participants to explain what it would mean to take part in this study.

Four potential participants were unable to take part in the EXERCISES study. Two were residing in a care home and were unable to travel to the MoveEx Lab. Two did not meet the inclusion criteria (a FAC score of more than three). One other did not respond, after all relevant study information had been provided. Of the 29 stroke survivors who expressed an interest in taking part in the EXERCISES study, 24 (83%) provided informed consent.

6.2.2 Screening

Following consent, one individual withdrew due to other commitments. One other was living in an assisted living complex and could not be assisted to travel to the MoveEx Lab. I carried out second

home-visits with 22 participants to complete screening procedures. At this point, two individuals were excluded as they did not meet the inclusion criteria (one with a FAC score of one and another of four). One of these individuals was also living in a care home and had expressed that there may have been difficulty in the home providing transport. One other person was withdrawn from the study based on a recommendation from KM, as they presented with significant mental health issues.

6.2.3 Randomisation

Nineteen participants were therefore randomised to order of CPET: order A treadmill with BWS at baseline, and cycle ergometry at outcome (n = 10) and order B cycle ergometry at baseline and treadmill with BWS at outcome (n = 9). At the time of baseline CPET, one individual had severe arterial hypertension of 200 mmHg over 100 mmHg and was withdrawn from the study in line with ACSM contraindications to exercise (14). No participant withdrew from the study based on their random allocation of CPET order.

6.2.4 Allocation

Eighteen out of 24 participants (75%) were sequentially allocated to one of three exercise intervention groups: aerobic (n=7), strength (n=6), combination (n=5).

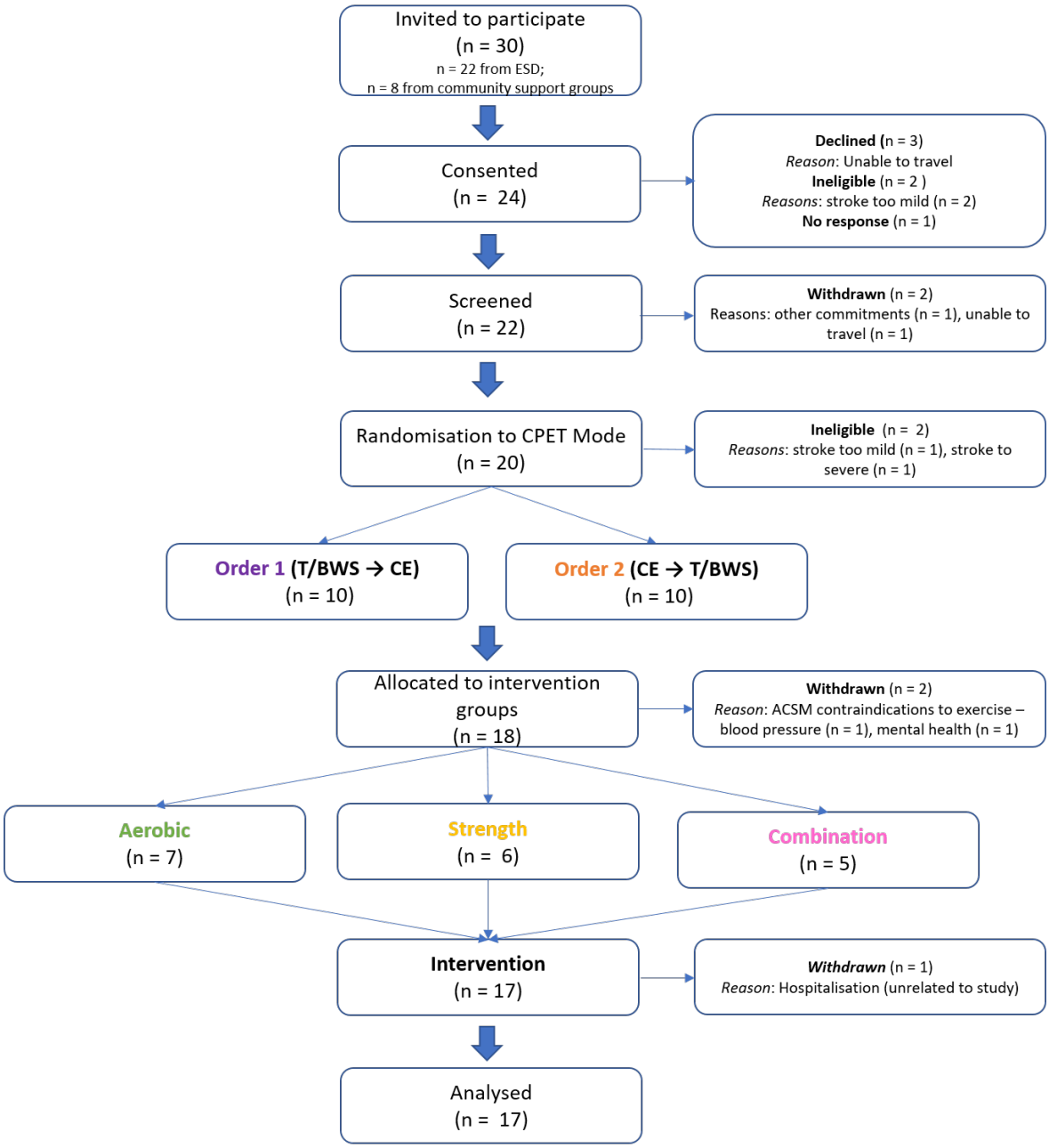

Figure 21: A flow chart describing screening, recruitment, randomisation and allocation of participants recruited to the EXERCISES study

6.2.4 Adherence and attrition

No participant voluntarily withdrew from the study. One participant, however, was withdrawn from the study after five exercise sessions, due to a non-study related, serious adverse event requiring hospitalisation. Through discussions with the participant and their carer, KM and KMa, it was decided it was not necessary to stop the study and review the protocol. However, because the participant had been hospitalised, to adhere to our protocol for adverse events, the individual was withdrawn from the study.

The remaining 17 participants completed all 12 exercise sessions. Flexibility in attending exercise sessions was permitted to increase the attractiveness of participating in the study. For example, if a participant missed a session due to an appointment, they were invited back at their earliest convenience to make it up. Individual sessions were cancelled due to reasons such as community clinical team home-visits, other appointments, feelings of fatigue, the inability to travel on that day, or due to research team commitments.

6.3 Participant characteristics

Table 26 describes baseline characteristics of participants. There were 14 males and 4 females. The mean age was 64 years (range 45 to 78 years) and the mean time since stroke was 39.1 months (range 6 to 193 months). Sixty-one percent had a left sided weakness and 39% a functional ambulation score (FAC) score of two.

Table 26: Summary of participant characteristics at baseline

	(n = 18)
Gender, male/female, (*n)*	14 / 4
Age *(years)*	64.44 ± 8.50
Height *(cm)*	172.75 ± 9.37
Weight *(kg)*	83.93 ± 15.54
BMI	28.06 ± 3.87
Stroke	
Type, ischemic/haemorrhagic *(n)*	7 / 11
Time since onset *(months)*	39.11 ± 60.74
Paretic side, left/right (*n)*	11 / 7
Communication impairments *(n)*	7
Functional Ambulation Category (*n*)	
2	7
3	10
4	1*
Mean Score	2.66 ± 0.59
Gait aids *(n)*	
Quad stick	10
Stick	5
Two sticks/crutches	2
Rollator frame	1
Comorbidities *(n)*[a]	
Hypertension	7
Hyperlipidaemia	7
Asthma	2
CVD	6
Diabetes	2
Arthritis	5
Medications *(n)*	
Beta-blockers	1
Ace-inhibitors	7
Pre-stroke exercise level *(n)*	
Sedentary/ light	4
Moderate/ vigorous	14

Expressed as means ± SD

*Participant had a FAC score of 3 when assessed for study eligibility at a home-visit. When they came for their baseline CPET, their ambulation had improved and therefore scored 4 on the FAC. The individual continued to take part in the study.

[a] Participants may have had multiple co-morbidities

Abbreviations

BMI body mass index **cm** centimetres **CVD** cardiovascular disease **kg** kilograms

6.4 Measures

This section describes the outcome measures used in the study. The EXERCISES study is a feasibility study, therefore, inferences about causal relationships were not made. The primary focus was in exploring broader trends in the data regarding the suitability of outcome measures.

6.4.1 Cardiopulmonary exercise test and maximal aerobic capacity

The use of two different data collection methods to determine VO_{2peak} precludes the ability to estimate changes over time. As this was a feasibility study, the benefits of participants experiencing both modes of CPET (described later in this chapter), outweigh the potential to infer any changes in cardiorespiratory fitness as a result of exercise training. Therefore, for the purpose of this thesis, baseline and outcome data have been combined and presented by CPET mode, so the feasibility of each CPET mode can be explored. Peak VO_2 was reported as the highest value attained during CPET. Table 27 summarises these data.

There were no adverse events that occurred as a result of either CPET protocol. There were no episodes of angina, abnormal blood pressure changes pre- or post-CPET and no significant ECG changes as a result of exhaustive exercise. There were however, five instances of arthritic knee and/or hip pain when cycling or walking.

Treadmill with body weight support

A total of 18 participants undertook CPET on the treadmill with BWS; eight at baseline and 10 at outcome. Participants were able to adequately access the treadmill, with the addition of a small step at the base of the treadmill. All participants required the assistance of two people to step, and in some cases, the BWS harness was also used to facilitate stepping up. During CPET on the treadmill with BWS, KMa or I assisted by increasing or stabilising knee flexion and ankle dorsiflexion to maintain locomotive movement, for most participants. All participants required verbal cues for prompting proper gait when walking on the treadmill.

The mean VO_{2peak} achieved on the treadmill with BWS was 10.81 (SD 2.87) mL/kg/min. Values are approximately 57% of normative values described for healthy adults aged 60 to 69 years (66) (figure

22). The mean test time for the treadmill with BWS ranged from 0.12 to 12.59 minutes (mean 6.01 minutes). The highest speed which participants attained was 1.49 (SD 0.88) mph.

	Completed treadmill with BWS (n=18/18)*	**Completed cycle ergometer** (n=15/18)*
Gender, male/female, (*n*)	14 / 4	12 / 3
Age *(years)*	64.44 ± 8.50	63.33 ± 8.80
Height *(cm)*	172.75 ± 9.37	172.97 ± 9.58
Weight *(kg)*	83.93 ± 15.54	84.50 ± 16.59
BMI	28.06 ± 3.87	28.18 ± 4.20
Relative VO_{2peak} *(mL/kg/min)*	10.81 ± 2.87	13.28 ± 2.86
Absolute VO_{2peak} *(mL/min)*	917.44 ± 269.31	1123.33 ± 283.67
RER	0.98 ± 0.07	1.12 ± 0.15
HR_{peak} *(bpm)*	96.66 ± 16.78	103.83 ± 32.21
Exercise time *(mins)*	6.09 ± 3.66	7.87 ± 3.88
CPET protocol stage achieved	2 ± 1	8 ± 3
Maximum speed *(km)*	1.49 ± 0.88	-
Maximum resistance *(watts)*	-	44.33 ± 16.35

Expressed as means ± SD
*Total number of baseline and outcome tests combined**/**total number of participants
Abbreviations
bpm beats per minute **HR_{max}** maximum heart rate **km** kilometres **METS** metabolic equivalents **mins** minutes **mL/kg/min** millimetres per kilogram of body weight per minute **mL/min** millimetres per minute **RER** respiratory exchange ratio **RPE** rating of perceived exertion

Cycle ergometry

Overall, 15 participants undertook a CPET on the cycle ergometer: 10 at baseline and five at outcome. For some, a hoist was used to transfer participants from their wheelchair to the cycle ergometer. Some participants stepped up with the assistance of one or two people onto a step, before perching on the seat and receiving help to step over the central frame of the ergometer. During the CPET, assistance was also required in the form of increasing or stabilising knee flexion and extension when cycling.

The mean VO_{2peak} achieved on the cycle ergometer was 13.28 (SD 2.86) mL/kg/min. Values are approximately 45% of normative values described for healthy adults aged 60 to 69 years (66) (figure 22). The mean test time ranged 2.13 to 15.32 minutes (mean 7.87 minutes). The highest amount of resistance which participants attained was 44.33 (SD 16.35) watts.

Table 27: Summary of exploratory CPET variables, displayed by CPET mode (n=18)

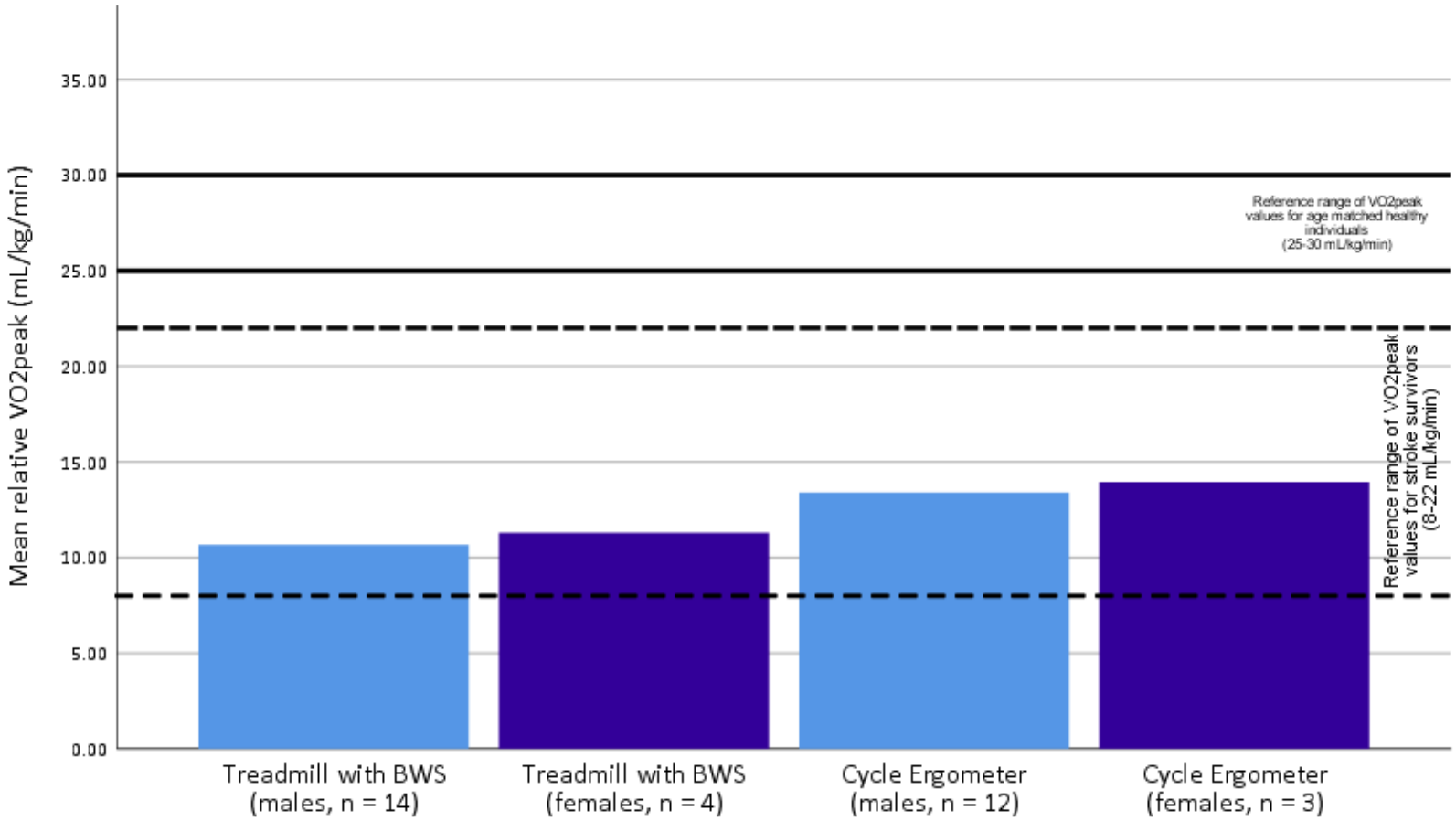

Figure 22: A bar graph to show mean relative VO_{2peak} values, displayed by CPET mode and by gender.[2]

[2] *The figure displays mean relative VO_{2peak} values achieved by males and females, derived from both testing modes: treadmill with BWS and cycle ergometer. Displayed on the graph are reference values for stroke survivors (8 – 22 mL/kg/min) (59), illustrated between the two dashed black reference lines; and age-matched healthy individuals (25 – 30 mL/kg/min) (59), illustrated between the two solid black reference lines.*

Ability to achieve maximal effort

As stroke survivors are unlikely to achieve a plateau in in oxygen consumption, despite an increase in workload, a respiratory exchange ratio of more than one and/or 80% of age-predicted maximum heart rate, was chosen to be indicative of maximal effort. These data (table 28; figures 23 and 24) are important for exploring the feasibility and appropriateness of CPET protocols to obtain accurate values of cardiorespiratory fitness.

Of the 18 treadmill tests, no participant reached 80% of their age-predicted maximum heart rate (mean peak heart rate = 96.66 bpm) and less than half (44.4%) reached a respiratory exchange ratio of more than one (mean RER = 0.98). In comparison, all participants who completed a cycle ergometer CPET protocol reached a respiratory exchange ratio of more than one (mean RER = 1.21). However, as with the treadmill test, no participant attained 80% of their age-predicted maximum heart rate during cycling ergometry (mean peak heart rate = 103.82 bpm) (table 28).

Table 28: Criteria for reaching maximal effort

	Treadmill with BWS (n=18/18) [a]	**Cycle ergometer** (n=15/18) [a]	Between group differences (*p*)
HR_{peak} *(bpm)*	96.66 ± 16.78	103.83 ± 32.21	0.49
RER	0.98 ± 0.09	1.21 ± 0.15	≤0.001*
Predicted 80% of $APHR_{max}$ *(bpm)*	139.60 ± 5.00	140.47 ± 4.49	-
Criteria for reaching VO_{2max} *(n)*			
RER ≥1.0	8 (44.4%)	14 (100%)	-
80% predicted $APHR_{max}$ [b]	0	0	-

Expressed as means ± SD
*Denotes significant findings
[a] Total number of baseline and outcome test combined/total number of participants
[b] Equation: 220 – (0.7 x age) x 0.8
Abbreviations
bpm beats per minute **BWS** body-weight support **HR_{max}** maximum heart rate **mL/kg/min** millimetres per kilogram of body weight per minute **mL/min** millimetres per minute **RER** respiratory exchange ratio **VO_{2peak}** peak aerobic capacity

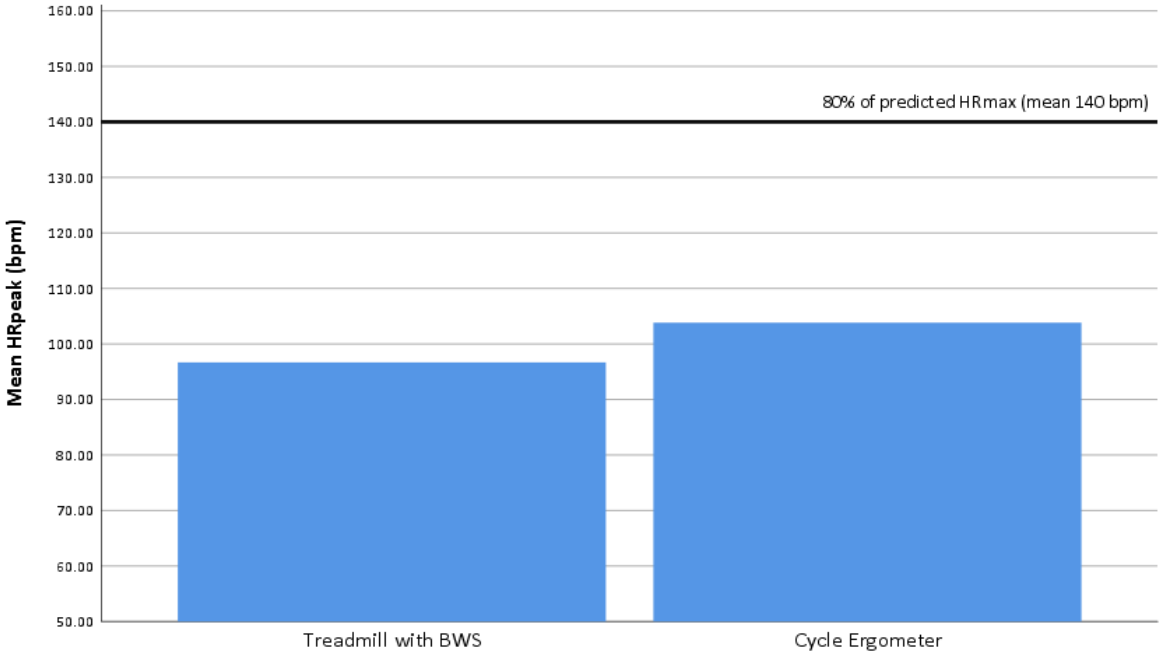

Figure 23: A bar graph illustrating the mean peak heart rate, displayed by CPET mode[3]

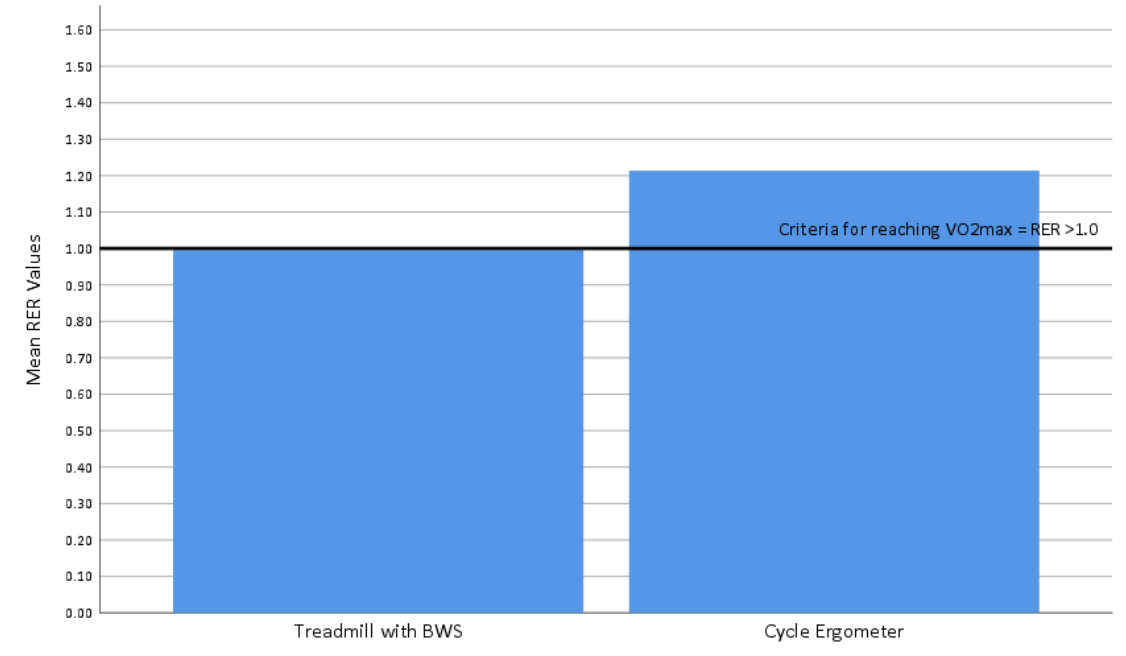

Figure 24: A bar graph illustrating the mean respiratory exchange ratio achieved by participants, displayed by CPET mode[4]

[3] *The mean value for 80% of predicted heart rates from the equation: 220 – (0.7 x age) (140 bpm), is illustrated by the solid black reference line.*

[4] *The criteria for reaching VO_{2peak} is a respiratory exchange ratio of more than 1.0 (34) as illustrated by the solid black reference line.*

A paired *t*-test was conducted to test for differences in values of respiratory exchange ratio and peak heart rate, between treadmill with BWS and cycle ergometry CPET protocols. A statistically significant difference was found between respiratory exchange ratio values (CI = -0.33 to -0.13), but not for peak heart rate (CI = -29.07 to 14.76).

Reasons for test termination

Table 29 summaries the reasons for CPET termination. No participant terminated the test because of actual maximal effort (a respiratory exchange ratio of more than one and/or 80% of age-predicted maximum heart rate) or because of perceived maximal effort (e.g. RPE of more than 17). For CPET undertaken on the treadmill with BWS, the most common reason was the inability to maintain speed (33%). Leg fatigue was the most common reason for test termination CPET undertaken on the cycle ergometer (53%). For one participant on the cycle ergometer, the test was stopped by me when I observed to have become fatigued and struggled to hold onto the ergometer handlebars for balance with their non-affected arm.

Table 29: Reasons for test termination

	Treadmill with BWS (n=18)*	**Cycle Ergometer** (n=15)*
Stopped by tester	-	2 (13.3%)[a]
Breathlessness	3 (16.7%)	1 (6.7%)
Leg fatigue	3 (16.7%)	8 (53.3%)
Mask discomfort	2 (11.1%)	2 (13.3%)
Harness discomfort	3 (16.7%)	-
Unable to maintain speed (rpm/mph)	6 (33.3%)	2 (13.3%)
Pain	1 (5.6%)	-

*Baseline and outcome tests combined.
[a] I observed general fatigue in one participant; this was particularly in the non-affected arm from holding on to the cycle ergometer handlebars, which was required to maintain balance. One other participant experienced arthritic pain in the hip when in full flexion and did not want to begin the test.
Abbreviations
BWS body weight supported **CE** cycle ergometer **mph** miles per hour **rpm** revolutions per minute

Adverse events during CPET

No study-related adverse events or unanticipated adverse events occurred during CPET procedures. Although one participant, once seated on the ergometer, experienced arthritic pain in the hip when in full flexion and therefore, did not want to complete the test.

6.4.2 Cognitive health

Cognitive health was assessed by the MoCA, pre- and post-intervention. Table 30 is a summary of participants' scores at baseline and the change score to outcome.

The time taken to administer the MoCA ranged from 10 to 15 minutes. Three participants did not complete the MoCA at baseline and three did not at outcome. The proportion of non-completed scales was 16.7% at both baseline and outcome. Reasons for non-completed scales included one withdrawal from the study, refusal to complete (n = 3), did not have time to complete (n = 1) and because of communication impairments (n = 1).

For those who completed at least some of the MoCA, the proportion of missing data ranged between 16.7% and 33.3%. Item non-response was particularly prevalent from the language and delayed recall domains on the MoCA. This may be attributed to challenges providing verbal responses for those living with post-stroke communication difficulties and providing written responses, for those who had weakness or paresis on their stronger side. In addition, it appeared that fatigue and the time of day for which the MoCA was completed, also contributed to challenges for completion. There was a minor indication of some ceiling effects across global scores, however the small sample size of this study limits the interpretation of effects.

A paired *t*-test (n=15) was used to compare the global mean score scores of the MoCA, pre- and post-intervention. Mean baseline global scores were 22.13 ± 4.51 and mean outcome global scores were 21.86 ± 6.99. With a mean difference of -0.26 ± 5.83 (95% confidence interval -2.96 to 3.49), no significant difference in global MoCA scores from baseline to outcome was found *(p* = 0.86).

Table 30: Mean baseline MoCA scores and percentage change score at outcome, reported by intervention group

	Baseline				**Percentage change at outcome**			
	Intervention group allocation				Intervention group allocation			
	All (n=15)	Aerobic (n=7)	Strength (n=5)	Combination (n=3)	All (n=16)	Aerobic (n=7)	Strength (n=6)	Combination (n=3)
Total (max. 30 points)	22.13 ± 4.51	22.42 ± 2.87	19.80 ± 6.57	25.33 ± 1.52	- 3.43%	-5.17%	-8.83%	5.25%
Visuospatial/executive (max. 5 points)	3.93 ± 1.38	4.00 ± 1.41	3.80 ± 1.78	1.00 ± 1.00	-7.63%	-4.00%	26.32%	33.00%
Naming (max. 3 points)	2.93 ± 0.25	2.85 ± 0.37	3.00	3.00	-2.73%	-5.61%	0	0
Attention (max. 6 points)	4.33 ± 1.54	4.42 ± 1.13	3.60 ± 2.07	5.33 ± 1.15	-3.70%	-22.62%	18.33%	12.38%
Language (max. 3 points)	1.28 ± 0.82	1.25 ± 0.75	1.00 ± 1.15	1.66 ± 0.57	-42.19%	-16.00%	-166.00%	0
Abstraction (max. 2 points)	1.66 ± 0.48	1.42 ± 0.53	1.80 ± 0.44	2.00	10.84%	14.08%	0	16.50%
Delayed recall (max. 5 points)	2.85 ± 1.51	2.85 ± 1.86	2.50 ± 1.29	3.33 ± 1.15	25.26%	28.07%	40.00%	9.91%
Orientation (max. 6 points)	5.40 ± 1.18	5.57 ± 0.78	4.80 ± 1.78	6.00	1.30%	8.98%	-5.21%	-5.50%

Expressed as means ± SD

Possible scores achieved on the MoCA range from 0 to 30, with higher scores indicating better cognitive function. A score of 26 or more is considered normal (279).

In line with the systematic review presented in chapter two, the relationship between cardiorespiratory fitness and cognitive health was explored. A Pearson correlation was calculated examining the relationship between VO_{2peak} values, obtained from CPET undertaken on the treadmill with BWS and global cognition scores, as measured by the MoCA. A weak positive correlation that was not significant was found (r = 0.27, p = 0.28) (figure 25).

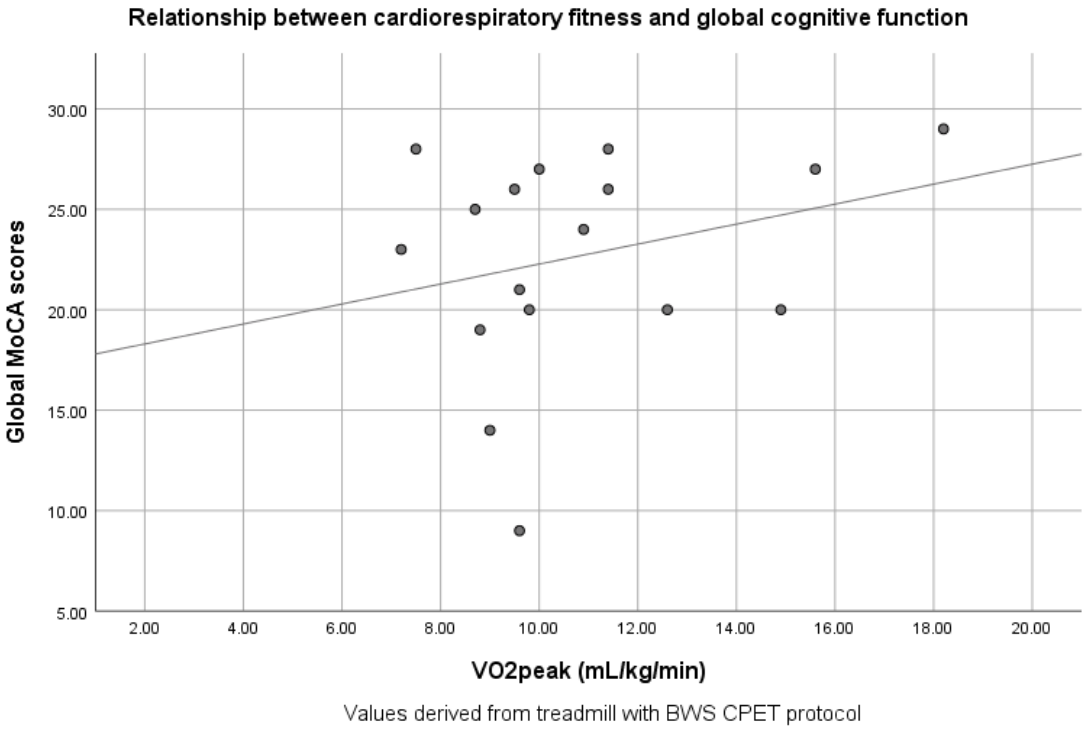

Figure 25: A scatter graph to show the relationship between total MoCA scores and relative VO_{2peak} values, derived from CPET undertaken on the treadmill with BWS

A Pearson correlation was calculated examining the relationship between VO_{2peak} values, obtained from CPET undertaken on the cycle ergometer and global cognition scores, as measured by the Montreal Cognitive Assessment. A weak negative correlation that was not significant was found (r = -0.08, p = 0.78) (figure 26).

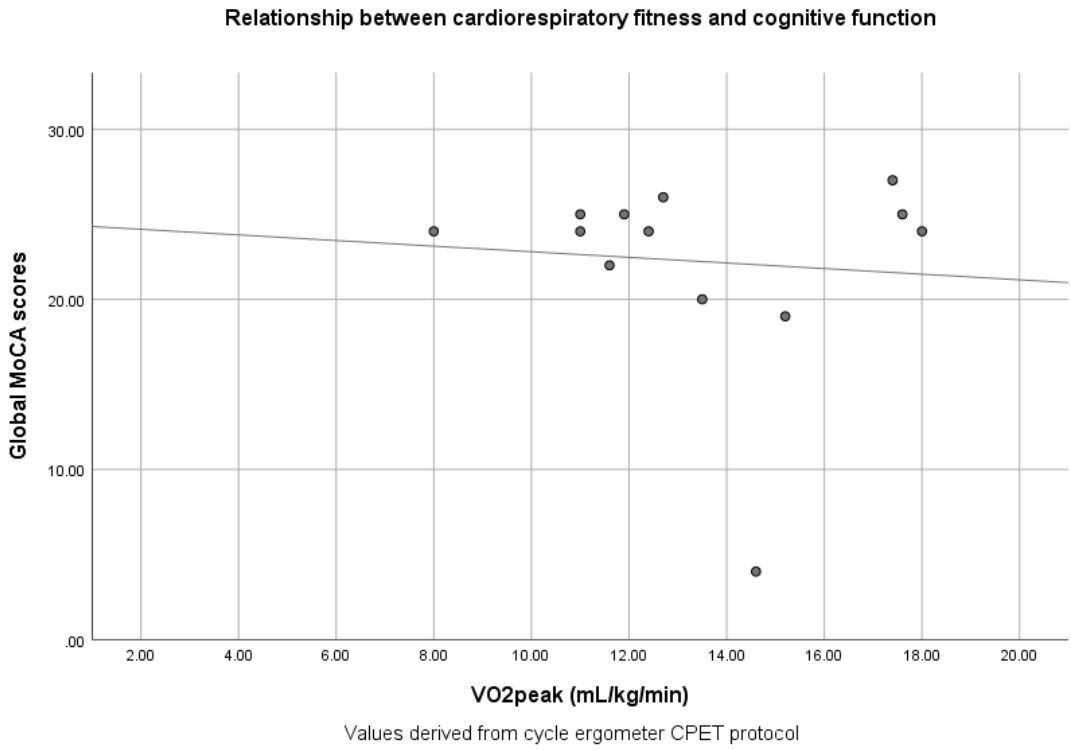

Figure 26: A scatter graph to show the relationship between total MoCA scores and relative VO_{2peak} values, derived from CPET undertaken on the cycle ergometer

6.4.3 Quality of life

Quality of life was assessed by the SSQoL questionnaire, pre- and post-intervention. Table 31 is a summary of participants' scores at baseline and the change score to outcome.

The time taken to administer the SSQoL questionnaire ranged from 15 to 25 minutes. Six participants did not complete the questionnaire at baseline (66.7%) and four at outcome (77.8%). Reasons for non-completed scales included withdrawal from the study (n = 1), communication impairments (n = 3), refusal to complete (n = 2), and non-return of questionnaire (n =4).

For those who completed at least some of the SSQoL, the proportion of missing data ranged between 22.2% and 38.9%. Item non-response was particularly prevalent in items corresponding to personality, self-care and social roles on the SSQoL questionnaire. Similar to the MoCA, reasons for non-completion of the SSQoL questionnaire included: challenges providing verbal responses, for those living with post-stroke communication difficulties and providing written responses for those who had weakness or paresis on their stronger side. In addition, the instructions for completing the SSQoL questionnaire using the five-point Likert-scale response categories, appeared to be unclear and, in some cases, misleading. Participants had difficulty in choosing a response on

the Likert-scale that they felt accurately reflected their views or abilities. No floor or ceiling effects were observed with the use of the scale in the present study.

A paired sampled *t*-test (n = 10) was calculated to compare the mean baseline score to the mean outcome score of the SSQoL questionnaire. The mean baseline was 126.10 ± 24.92 and the mean outcome score was 137.50 ± 40.22. With a mean difference of 11.40 ± 31.96 (95% confidence interval -34.26 to 11.46), there was no significant difference between baseline and outcome SSQoL questionnaire scores (p = 0.28).

Table 31: Mean baseline Stroke Specific Quality of Life scores and change score to outcome, reported by intervention group

	Baseline				**Change score to outcome**			
		Intervention group allocation				Intervention group allocation		
	All (n=12)	Aerobic (n=5)	Strength (n=4)	Combination (n=3)*	All (n= 10)	Aerobic (n=4)	Strength (n=4)	Combination (n=2)
Total	133.76 ± 41.84	121.60 ± 15.42	133.75 ± 43.16	149.00 ± 67.39	11.40 ± 31.96	11.50 ± 18.28	16.00 ± 25.04	2.00 ± 77.78
Energy	7.15 ± 3.43	6.40 ± 2.30	6.25 ± 2.98	9.00 ± 4.96	2.00 ± 2.30	1.00 ± 2.58	2.00 ± 2.16	4.00 ±1.41
Family roles	7.30 ± 3.14	6.80 ± 2.38	6.25 ± 2.87	9.00 ± 2.24	-1.20 ± 6.30	-1.00 ± 3.82	-2.25 ± 9.97	0.50 ± 2.12
Language	14.61 ± 7.48	15.40 ± 8.59	9.25 ± 6.50	19.00 ± 4.32	3.20 ± 5.78	3.00 ± 4.96	6.00 ± 8.87	-2.00 ± 0
Mobility	14.53 ± 9.34	9.80 ± 3.03	15.75 ± 8.65	19.25 ± 7.71	3.50 ± 5.58	5.25 ± 8.35	1.25 ± 2.21	4.50 ± 3.53
Mood	15.46 ± 5.65	13.60 ± 2.793	19.75 ± 3.09	16.50 ± 8.50	1.00 ± 4.80	-0.75 ± 3.77	0 ± 4.00	6.50 ± 6.36
Personality	10.58 ± 5.88	8.00 ± 3.31	15.75 ± 5.73	8.00 ± 6.24	1.00 ± 5.18	0 ± 4.24	-2.00 ± 0.81	9.00 ± 4.24
Self-care	13.61 ± 6.23	13.00 ± 5.52	10.75 ± 7.32	17.25 ± 5.67	-0.80 ± 8.10	3.50 ± 5.44	-2.75 ± 10.90	-5.50 ± 3.53
Social roles	10.16 ± 6.68	6.25 ± 1.50	11.50 ± 7.85	12.75 ± 8.26	3.30 ± 2.58	2.25 ± 1.25	4.75 ± 2.36	2.50 ± 4.94
Thinking	8.50 ± 4.37	7.00 ± 1.41	7.50 ± 5.80	11.00 ± 4.69	1.30 ± 3.33	0 ± 2.94	2.25 ± 3.20	2.00 ± 5.65
Upper extremity function	13.61 ± 6.07	15.40 ± 4.82	10..75 ± 6.94	14.25 ± 7.18	0.90 ± 5.54	-0.75 ± 6.60	2.00 ± 3.16	2.00 ± 9.89
Vision	12.15 ± 3.64	14.80 ± 1.78	12.25 ± 2.75	9.50 ± 5.00	-0.10 ± 2.55	0 ± 1.63	-2.00 ± 1.82	3.52 ± 0.70
Work/productivity	7.92 ± 4.03	8.40 ± 2.30	6.75 ± 5.67	8.50 ± 4.79	0.50 ± 2.41	-0.75 ± 0.50	2.50 ± 2.38	-1.00 ± 2.82

Expressed as means ± SD

6.4.4 Activities of daily living

Activities of daily living were assessed by the Barthel Index, pre- and post-intervention. Table 32 is a summary of participants' scores at baseline and the change score to outcome.

The time taken to complete the Barthel Index ranged from five to 10 minutes. The proportion of non-completed scales was 11.1% at baseline and 22.2% outcome. Reasons for non-completed scales included one withdrawal from the study, refusal to complete (n = 2), unreturned questionnaire (n = 1) and communication impairments (n = 2). For those who completed at least some of the Barthel Index, the proportion of missing data ranged between 11.1% and 33.3%. Item non-response was a particular issue for the 'stairs' item of the Barthel Index. No floor or ceiling effects of the Barthel Index were detected, however these findings should be interpreted with caution. Included participants in this study are living with the long-term consequences of stroke and therefore may not have the capacity to improve in activities of daily living.

A paired sampled *t*-test (n = 14) was calculated to compare the mean baseline score to the mean outcome score of the Barthel Index. The mean baseline was 62.50 ± 20.91 and the mean outcome score was 66.07 ± 23.46. With a mean difference of 2.69 ± 10.91 (95% confidence interval -9.91 to 2.77), there was no significant difference between baseline and outcome Barthel Index (p = 0.24).

Table 32: Mean baseline Barthel Index scores and change scores by intervention group

	Baseline				**Change score to outcome**			
		Intervention group allocation				Intervention group allocation		
	All (n=16)	Aerobic (n=7)	Strength (n=5)	Combination (n=4)	All (n=14)	Aerobic (n=6)	Strength (n=5)	Combination (n=3)
Total	62.81 ± 19.49	58.57 ± 21.93	61.00 ± 22.74	72.50 ± 8.66	3.57 ± 10.99	-2.50 ± 10.36	8.00 ± 11.51	8.33 ± 7.63
Feeding	5.93 ± 2.01	6.42 ± 2.43	5.00	6.25 ± 2.50	0.38 ± 1.38	0	1.00 ± 2.23	0
Bathing	1.87 ±3.09	2.14 ± 3.93	3.00 ± 2.73	0.00	0.71 ± 3.31	0 ± 3.16	0 ± 3.53	3.33 ± 2.88
Grooming	4.33 ± 2.58	5.00 ± 3.16	5.00	2.50 ± 2.88	-0.76 ± 2.77	-3.00 ± 2.73	0	1.66 ± 2.88
Dressing	4.66 ± 2.96	5.00 ± 3.16	4.00 ± 2.23	5.00 ± 4.08	0.38 ± 2.46	0	1.00 ± 2.23	0 ± 5.00
Bowels	8.66 ± 3.51	10.00	8.00 ± 4.47	7.50 ± 5.00	0.38 ± 3.20	-1.00 ± 2.23	2.00 ± 4.47	0
Bladder	7.66 ± 4.16	5.83 ± 4.91	8.00 ± 4.47	10.00	-0.38 ± 1.38	-1.00 ± 2.23	0	0
Toilet use	8.00 ± 3.68	7.85 ± 3.93	7.50 ± 2.88	8.75 ± 4.78	0 ± 2.04	0.83 ± 2.04	0	0-1.66 ± 2.88
Transfers	10.62 ± 3.59	10.00 ± 4.08	11.00 ± 4.18	11.25 ± 2.50	1.78 ± 2.48	1.66 ± 2.58	2.00 ± 2.73	1.66 ± 2.88
Mobility	10.31 ± 4.26	8.57 ± 4.75	11.00 ± 4.18	12.50 ± 2.88	0 ± 4.56	2.00 ± 2.73	-3.00 ± 4.47	1.66 ± 5.77
Stairs	3.92 ± 3.49	4.00 ± 4.18	2.00 ± 2.73	6.25 ± 2.50	1.25 ± 4.33	-1.25 ± 6.29	2.00 ± 2.73	3.33 ± 2.88

Expressed as means ± SD

6.5 Measures taken during exercise interventions

Appendix 28 includes a table of all the data collected during the exercise intervention, per participant, per exercise session.

6.5.1 Pre-exercise session

Prior to the exercise sessions, each participant underwent a pre-exercise screen to ensure their readiness to exercise that day; including resting measures of heart rate and blood pressure.

Table 33 displays participants' the mean resting heart rate prior to each exercise session, for each exercise intervention group.

Table 33: Pre-exercise resting heart rate (bpm), for each exercise intervention group

	Intervention group			
Exercise session	**All** (n = 17)	**Aerobic** (n = 7)	**Strength** (n = 5)	**Combination** (n = 5)
Session 1	69.94 ± 12.87	72.28 ± 8.34	70.80 ± 11.12	65.80 ± 20.06
Session 2	69.17 ± 13.34	73.28 ± 10.09	67.80 ± 8.16	64.80 ± 20.09
Session 3	70.27 ± 13.96	74.00 ± 13.06	71.16 ± 8.84	64.00 ± 20.00
Session 4	72.93 ± 15.04	76.85 ± 11.71	73.25 ± 15.12	67.20 ± 20.07
Session 5	73.77 ± 14.80	74.42 ± 9.94	73.83 ± 7.57	72.80 ± 26.64
Session 6	74.38 ± 16.35	74.71 ± 11.64	75.50 ± 13.83	72.60 ± 26.23
Session 7	72.94 ± 16.54	74.42 ± 15.69	73.40 ± 12.89	70.40 ± 23.38
Session 8	72.17 ± 14.84	71.85 ± 10.57	73.40 ± 9.34	71.40 ± 24.97
Session 9	70.35 ± 14.63	72.28 ± 14.94	70.20 ± 9.28	67.80 ± 20.51
Session 10	71.23 ± 15.45	73.42 ± 11.67	71.80 ± 15.73	67.60 ± 21.87
Session 11	69.64 ± 14.26	70.71 ± 11.07	68.60 ± 10.45	69.20 ± 22.73
Session 12	72.18 ± 15.26	79.00 ± 10.63	68.00 ± 10.77	68.20 ± 22.47
Range	62.00	50.00	44.00	62.00
Minimum value	40.00	52.00	58.00	40.00
Maximum value	102.00	102.00	102.00	102.00

Values expressed as mean ± SD (with the exception of range, minimum and maximum values)

Figure 27 illustrates the mean pre-exercise session resting heart rate measure, across all exercise sessions, for each exercise intervention group. The total range of pre-exercise session resting heart rate was 62.00 beats per minute (minimum = 40.00, maximum = 102.00).

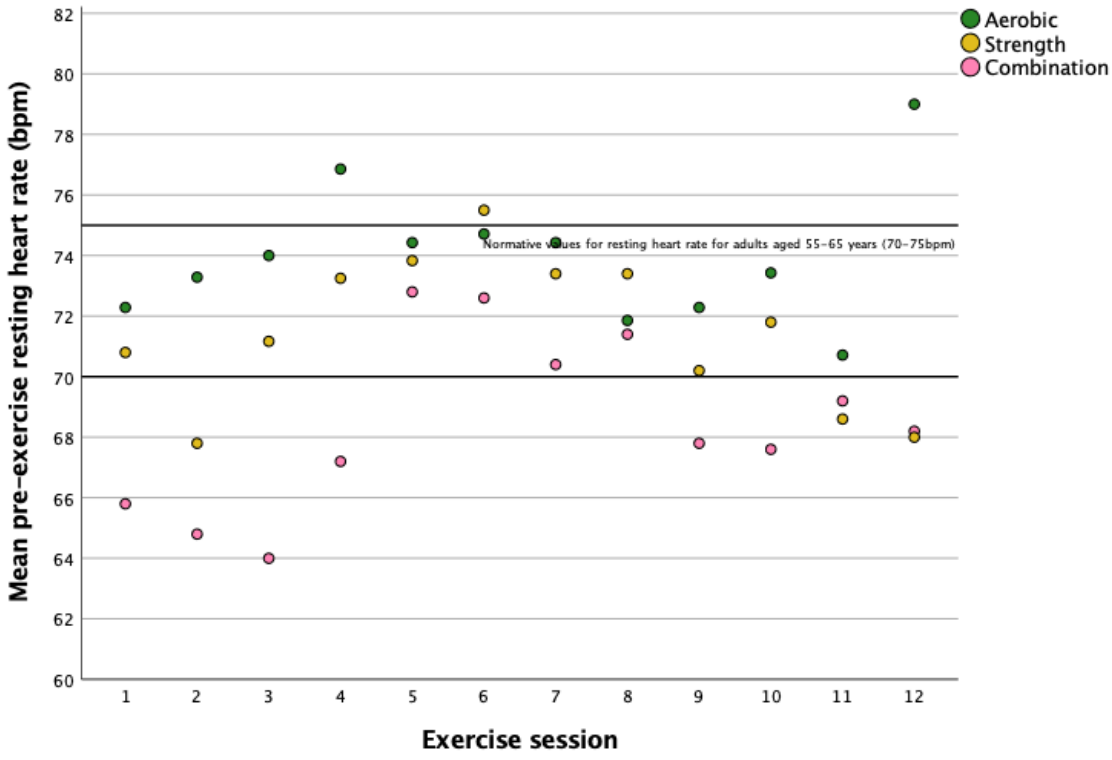

Figure 27: Mean pre-exercise session resting heart rate, for each exercise session

Table 34 displays participants' resting systolic blood pressure prior to each exercise session, for each exercise intervention group. Systolic blood pressure is recognised as an indicator of cardiovascular health, whereby elevated values are associated with increased cardiovascular and cerebrovascular disease risk (49). Pre-exercise systolic blood pressure may be used to determine safety to exercise at that time point and also for comparison with exercise blood pressure (50). For this reason, I have chosen to report systolic blood pressure values.

Table 34: Pre-exercise systolic resting blood pressure (mmHg), for each exercise intervention group

	Intervention group			
Exercise session	**All** (n = 17)	**Aerobic** (n = 7)	**Strength** (n = 5)	**Combination** (n = 5)
Session 1	145.11 ± 14.39	143.28 ± 14.81	134.66 ± 19.63	134.20 ± 11.81
Session 2	143.70 ± 15.41	140.71 ± 10.25	148.00 ± 24.04	143.60 ± 13.25
Session 3	139.00 ± 17.04	142.00 ± 16.55	134.66 ± 19.63	140.00 ± 17.23
Session 4	138.87 ± 13.15	137.28 ± 14.27	138.75 ± 10.50	141.20 ± 15.78
Session 5	138.58 ± 13.97	141.16 ± 15.94	134.50 ± 13.57	140.40 ± 13.92
Session 6	140.83 ± 14.75	138.28 ± 14.03	141.83 ± 14.49	143.20 ± 18.64
Session 7	136.94 ± 15.82	134.85 ± 15.56	140.40 ± 13.31	136.40 ± 20.94
Session 8	133.76 ± 11.55	136.71 ± 13.08	131.40 ± 13.95	132.00 ± 7.48
Session 9	137.94 ± 15.14	137.14 ± 14.58	135.00 ± 17.02	142.00 ± 16.61
Session 10	138.52 ± 12.77	144.00 ± 12.09	133.00 ± 13.49	136.40 ± 12.46
Session 11	135.41 ± 15.94	136.42 ± 12.88	127.60 ± 21.73	141.80 ± 12.91
Session 12	134.81 ± 10.70	134.16 ± 6.24	129.60 ± 15.82	140.80 ± 7.15
Range	76.00	55.00	76.00	57.00
Minimum value	102.00	109.00	102.00	115.00
Maximum value	178.00	164.00	178.00	172.00

Values expressed as mean ± SD (with the exception of range, minimum and maximum values)

Figure 28 illustrates the mean pre-exercise session resting blood pressure, across all exercise sessions, for each exercise intervention group. The total range of pre-exercise session resting systolic blood pressure was 76.00 mmHg (minimum = 102.00, maximum = 178.00).

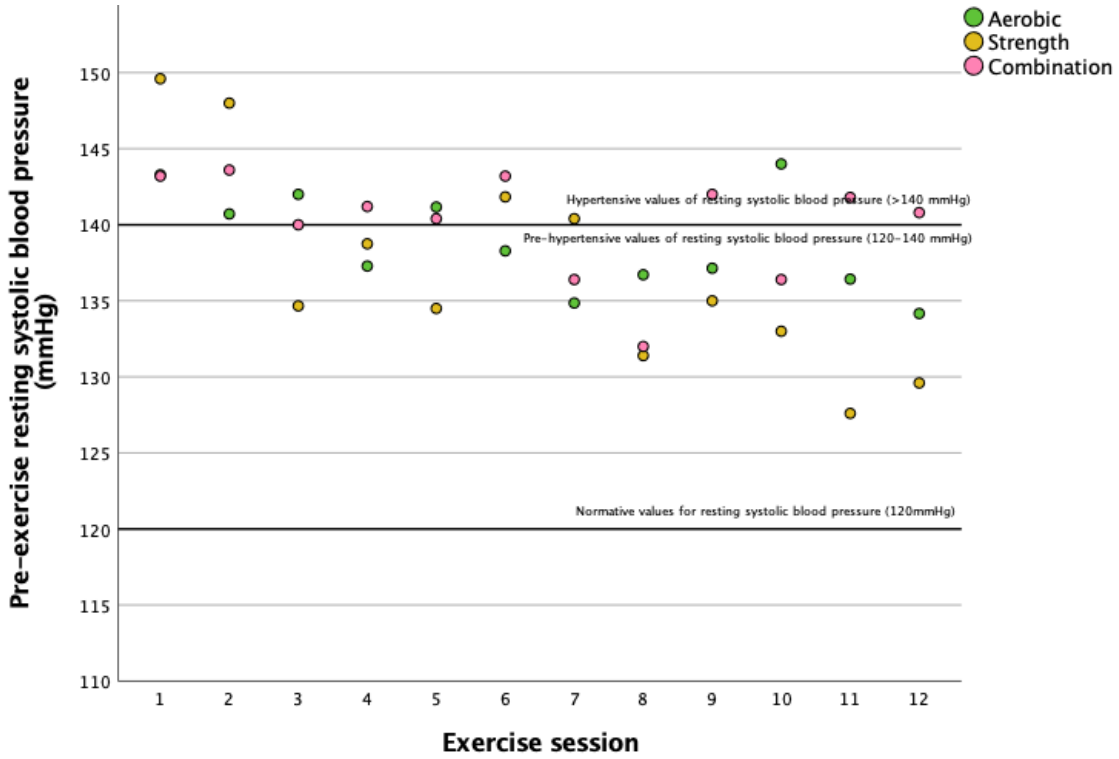

Figure 28: Mean pre-exercise session resting systolic blood pressure, for each exercise session

6.5.2 During exercise session

The following sections describe the data collected during exercise sessions.

Table 35 displays the data collected during exercise sessions, related to the feasibility of intervention delivery, such as number of sessions and number of exercises performed; and the fidelity of exercise prescription, such as peak heart rate.

Table 35: Data collected during the exercise sessions, for each exercise intervention group, related to the fidelity of the exercise intervention

	Intervention group			
	All (n = 17)	**Aerobic** (n = 7)	**Strength** (n = 5)	**Combination** (n = 5)
Total number of sessions attended/expected	199/204	83/84	56/60	60/60
Number of exercises performed	3.39 ± 1.04	3.02 ± 0.91	3.65 ± 1.04	3.62 ± 1.08
Number of exercises performed[a]	6.00	5.00	5.00	6.00
HR_{peak} (bpm)	107.35 ± 21.44	108.58 ± 19.63	112.25 ± 19.76	100.10 ± 24.40
HR_{peak} (bpm)[a]	158.00	145.00	79.00	109.00
% of age-predicted HR_{max} intensity achieved[b]	61.49 ± 11.07	62.95 ± 9.14	63.52 ± 10.02	56.88 ± 13.67
RPE_{peak} (Borg 6-20)	12.88 ± 1.44	13.21 ± 1.34	12.62 ± 1.77	12.88 ± 1.44
RPE_{peak} (Borg 6-20)[a]	11.75	7.67	11.75	11.75
% of prescribed intensity)[c]	88.89 ± 9.93	91.15 ± 9.27	87.08 ± 12.21	87.41 ± 7.89
Time spent exercising (mins)	22.50 ± 10.50	24.52 ± 11.37	20.25 ± 12.50	20.59 ± 7.03
Time spent exercising (mins)[a]	43.00	43.00	40.00	32.00
Number of sets performed	3.52 ± 2.14	-	4.26 ± 2.97	2.96 ± 1.05
Number of repetitions performed	9.29 ± 3.89	-	7.75 ± 2.53	9.30 ± 3.28

Values expressed as mean ± standard deviation, unless stated otherwise
[a]Values expressed as range
[b]220 – (0.7 x age)
[c]Exercise was prescribed at a RPE of 14-15. Percentage scores are out of 14.5
Abbreviations
HR_{peak} Peak heart rate **mins** minutes **RPE_{peak}** Peak rating of perceived exertion

Heart rate

Participants wore heart rate monitors throughout each exercise session to monitor safety and exercise intensity. Participants, on average, performed three activities per session. The peak heart rate during each activity was recorded. I calculated the mean of all activities per session, to provide an overall peak heart rate for each of the 12 exercise sessions. To account for missing data, the mean peak heart rate for each intervention week was calculated, providing six data points for each participant (figure 27).

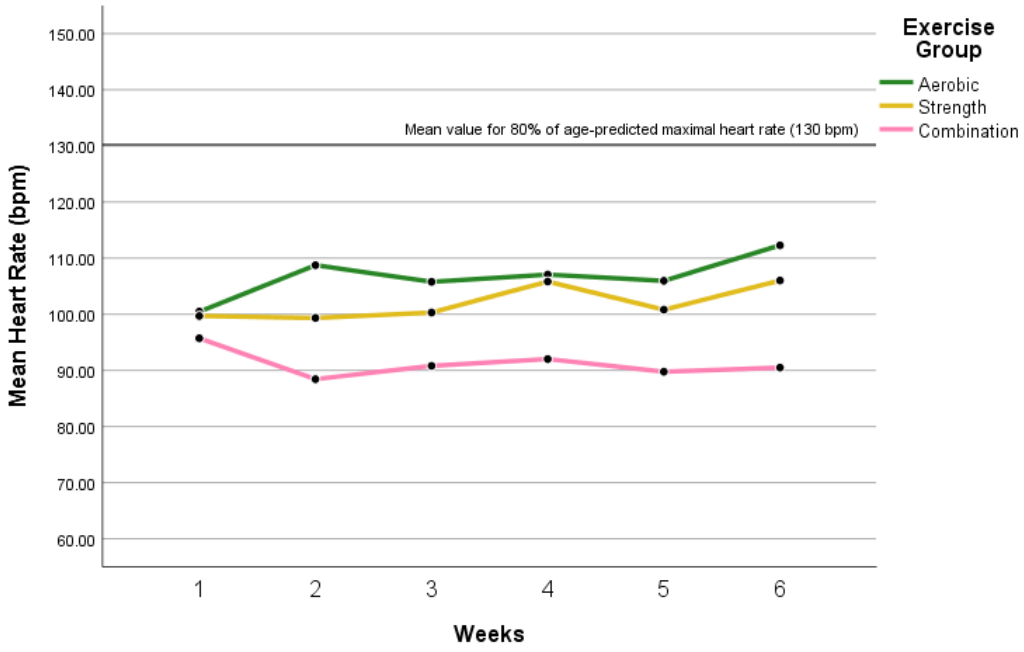

Figure 29: A line graph to show the mean heart rate for each exercise group, per week of the exercise intervention[5]

Overall, the highest values of peak heart rate were observed in the aerobic intervention group. This group also had the greatest range in peak heart rate (145.00 bpm). It was more likely that participants in this group would perform continuous cycling (or similar) for the duration of the session. The combination intervention group was found to have the lowest mean peak heart rate over the intervention. This may be a result of alternating aerobic and strength exercises, serving as an active recovery period. The sporadic results reported across the intervention for the strength exercise only groups may be attributed to the type of exercise performed and whether or not it

[5] *Data is reported per week of the exercise intervention. Eighty percent of the age predicted maximal heart rate was calculated by: (208 – (0.7 x mean age of sample)) x 0.8*

activated larger muscle groups, such as sit-to-stands or squats, as opposed to smaller upper extremity movements.

% of prescribed intensity achieved (via heart rate)

Overall, participants in the aerobic group exercised at approximately 63% of their age-predicted peak heart rate (220 - (age x 0.7). For the strength group, participants exercised at approximately 64% and for those in the combination group, this was 57%. Similar values were also observed when exploring what percentage of prescribed intensity participants achieved, relative to their peak heart rate when they undertook baseline CPET. This was 65%, 62% and 53% for aerobic, strength and combination groups, respectively. The intensity that participants achieved on average throughout the intervention adhered to what was intended: 40% to 70% of peak heart rate.

Ratings of perceived exertion

Participants were asked to describe their peak RPE, from the Borg 6 to 20 Scale (343) at the peak of each exercise they performed in every session. To account for missing data, as for peak heart rate, I calculated mean peak RPE for the overall session and for each intervention week, the latter providing six data points for each participant (figure 28).

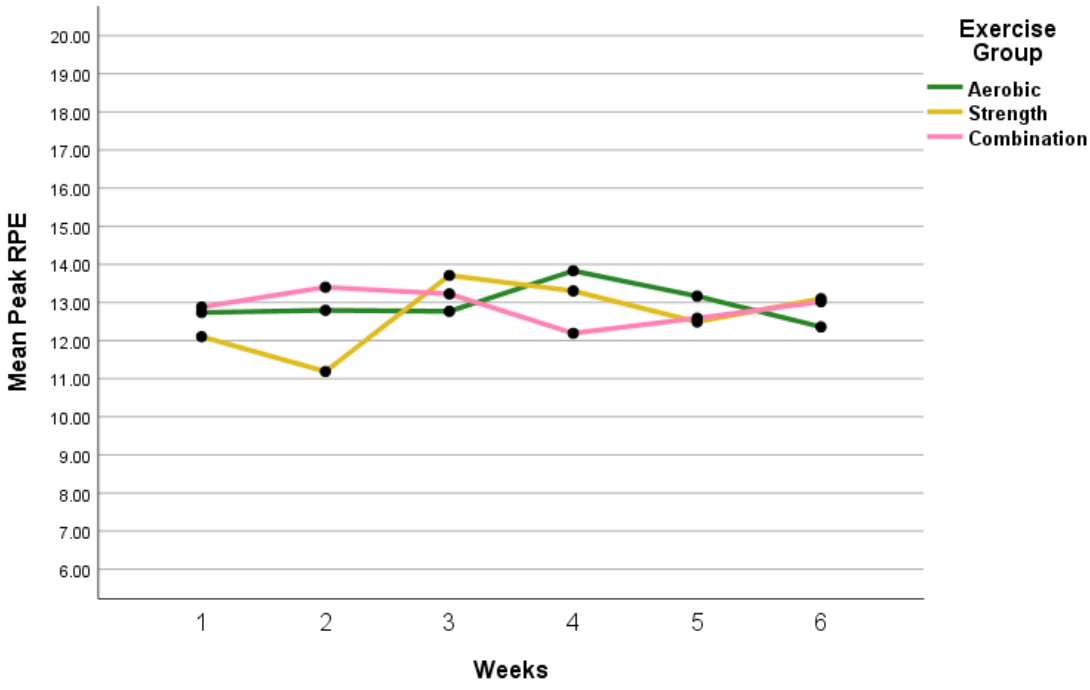

Figure 30: A line graph to show the mean peak RPE for each exercise group, for each week of the exercise intervention

Participants' peak RPE was similar across intervention groups. Values were within the prescribed range of 10 to 11 at the beginning of the intervention and aligned with the progression of up to 14 to 15 towards the end of the intervention (51). The aerobic exercise group had the smallest range of RPE values (7.67), with a slightly larger range in strength and combination groups (11.75 for both).

% of prescribed intensity (via RPE)

Across all three groups, participants' RPE was approximately 13 on the Borg 6 to 20 Scale. This means that those allocated to the aerobic exercise group were exercising at 91% of their prescribed exercise intensity (via RPE). For the strength and combination groups, this was 87%.

Time spent exercising

Across the exercise groups, the mean time participants spent exercising was 25 minutes, 20 minutes and 21 minutes for aerobic, strength and combination exercise intervention groups, respectively. The range in minutes of exercise time was similar across the groups: aerobic exercise (43 minutes; minimum = 5 minutes, maximum = 48 minutes), strength (40 minutes; minimum = 5 minutes, maximum = 45 minutes) and combination (32 minutes; minimum = 7 minutes, maximum = 39 minutes). 6.5.3 Post-exercise session

Post-exercise, measures of heart rate and blood pressure were recorded. This was to ensure participants were adequately 'warmed down' and haemodynamic values had returned to individual resting values. Table 36 displays the mean resting heart rate post-exercise session, for each exercise intervention group.

6.5.3 Post-exercise session

Post-exercise, measures of heart rate and blood pressure were recorded. This was to ensure participants were adequately 'warmed down' and haemodynamic values had returned to individual resting values. Table 36 displays participant's the mean resting heart rate post-exercise session, as per exercise intervention group allocation.

Table 36: Post-exercise resting heart rate (bpm), for each exercise intervention group

	Intervention group			
Exercise session	**All** (n = 17)	**Aerobic** (n = 7)	**Strength** (n = 5)	**Combination** (n = 5)
Session 1	78.62 ± 14.93	79.71 ± 9.35	79.49 ± 15.10	75.75 ± 24.91
Session 2	74.64 ± 15.25	75.57 ± 8.14	74.80 ± 5.80	73.20 ± 28.17
Session 3	76.88 ± 13.27	78.85 ± 9.35	79.83 ± 10.16	70.60 ± 20.47
Session 4	76.37 ± 15.23	81.14 ± 7.44	79.75 ± 17.68	67.00 ± 19.79
Session 5	78.50 ± 14.98	79.85 ± 7.90	82.00 ± 12.26	72.40 ± 24.58
Session 6	77.68 ± 11.09	81.57 ± 5.91	81.60 ± 9.63	66.00 ± 13.36
Session 7	78.58 ± 13.86	78.42 ± 9.43	83.20 ± 11.62	74.20 ± 21.20
Session 8	81.43 ± 13.15	78.57 ± 10.70	84.20 ± 13.49	83.00 ± 18.92
Session 9	77.64 ± 15.73	77.85 ± 11.17	82.20 ± 9.47	72.80 ± 25.66
Session 10	79.00 ± 13.24	80.42 ± 7.18	83.40 ± 11.61	72.60 ± 20.26
Session 11	78.27 ± 13.63	80.42 ± 6.29	80.00 ± 10.31	73.20 ± 23.09
Session 12	83.50 ± 14.98	86.66 ± 13.73	85.00 ± 11.78	78.20 ± 20.36
Range	46.89	15.92	26.18	46.89
Minimum value	54.83	71.58	68.82	54.83
Maximum value	101.73	87.50	95.00	101.73

Values expressed as mean ± SD (with the exception of range, minimum and maximum values)

Figure 31 illustrates the mean post-exercise session resting heart rate, across all exercise sessions, by exercise intervention group. The total range of post-exercise session resting heart rate is 46.89 beats per minute (minimum = 54.83, maximum 101.73).

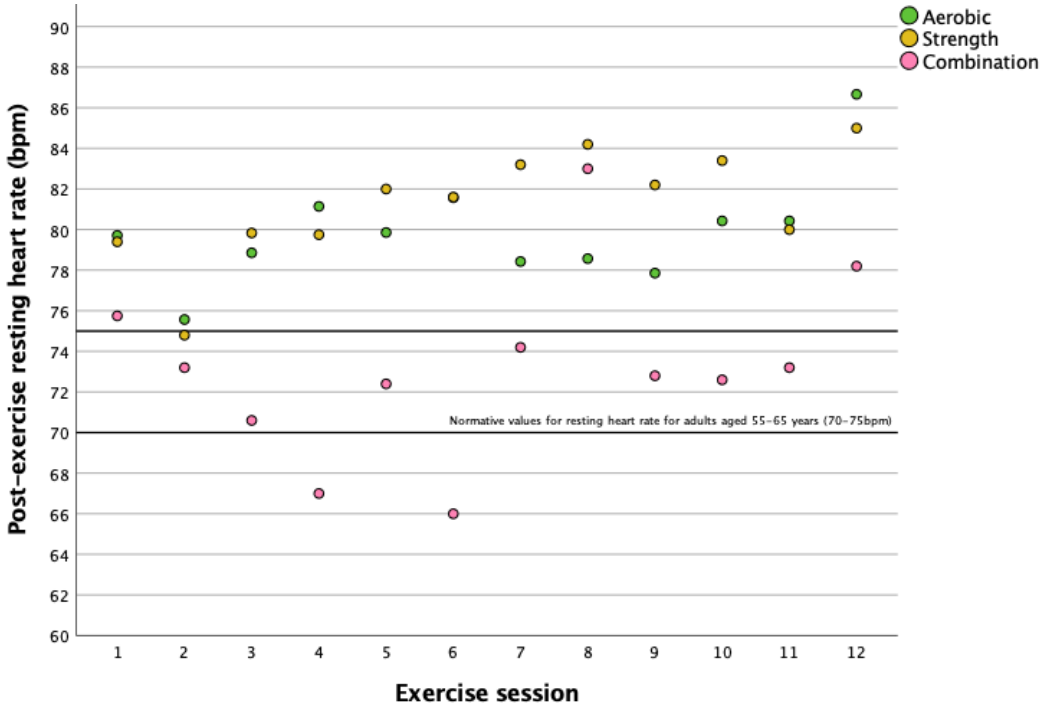

Figure 31: Mean post-exercise session resting heart rate, for each exercise session

Table 37 displays participants' resting systolic blood pressure post-exercise session, for each exercise intervention group.

Table 37: Post-exercise mean resting systolic blood pressure (mmHg), for each exercise intervention group

	Intervention group			
Exercise session	**All** (n = 17)	**Aerobic** (n = 7)	**Strength** (n = 5)	**Combination** (n = 5)
Session 1	135.37 ± 12.64	137.00 ± 10.86	136.80 ± 19.75	130 .75 ± 2.36
Session 2	137.58 ± 15.48	134.14 ± 10.85	131.40 ± 18.60	148.60 ± 14.70
Session 3	131.50 ± 11.05	129.85 ± 7.49	132.66 ± 15.94	132.40 ± 10.45
Session 4	133.31 ± 10.63	132.42 ± 8.65	130.50 ± 9.46	136.80 ± 14.82
Session 5	133.94 ± 9.35	135.71 ± 6.23	126.50 ± 8.93	140.40 ± 8.56
Session 6	132.93 ± 16.15	133.14 ± 17.22	129.60 ± 12.42	136.75 ± 21.63
Session 7	132.94 ± 15.98	132.85 ± 8.62	127.80 ± 14.58	138.20 ± 25.10
Session 8	128.31 ± 10.47	127.42 ± 11.70	134.60 ± 8.44	122.00 ± 7.70
Session 9	131.52 ± 10.93	133.42 ± 10.59	127.80 ± 13.57	132.60 ± 10.01
Session 10	128.29 ± 7.51	129.85 ± 5.95	126.60 ± 10.95	127.80 ± 6.68
Session 11	132.41 ± 13.11	127.85 ± 7.79	132.20 ± 15.83	139.00 ± 15.98
Session 12	125.75 ± 19.80	130.33 ± 14.13	116.20 ± 30.01	129.80 ± 12.39
Range	78.00	49.00	65.00	67.00
Minimum value	104.00	112.00	104.00	115.00
Maximum value	182.00	161.00	169.00	182.00

Values expressed as mean ± SD (with the exception of range, minimum and maximum values)

Figure 32 illustrates the mean post-exercise session resting blood pressure, across all exercise sessions, and exercise intervention groups. The total range of post-exercise session resting systolic blood pressure is 78.00 mmHg (minimum = 104.00, maximum 182.00).

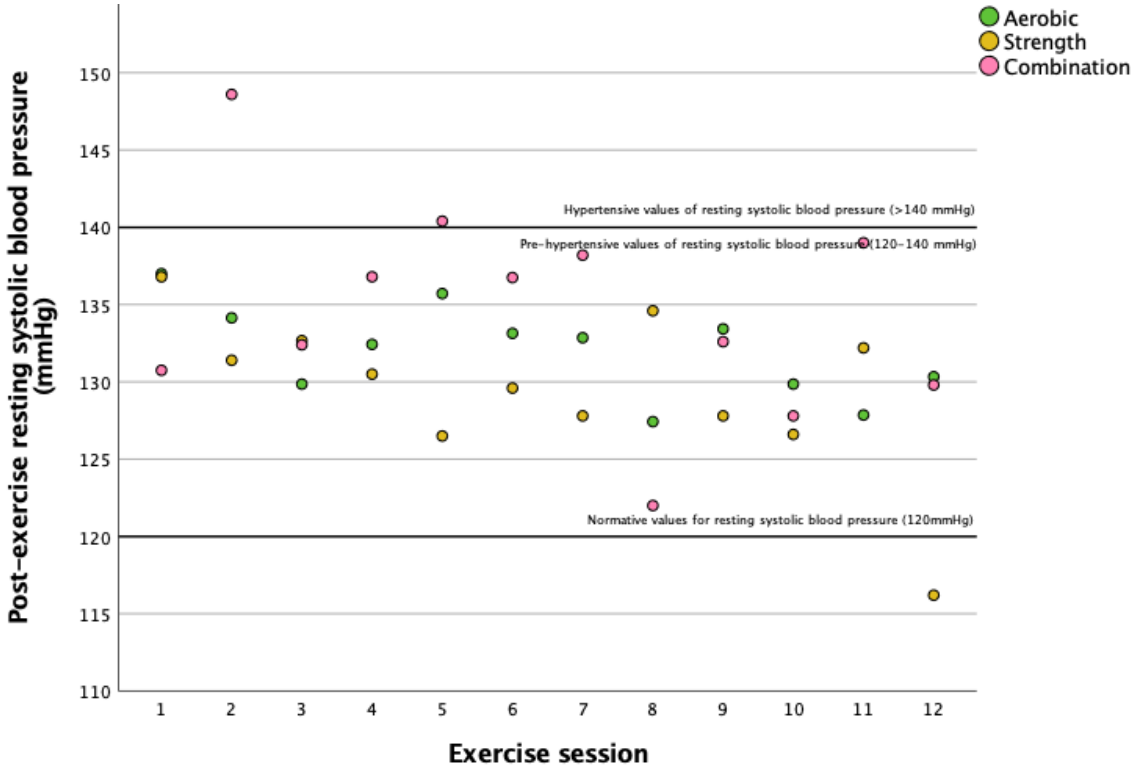

Figure 32: Mean post-exercise session resting blood pressure, for each exercise session

6.5.4 Adverse events during intervention

Throughout the intervention, no study-related adverse events or unanticipated adverse events occurred. As described earlier in the chapter, one participant (strength intervention group) was withdrawn after five sessions, as a result of a non-study related, serious adverse event that required hospitalisation.

6.5.5 Intervention delivery adaptations

Throughout the period of data collection, barriers of exercise participation were identified. For some participants, their level of physical disability precluded their ability and access to some modes of exercise training. As a result of this, and in order to continue and progress, some adaptations to the delivery of some activities had to be adapted. Table 33 details barriers identified by participants and the research team.

Table 38: Barriers identified by participants and the research team throughout the delivery of the exercise intervention and their recommended adaptation

Barriers identified	Adaptations
Holding on to ergometer handles (As a result of reduced grip strength on hemi-paretic side)	Use of a hand fixation with wrist cuff, to aid in grip
Sitting on the rowing machine (As a result of impaired sitting balance and/or the inability to flex sufficiently at the hip and knee to be seated)	Removing the seat and slide mechanism, so that a participant is able to remain seated in their wheelchair or on a chair, with their feet strapped into feet rests. The arm rests of the wheelchair were also removed so that the rowing technique was not restricted.

6.6 Qualitative findings

The following sections report the findings of the embedded, qualitative sub-study. As described in the methodology, findings are reported in line with the COREQ checklist for qualitative studies (382) (appendix 20).

6.6.1 Participant characteristics

Six participants were purposively sampled to ensure a range of perspectives were considered including past experience of formal exercise training, time since stroke, intervention group and order of exercise testing (appendix 29). All participants were interviewed alone, with the exception of one, where their carer was also present. Interviews lasted for a mean of 29.28 ± 10.80 minutes. The following commentary provides a brief description of each participant who took part in an interview (all names are pseudonyms).

Jane is 69 years old and experienced a haemorrhagic stroke nine months ago. She is able to walk less than 10 meters with a quad stick and an aid but is mainly wheelchair dependent. This is because of severe arthritis in her knees and a hip replacement three months prior to study enrolment. Before her stroke, Jane was a regular gym-goer.

John is 66 years old and experienced a haemorrhagic stroke 15 months ago. He is able to walk short distances with two sticks and the support of one person. John previously engaged in regular exercise at the gym.

Joe is 69 years old and experienced a haemorrhagic stroke 13 months ago. Joe lives alone and is able to walk short distances with the use of a Rollator frame. Pre-stroke, Joe described his physical activity levels to be moderate, but with limited experience of formal exercise.

Paul is 58 years old and experienced an ischaemic stroke four years ago. He walks short distances with a stick and has very limited movement in his left arm and hand. Paul lives alone but with help from family. Prior to the stroke, he had a very active job and swam weekly.

Mary is 54 years old and experienced a haemorrhagic stroke over 15 years ago. She is now living with moderately severe aphasia and walks short distances with a stick. Mary described her pre-stroke physical activity levels to be moderate. Since the stroke, her only exercise participation has been in the form of physiotherapy.

David is 77 years old and experienced an ischaemic stroke 11 months ago. He is now mainly wheelchair dependent but can walk less than 10 meters with a quad stick and an aid. David's pre-stroke activity levels were light, and he has had no experience of a gym or formal exercise training.

6.6.2 Themes

Themes that emerged from the qualitative sub-study were organised into two overarching categories: participants' experience of CPET and participants' experience of the exercise intervention. From the data, a third category was formulated: 'moving forward'.

In relation to participants' experience of CPET, three main themes were identified: (1) **Readiness**, (2) **Competence** and (3) **Intimidation**. Four themes were identified in relation to participants' experience of the intervention: (1) **Enjoyment**, (2) **Belonging**, (3) **Motivation** and (4) **Achievement**. The 'Moving Forward' category encompasses the idea that participants aspired to continue exercising following the EXERCISES study.

Table 34 details the three categories and provides a summary of higher-order themes and sub-themes for each. The final column is an illustrative quote from the interview data.

Table 39: Summary of higher-order themes and sub-themes identified from the interview data, supported by direct quotations from participants

Higher-order themes	Sub-themes	Supporting quotation
Experiences of CPET *"Once you get into it [cycling], it was easier. I was on it for 7 minutes."*		
Readiness	• Preparedness • Information giving	*"To hold the mask on [my face] and to see it was comfortable. I think if I hadn't seen it, there might have been a strong possibility I would have panicked, because it's really closed in."*
Competence	• Confidence in ability • Safety facilitated by rapport • Dissonance in achievement	*"[The bike] was easier than I thought."*
Intimidation	• Apprehension • Medicalised characteristics	*"I was hoisted up on to the bike. Horrible… I felt I was just a load."*
Experiences of the intervention *"[Exercise] it's beneficial. In that time, you get to meet a few people anyway, which gives you confidence you're not the only one."*		
Enjoyment	• Enthusiasm • Social atmosphere	*"It was good. Gave me something to look forward to"*
Belonging	• Relatedness • Camaraderie	*"There was about four other people in there as well. We all sort of encouraged each other on… It was really nice. Can get a bit dreary on the cycle and they say, 'Come on, you can do it!'"*
Motivation	• Desire to improve • Social connectedness • To provide vicarious experiences	*"I just want to get better. If I can get better myself then I know other people can, you know? It will help others and they'll think, well if he can do it, I can do it! That's my attitude."*
Achievement	• Recognition of self-improvement • Increases in confidence	*"I can sit and stand up more easier now than I could. That was bit of a problem in the beginning, I think. I couldn't get up, could I? My balance wasn't that good. I think I've achieved that, and I think I achieved it quite quickly as well."*
Moving forward *"It's made me want to improve. Keep the improvement up."*		
Loss	• Duration • Routine	*"It's left a void… miss it yeah"*
Aspirations	• Accomplishment • Determination	*"I definitely need to do something. I don't wanna end up in a wheelchair."*
Barriers	• Accessibility • Impact of stroke	*"For people with strokes, gyms won't let them [exercise] because they don't know how to cope."*

The following sub-sections describe high-order themes and sub-themes in more detail, supported by direct quotations from participants.

Experiences of CPET

Participants were asked to recall their experience of both modes of CPET at baseline and at outcome. In the interviews, none of the participants expressed a preference over the treadmill with BWS or the cycle ergometer, as a CPET mode.

Three key themes were identified: (1) **Readiness** and (2) **Competence** and (3) **Intimidation**.

Readiness

The theme of *readiness* encapsulates feelings of preparedness for undertaking CPET and highlights the importance of information giving. Participants reflected on the early stages of study enrolment. Participants said that they felt well-informed and knowledgeable about what to expect on the day, thus actual experiences were in line with previous expectations. Comments from participants suggested there was a sense of readiness for undertaking CPET.

> *"Allie had said what's going to happen. She talked about the mask over my mouth, which I think measures how much my oxygen intake is under exercise.'* – **John**

Priming participants with knowledge about the equipment used and procedures during CPET was important. This appeared to ease any anxieties or apprehension. Participants appeared to be appreciative of the time taken to be shown a video of two stroke survivors mimicking CPET procedures. At home-visits, they were able pleased to experience some apparatus prior to the test, such as the mask.

> *"To hold the mask on [my face] and to see it was comfortable. I think if I hadn't seen it, there might have been a strong possibility I would have panicked, because it's really closed in."* – **Mary**

Competence

The theme of *competence* captures a participant's increase in confidence to exercise safely. It highlights how their ability during CPET surpassed their own expectations and how this accomplishment boosted their confidence when starting the exercise intervention.

For most participants, conventional exercise apparatus that is not adaptable to their needs was expressed as a reason for not engaging in exercise training post-stroke. However, participants' ability to sit on the cycle ergometer or to step up and stand on the treadmill with BWS (in most cases from a wheelchair) during CPET, proved they could overcome this barrier. Achievements in using exercise apparatus they initially perceived to be inaccessible, allowed participants to identify a sense of security regarding their own physical potentials.

"I was surprised that I was able to get on the treadmill, because I thought there's no way I'm going to get on that. I was quite surprised how you got me on it." – ***Jane***

Not only were participants surprised by their ability to use exercise apparatus, they also exceeded their expectations regarding exercise performance. Some found cycling to be easier than previously imagined.

"Once you get into it [cycling], it was easier. I was on it for seven minutes!" – **Joe**

However, there was some dissonance in the level competence participants felt towards what they expected to achieve during CPET and what they actually achieved.

"Well, in terms of measuring what I was capable of doing, I didn't feel I was pushed." – **John**

Furthermore, some expressed disappointment that they were unable to reach what they felt to be their maximum performance.

"*From my point of view, I was quite disappointed that I did 13 minutes [on the treadmill]. I thought, 'My God, I could improve a lot more than that!'"* – **Joe**

Participants' increase in competence was facilitated by the relationship and rapport they developed with the research team. The expertise of the research team was made known to the participants, with the aim of reducing apprehension and to create a safe environment to build confidence while exercising.

"I was quite happy with their abilities." – **Mary**

"Yes, totally safe. If I had any problems, they'd make sure I'm okay, made sure I'm safe." – **Paul**

Intimidation

Key aspects highlighted within the theme of *intimidation* included apprehension and the medicalised characteristics of CPET.

Some participants appeared to have felt, understandably, apprehensive and nervous prior to CPET. There appeared to be a lack of confidence in what they felt they could achieve. There was an acknowledgement of physical limitations that influenced one's self-perceived ability, particularly in regard to walking on the treadmill.

"Initially, I was a bit apprehensive... My walking has been affected. I have drop foot and my ankle is very weak. My brain can't cope with slopes - I go into Eddie the Eagle mode. So, on the treadmill I was thinking, 'Oh shit! I'm going to fall flat on my face!' " – **Mary**

The somewhat 'medical' setting of the MoveEx Lab, contributed to feelings of intimidation. Negative responses that were reminiscent of experiences in hospital occurred in relation to the some of the equipment used for CPET, in particular the face mask.

"The mask like reminds you of instantly when you're in hospital, I didn't like that." – **Joe**

This study emphasised the inclusion of those with severe movement impairments and the increase of accessibility to exercise equipment. This was achieved with the use of turntables or hoists. In some cases, participants were hoisted out of their wheelchair and on to a cycle ergometer, or the BWS harness on the treadmill was used to facilitate stepping up. For some participants, this allowed a sense of achievement and they were pleased to be able to use exercise apparatus they may have not usually been able to. However, for another, use of the hoist withheld their autonomy, created a sense of dependency and lack of control.

"I was hoisted up on to the bike. Horrible… I felt I was just a load." – **David**

Summary of CPET Experiences

Although there were some apprehension prior to CPET, participants said they felt safe throughout the test. This appeared to be a result of the preparations made prior to the test and the rapport built with the research team. Participants' ability to complete an exercise test surpassed their expectations, in terms of both using exercise apparatus and their performance. However, some

participants talked about personal limitations in that they did not feel they were pushed to their maximal capacity and felt they could achieve more.

Experiences of the intervention

When asked to recall their experience of the exercise intervention, participants emphasised their enjoyment of the intervention. This appeared to be a result of social interaction with others, a new-found confidence and from the recognition of their own achievements. From the interview data, four themes were identified with regards to participant's experiences of the exercise intervention: (1) **Enjoyment**, (2) **Belonging**, (3) **Motivation** and (4) **Achievement**.

Enjoyment

Enjoyment was a resounding theme for all participants who were interviewed. Most participants relayed enthusiasm and spoke about how the exercise training was something for them to look forward to.

"It was good. Gave me something to look forward to!" – **Paul**

For most, community physiotherapy had come to an end and they were left to their own independent rehabilitation activities. One said the intervention came along at the right time, and they were enthusiastic to get started, as the intervention provided them with the opportunity to advance their stroke rehabilitation. There appeared to be an eagerness and an excitement in attending exercise sessions.

"I was feeling a bit low, then your exercises came along which I really pleased with 'cos the physios had then finished, the community physio that is, which I think is a shame. I thought it was good timing that your thing then come on the scene. I was very pleased and I was looking forward to starting." – **Jane**

All participants drew on the positive influence the research team had over their experience of the exercise intervention. The supervised component of the exercise intervention was highlighted to be a contributor of enjoyment and a facilitator to attendance. Participants referenced the significance the research team had in encouragement and support throughout the intervention.

"I enjoyed it I'd come three times [a week]. I'd have been there all the time, the girls were great. I really enjoyed it." – **Joe**

Belonging

A common theme in the interviews was a sense of *belonging* with other participants. This theme captures elements of social, emotional and peer support, provided by the group. This also includes the sense of relatedness felt among participants.

Participants described how they were able to relate to each-other's experience of stroke. They valued the social opportunity, as it provided informal peer support. As a result, a sense of camaraderie was felt and there was a communal recognition of the value of exercise.

"[Exercise] it's beneficial. In that time, you get to meet a few people anyway, which gives you confidence you're not the only one." – **Jane**

"It definitely give you confidence 'cos you're out meeting people still and in the group with other patients". – **Paul**

The sense of relatedness was extended to relatives who also attended the intervention with participants. This social atmosphere was valuable in that they were able to benefit from informal support available from other relatives of participants who observed the exercise sessions.

"My brother-in-law was taking me up there and I think he got as much out of it as I did. He just likes sitting there and talking to people, you know?" – **Joe**

For the majority of participants, exercise sessions were delivered in the format of a group circuit. Participating in group exercise provided a social atmosphere for those attending. Participants talked about the confidence boost they received as a result of the positive peer support and encouragement given by others.

"There was about four other people in there as well. We all sort of encouraged each other on… It was really nice. Can get a bit dreary on the cycle and they say, 'Come on, you can do it!'" – **Paul**

Belonging as a theme is associated with the enjoyment of the intervention. This sense of community was of value to participants in that there was a fun, energetic environment. Elements of the social atmosphere also appeared to act as a motivator to continue participation.

Motivation

Analysis of interview data revealed a number of factors that motivated participants to continue taking part in the EXERCISES study. Overall, this theme captures the essence of participants' desire to improve and achieve their goals.

"When I first started, I said to Allie, I'm not a competitive person, I'm not competitive at all. But every week, you want to get better, you know? I think a competitive side of me was drawn out. Sort of within yourself, not that you were trying to beat someone else, it was just for you." – **Joe**

There was an emphasis on individual aspirations, in that the desire to improve and prevent further decline post-stroke was at the forefront in motivating participants to continue attending.

"*I don't want to spend all my time in this wheelchair."* – **David**

As previously stated, the felt sense of community and social connectedness with others fed participant's motivation to attend exercise sessions. Motivation was nurtured by encouragement and support from other participants.

"I miss it, yeah. It is everything… Getting out the house, doing the exercise, the people there."

– **David**

Participants welcomed the opportunity to exercise, not only for prospects of self-improvement, but because they felt they were able to help others. Allowing others to have vicarious experiences of success motivated individuals to participate.

"I just want to get better. If I can get better myself then I know other people can, you know? It will help others and they'll think, well if he can do it, I can do it! That's my attitude." – **Paul**

Some participants also valued the opportunity to contribute to stroke research.

"I didn't lose any motivation because I was working for Allie and stroke recovery. I was really pleased to be able to help 'cos I'm a UEA graduate. When it first came through, I would do anything to help UEA students. I was very open to help." – **John**

In addition, *achievement*, although termed as an independent theme, was also seen to be a motivator to attend the exercise intervention. Recognising their own accomplishments provided participants with the confidence to maintain momentum and reinforced the importance of exercising.

"I improved greatly from the first day. I really pushed myself to improve." – **Joe**

Achievement

Achievement as a theme encompasses participants' recognition of self-improvement. All participants felt they had improved in one or more outcomes post-intervention. They said they felt fitter, stronger and were able to undertake functional activities with a greater ease.

"Yes, I know my fitness has got better 'cos I can walk for longer. My one aim all the time I was in hospital was to get out and get on an exercise bike… I was always doing something I wanted to do every time." – **John**

"I can sit and stand up more easier now than I could. That was bit of a problem in the beginning, I think. I couldn't get up, could I? My balance wasn't that good. I think I've achieved that, and I think I achieved it quite quickly as well." – **Jane**

Consolidation from others was important to participants, to recognise how far they have come since enrolling in the EXERCISES study.

"My mother and sister said I was walking taller and not so bent over." – **Mary**

Most prominent within the interview data was increases in self-confidence. Self-confidence to exercise was facilitated by recognising individual achievements and improvements in outcomes. The dynamics of a group circuit exercise session also facilitated confidence among participants. One participant talked about how their attitude to exercise and recovery changed positively as a result of participating in the EXERCISES study. The intervention provided a safe environment for participants to progress and gain overall confidence within themselves.

"I think it gave me a lot of confidence in myself, you know." – **Joe**

When working towards a particular goal, knowledge of one's own ability boosted competency in performing an exercise or an activity. This is further supported by noticeable self-improvements in exercise or functional ability. Through the intervention, new strategies or skills were taught to empower participants to undertake new movements safely and confidently.

"It's given me the confidence when I do go up the steps again, to know that I've done it." – **Jane**

However, recognising achievement was not consistent across all participants. Some had the belief that the exercise intensity they were prescribed did not reflect what they felt to be attainable, therefore resulting in a sense of disappointment.

"I didn't feel I was pushed; I think I could have been pushed a bit more." – **David**

Others, although improvements in exercise outcomes were noticed, they commented that the duration of exercise intervention was not long enough to achieve their goals.

"I really pushed myself to improve, which I did. I improved on the rowing machine, I went up from I think level 2 or 3… And the last couple weeks I was on 10. I think if I'd been there a few more weeks I would I have done a full 10 minutes on [level] 10." – **Joe**

For participants, there was great value in regular feedback and in monitoring their progress. For some, they felt there was a lack of this, and more could be done to offer continual feedback about their achievements throughout the intervention.

"I thought I could have been pushed harder to increase my overall fitness really. There was never any targets set that I was expected to be set and that was a bit of a disappointment. I didn't have anything to aim for… A target set for me, rather than just keep going… Give 'em a goal! Say you've done this this week, next week we will be aiming to do this level, so there is time for it to sink in with the patient before they come." – **John**

Summary of intervention experiences

Participants emphasised their enjoyment of the exercise intervention. Their enjoyment fed into their motivation to adhere to the intervention, which was also facilitated by their felt-sense of camaraderie and relatedness, given the shared-purpose of stroke rehabilitation. Participants relayed feelings of a 'loss' when the EXERCISES study came to end. In turn, they frequently commented on their determination to continue exercising, based on recognising their own achievements in both confidence and functional ability. These themes are important parameters to consider when designing future intervention.

Moving forward

The interviews revealed participants' aspirations to continue taking part in formal exercise training, once their participation in the research project had come to an end. From this, the category,

'moving forward' was formulated. This theme encapsulates the previous themes derived from participants' experiences of the intervention, including enjoyment, confidence and achievement and how they each motivate individuals to move forward into future exercise training. However, individuals were aware of some barriers they face, including the availability of adaptive exercise apparatus to suit their needs.

Loss

When the EXERCISES study came to an end, participants relayed feelings of a '*loss'*. Participants made various statements about the duration of the intervention. They mainly revolved around it not being long enough. A sense of frustration was revealed when the intervention came to an end, as participants felt the duration of the intervention was not long enough for them to achieve their goals.

"It's left a void… miss it yeah" – **David**

Participants described how attending the exercise intervention became a part of their routine. It was also evident that attitudes towards exercise had changed and participants have begun to value the potential benefits exercise can have. The sense of loss and the desire to find something else to do, confirms how participants valued the social opportunity to be with others. This relates to the previous theme of enjoyment.

"A little bit lost if you know what I mean. It was a part of my week and in the future, it's gone so I feel like I need to think of something else to do." – **Paul**

Aspirations

Participants frequently commented on what they want to achieve next, demonstrating their determination and aspirations to move forward with exercise training.

"Next? Cycling, what I was doing with you. Generally getting my legs stronger, anything to get me walking again, anything. Something about my arm, I need to get this moving, so I'll try sort that out." – **Jane**

Participants were able to reflect on what they accomplished throughout the exercise intervention and look forward to maintaining it and even striving to achieve more. This particularly resonates with increased confidence.

"It's made me want to improve. Keep the improvement up, I still want to keep my weight down."

– **Paul**

As referred to earlier, the desire to improve and prevent further decline post-stroke was a motivator to adhere to attending the exercise intervention. It also appears to be a factor that inspires participants to continue with exercise training.

"I definitely need to keep doing something. I don't wanna end up in a wheelchair." – **Mary**

Barriers

Despite these aspirations to continue exercising, participants' knowledge some barriers they may face as a result of the impact of stroke. Some referred to how exercise apparatus is not designed to be adaptive to their needs and abilities.

"You know, it's difficult getting on and off things, so you'd have to spend a lot of time doing it." –

Joe

Others were aware of additional co-morbidities they were living with, such as arthritis, that were perceived to be a barrier of future exercise participation.

"I was restricted 'cos of these pains in my groin on more than one occasion, on the bike." – **David**

Participants also expressed the lack of provisions available within the community. They recognised how facilities and professional expertise in exercise training after stroke was limited. In turn, this may restrictive inclusivity and opportunities to continue with formal exercise training.

"For people with strokes, gyms won't let them [exercise] because they don't know how to cope."

– **Mary**

Summary of moving forward

Participants described how the exercise intervention became a part of their routine and how they aspired to continue exercising once the EXERCISES study came to an end. Participants referred to how previous accomplishments and their newfound confidence inspired them to keep exercising. However, they also spoke about some barriers, such as accessibility, that may preclude them from engaging in future exercise training.

6.7 Summary of chapter

The purpose of this chapter was to report the findings of the EXERCISES study. The chapter provided a description of recruitment rates, the characteristics of included participants and reported outcome measures. To summarise, eighteen stroke survivors (mean age 64.4 years) were enrolled on the EXERCISES study, over a period of 10 months. Mean VO_{2peak} values were 10.81 ± 2.87 mL/kg/min and 13.28 ± 2.86 mL/kg/min, derived from treadmill and cycle ergometer CPET protocols, respectively. Cycle ergometry appeared to be the most suitable CPET mode as all participants were able to achieve maximal effort with this protocol. Exercise training twice a week for six-weeks also appeared to be safe, feasible and acceptable to participants. The exercise intervention was well-received by participants, who found it enjoyable and sociable. There were, however, limitations with the tools used to measure cognitive health, quality of life and activities and daily living; primarily a result of post-stroke communication impairments.

The following chapter aims to discuss these findings in relation to the original research questions and in the context of existing literature.

Chapter 7

The EXERCISES Study: Discussion

7.1 Introduction

This chapter presents a discussion of findings from the EXERCISES study. Study findings are discussed in relation to the original aims and objectives, and within the context of the wider literature. Where appropriate, qualitative and quantitative findings are triangulated. In this chapter, strengths and limitations of the EXERCISES study are presented, in addition to recommendations for future research.

7.2 Summary of findings

The EXERCISES study aimed to investigate the safety and feasibility for stroke survivors with moderate to severe movement impairments of (i) CPET and (ii) exercise-based interventions. Mixed methodology was used to address these two aims and their embedded objectives.

The first aim of the EXERCISES study was to investigate the safety and feasibility of delivering two methods of CPET modes (i) treadmill with BWS, and (ii) cycle ergometry; specifically,

- The ability of participants with moderate to severe movement impairments as a result of stroke, to undertake CPET;
- The acceptability of random allocation to CPET order;
- Participant feedback of their experience of CPET, including aspects of acceptability and satisfaction.

This study demonstrated that cardiopulmonary exercise testing is safe and feasible for stroke survivors with moderate to severe movement impairments. A total of 33 tests were undertaken by 18 participants; of which 19 were completed on a treadmill with BWS and 14 on an upright cycle ergometer. No adverse events occurred as a result of either CPET protocol. No participant withdrew from the study based on their random allocation of CPET order. All participants were able to adequately access exercise apparatus, with assistance. However, almost all participants needed

some degree of help to maintain movement (i.e. walking or pedalling). All participants who undertook CPET on a cycle ergometer achieved the pre-determined criteria for reaching maximal effort (respiratory exchange ratio of more than one), whereas less than half achieved this on the treadmill with BWS. My findings suggest that cycle ergometry, as a mode of CPET, is more appropriate than treadmill with BWS, for safety screening and obtaining measures of VO_{2peak} in stroke survivors living with moderate to severe movement impairments.

Interviews were undertaken with six participants to explore their experience of CPET. Three themes were identified: *readiness*, *competence* and *intimidation*. Although some initial feelings of apprehension were noted prior to baseline CPET, participants said they felt safe during CPET procedures. This appeared to be due to the preparations made prior to the test, for example the participant information video, and also, as a result of the rapport built between participants and members of the research team. Participants' ability to walk or cycle as part of CPET, generally exceeded their own expectations. They were surprised both at their ability to get on to the exercise apparatus; as well as their own ability to exercise for a longer period of time than expected. However, some participants talked about how they did not feel 'pushed' to their full ability, whilst undertaking CPET. Others referred to how the equipment, such as the BWS harness and face mask, may have hindered their ability to exercise.

The second aim of the EXERCISES study was to investigate the safety and feasibility of delivering exercise-based interventions to people with moderate-severe movement impairments as a result of stroke; specifically:

- Adherence to study protocol;
- Participant feedback of their experience of the exercise intervention, including aspects of acceptability and satisfaction;
- An evaluation of outcome measure tools, including their responsiveness to change and the potential for floor and ceiling effects;
- An estimate of recruitment rate and attrition to a subsequent definitive trial.

Eighteen stroke survivors completed a twice weekly, six-week exercise-based intervention. They were sequentially allocated to one of three intervention groups: (i) aerobic exercise, (ii) strength training or (iii) a combination of aerobic exercise and strength training. The interventions were found to be safe and feasible for stroke survivors with moderate to severe movement impairments. The EXERCISES study aimed to evaluate the suitability of measurement tools for cognitive health, quality of life and activities of daily living. Although this study was not designed, nor powered to detect change over time, the information gathered about understanding the appropriateness of tools is of value in the design of a future trial. Those with post-stroke communication impairments found completing the MoCA challenging, due to several questions requiring a verbal response. In the MoCA, there was some minor indication of ceiling effects across global scores of cognitive health. Most participants found interpreting the Likert scale responses on the SSQoL questionnaire difficult. It was found that some items on Barthel Index may not be applicable to those who are several years post-stroke. No floor or ceiling effects were detected among the results of the SSQoL questionnaire and Barthel Index. However, the small sample size of my study limits the usefulness of this analysis.

Three themes were identified when exploring the acceptability and satisfaction of the exercise intervention: *enjoyment, belonging, motivation* and *achievement*. Participants emphasised their enjoyment of the intervention, mainly as a result of the opportunity to interact with others. Their motivation to adhere to the intervention stemmed from a desire to improve, the social-connectedness with others and to be able to contribute to stroke-related research. Participants relayed feelings of loss when the EXERCISES study came to an end. Most expressed a determination to continue exercising regularly, once the exercise intervention was complete.

In the remainder of this chapter, I will discuss key feasibility outcomes that are important in informing the design of a future definitive trial.

7.2 Recruitment

Over a period of 10 months, 18 of the 24 stroke survivors that consented to take part were allocated to an exercise intervention group. Recruitment to this study, however, was not without challenges. Both the rural area where this study was undertaken, and the burden of travel, were factors in this. I visited three potential participants who were at the time, residing in a care home and one in an assisted living complex. Although all expressed an interest in participating, none were able to participate due to difficulties in travel arrangements and a lack of care staff to accompany them to the MoveEx Lab. The burden of travel has been noted across a number of studies describing recruitment to stroke research studies (399, 400) and may be exacerbated for those in care home settings.

The initial recruitment strategy for my study was via the Early-Supported Discharge Team at the local community health and care NHS Trust. The clinical team reported having limited time during appointments to share information regarding research participation, once they had addressed the clinical needs of the patient. Additionally, from the clinical team's experience, they felt a significant proportion of patients were either sufficiently recovered or presented with disabilities that were too severe for the study inclusion criteria. Though the clinical team suggested some patients may have the potential to meet the criteria at a later date. This calls for a review of the study's inclusion criteria and further research to define the optimal window of time to recruit 'chronic' stroke survivors. Previous research has reported the time since stroke, and therefore the phase of rehabilitation, to be a factor affecting recruitment (401, 402). For stroke survivors who were screened for possible inclusion to a stroke trial at least six-months post-stroke, McGill et al. (401) reported that just under half participated.

In an attempt to overcome challenges with recruitment, I amended the recruitment strategy to also invite individuals who attended community stroke support groups. Community stroke support groups as a platform for recruitment provided the opportunity for word of mouth. This offered a greater reach to potential participants, particularly to those in the chronic phases of stroke who may no longer be involved with formal stroke services. With this, the recruitment rate was

increased from one participant per month in the first eight months, to four participants per month in the latter four months of study recruitment. Recruitment to research studies has been found to be most effective among community-dwelling, chronic stroke survivors (401). My findings support this, given the increase in recruitment rates once invitations were extended to community stroke support groups. My findings suggest that a broad range of recruitment methods are needed to achieve target sample sizes. Further research is required to establish a range of recruitment strategies that could be employed at appropriate time-frames post-stroke and are feasible and acceptable to clinical teams. Recruitment strategies should also be considerate of travel burden and promote inclusivity of those residing in care homes.

7.2.1 Adherence

There was high adherence to study procedures by participants. All participants completed all twelve exercise sessions offered, except for one participant who was withdrawn after five sessions as described earlier. Likewise, attendance rates of previous randomised controlled trials exploring exercise after stroke have ranged from 65% to 100% (9). The high adherence rate of my study was comparable to others and supports the acceptability of exercise-based interventions for stroke survivors who are living with moderate to severe movement impairments.

Participants were able to choose which exercise session they would prefer to attend from a timetable. Having options was helpful in organising travel and accommodating other commitments. Flexibility in the time of day was also essential in providing support for those with post-stroke fatigue, as they were able to exercise at a time they felt most able to do so. For example, some individuals responded better in the morning, as opposed to later in the day.

However, the high adherence in my study should be interpreted with caution. To increase the desirability to take part, participants were always offered the opportunity to ‘make-up’ missed sessions at a later date. Similar flexibility in attendance was also offered in a previous randomised controlled trial, exploring treadmill training after stroke (403). The flexibility in attendance may therefore explain the high level of adherence across both studies. Where available, future studies should employ similar flexibility in intervention delivery, with the aim of promoting inclusivity of exercise after stroke programmes. With flexibility in attending exercise sessions, the limitations of

true adherence rates may outweigh the increased opportunity for inclusivity and the representation of those living with the long-term consequences of stroke.

7.3 The feasibility of cardiopulmonary exercise testing

Both the treadmill with BWS and cycle ergometry as CPET modes were found to be safe and feasible for stroke survivors with moderate to severe movement impairments. This finding builds on the previous research recommendations to explore the ability of severely impaired, chronic stroke survivors, undertaking CPET (404). Despite some challenges with the exercise apparatus and its accessibility, my findings suggest CPET undertaken on a cycle ergometry is a more suitable mode for stroke survivors with moderate to severe movement impairments.

7.3.1 Suitability and acceptability of cardiopulmonary exercise testing modes

The upright cycle ergometer as a mode of CPET, posed a number of limitations for stroke survivors with moderate to severe movement impairments to undertake CPET. Most participants found it challenging to get on to the upright cycle ergometer, as a result of the seat height and central frame they were expected to step over. However, the theme of 'competence' described in an earlier chapter, captured how participants were surprised at their own ability to use exercise apparatus that they initially perceived to be a barrier (such as stepping onto the treadmill). Almost all participants, once seated on the cycle ergometer, found this mode of CPET to be acceptable. We were not able to successfully seat all participants on the cycle ergometer however, thus there is still a need to further explore methods of modifying equipment for some stroke survivors.

To increase inclusivity and overcome challenges that CPET apparatus posed, I used a hoist to transfer participants from their wheelchair to the upright cycle ergometer seat. However, from a participant's perspective, using a hoist to transfer them on to the upright cycle ergometer, left them feeling like a "*load*". The interview data suggested that for some, using a hoist was reminiscent of being in hospital, creating a sense of dependency and a lack of control. Research among nursing staff working on a stroke rehabilitation ward produced similar findings (405). Nurses spoke about how the use of hoists may prevent individuals from making rehabilitation progress and obscure a focus on promoting functional recovery, by preventing patients to do things by themselves (405).

Although a different context to my study, these perceptions are important for promoting inclusion within exercise after stroke services. Findings provide insight into the acceptability of using such techniques and identifies possible barriers of participation.

As a result of hemi-paresis and impaired sitting balance (67, 155, 157), most studies have excluded stroke survivors who have severe movement impairments from participation in CPET (406). Researchers have begun to explore the use of alternative CPET modes to be more inclusive. To my knowledge, there is only one CPET protocol that is validated for stroke survivors to determine VO_{2peak} (164). This CPET protocol, using a total body recumbent stepper (TRBS), was developed specifically for stroke survivors who are living with hemiparesis, increased tone in the extremities, and/or balance deficits, thus were unable to tolerate CPET undertaken on either a treadmill or cycle ergometer. However, much like in my study, participants found it challenging to maintain the predetermined constant stepping cadence (i.e. speed) (164). Other studies have begun to explore other mode of CPET to account for lower limb motor impairment and paresis. One study trialled a unilateral arm crank (407) and another, the use of a robotics-assisted tilt table (408). These studies so far have been found to be useful in detecting levels of cardiorespiratory fitness in more severe stroke populations who otherwise would be excluded from CPET. However, the use of such CPET modes may be problematic for use within community settings; as this type of specialist equipment may not be readily available outside of research facilities. Future research should maintain an emphasis on inclusion of those with severe stroke; but should also aim to explore the feasibility of CPET modes outside of research facilities for the purpose of safety screening and exercise prescription within community exercise after stroke services.

7.3.2 Utility of cardiopulmonary exercise testing to assess safety to exercise

My findings suggested that treadmill with BWS, as a mode of CPET, may not be appropriate to assess the safety of stroke survivors with moderate to severe movement impairments to exercise. This is because participants were unable to attain sufficient intensities of exercise to determine their cardiopulmonary responses to exercise. Tests were generally stopped for non-cardiopulmonary reasons; most commonly, the inability to maintain the treadmill speed, before

the pre-determined criteria for achieving maximal effort was achieved. Premature test-termination for reasons other than maximal effort, may mean an insufficient amount of 'stress' is applied. True cardiopulmonary, vascular and musculoskeletal responses to incremental exercise may therefore be masked. It is recommended that CPET durations should be 8 to 12 minutes (149); whereas the mean test time for the treadmill with BWS in my study was approximately half of this. This further highlights limitations in the use of treadmill with BWS in allowing individuals to achieve a sufficient intensity for safety screening.

My study supports the use of VO_{2peak}, as opposed to VO_{2max}, among stroke survivors, as intensities achieved during CPET were not great enough to attain a 'plateau' in oxygen consumption. Peak aerobic capacity values achieved by participants in my study ranged from 7 to 18 mL/kg/min; and are somewhat lower than the previously described reference ranges for stroke survivors of 8 to 22 mL/kg/min (65). Accumulated data to formulate reference values has evolved from research with independently ambulatory stroke survivors who are mainly within the acute phases of stroke (65). Therefore, reference values of VO_{2peak} among stroke survivors may have been overestimated in previous work. Participants in my study included those unable to ambulate independently and who were up to 16 years post-stroke. It is therefore possible that the cardiorespiratory fitness of stroke survivors living with the long-term consequences of stroke is significantly lower compared with lesser severities of stroke or less time since stroke onset.

Furthermore, direct comparisons of my findings to previous work is difficult due to how cardiorespiratory fitness was defined. I reported the highest value of VO_2 attained during CPET, similar to (149). However, how VO_{2peak} is determined varies across research studies (159). For example, other studies have reported an average of VO_2 over the last 30 seconds of CPET (159). Variation in reporting VO_{2peak} may impact the content validity of CPET protocols and the accuracy of VO_{2peak} values (404).

In my study, the inability to achieve maximal effort on the treadmill may be partly explained by participants' accounts of their experience of CPET. Some participants said that in terms of measuring their abilities during CPET, they were not 'pushed' sufficiently. In contrast, during CPET undertaken on the cycle ergometer, participants attained sufficient exercise intensities to reach a

peak respiratory exchange ratio of more than one. This means that all participants achieved maximal effort and sufficient data was available to assess safety to exercise and data used to prescribe exercise.

To my knowledge, previous literature exploring CPET among stroke survivors has been undertaken with no qualitative investigation of participants' experience. Although a small feasibility study, my study is the first to include a qualitative analysis of participant's CPET experience. My findings suggest that participants benefited from undertaking CPET as it increased their confidence to exercise. This was captured within the theme of 'competence'. However, participants did report some feelings of intimidation because of the medicalised characteristics of CPET. To explore this further, there is a need for larger qualitative studies to better understand CPET from the perspective of stroke survivors.

7.4 The feasibility of exercise interventions

Based on retention and adherence rates, a twice weekly, six-week exercise intervention was feasible for stroke survivors with moderate to severe movement impairments. This was further supported by no study-related adverse events. The intervention was well-received and was acceptable to participants.

A systematic review of 33 studies, including 910 non-ambulatory stroke survivors, found that physical fitness training, in the form of assisted walking interventions, was safe and feasible (409). Inclusivity was promoted in the form of assisted walking from therapists, BWS harness or robotic equipment; of which all were found to be safe and feasible (146). A lack of available data prevented authors from determining the effectiveness of physical fitness training on health- and fitness-related outcomes (409). In addition, no study in this review addressed the effects of physical fitness training on cognitive health within stroke survivors who were non-ambulatory. My study, therefore, appears to be one of the first to explore the potential benefits of physical fitness training on cognitive health among stroke survivors with moderate to severe movement impairments.

7.4.1 Exercise fidelity

Fidelity, by definition is,

> '*the extent to which an intervention was delivered as conceived and planned—to arrive at valid conclusions concerning its effectiveness in achieving the target outcomes'* (53).

In the EXERCISES Study, intervention fidelity is important to understand the true feasibility and acceptability of exercise training for stroke survivors with moderate to severe movement impairments. It is also an essential methodological consideration to ensure valid and reliable testing of an intervention (54, 55).

In the present study, exploratory work was undertaken to explore the feasibility of three types of interventions: aerobic exercise, strength training and a combination of aerobic exercise and strength training. Exercise interventions were delivered in line with previous guidance (118), and attempts were made to overcome the variation in the dose of exercise prescription described in the literature. The fidelity of the interventions may be determined by exploring the extent to which intervention delivery, exercise prescription and participants' performance complied with what was detailed within the study's protocol.

There was high fidelity for intervention delivery from the perspective of attendance to exercise sessions. With the exception of one participant who was withdrawn after five sessions, all others completed all 12 exercise sessions over a six-week period. One component of the intervention, perceived by participants to enhance attendance to sessions, was the opportunity for socialisation. Where recruitment allowed, exercise was delivered in the format of a circuit, regardless of which intervention group they were allocated to. This group format of intervention delivery was well-received by participants. Across exercise after stroke programmes, it has been demonstrated that exercising as a group stimulates social interaction and provides opportunities for social support (116, 130). It appeared that the opportunity for social interaction in my study also underpinned the enjoyment of the exercise intervention; whereby participants who were interviewed felt that the group provided them with elements of social, emotional and peer support. My findings resonate

with other qualitative work where stroke survivors have reported that the social aspects of exercise participation motivated them to attend the exercise sessions (1, 56-58).

In my study, participants shared how they felt a sense of group camaraderie and cohesion, as a result of shared stroke experiences. This has been shown to be particularly true for those with post-stroke communication impairments. Blonksi et al. (59) found stroke survivors who were living with aphasia valued the opportunity to exercise in the presence of others with similar experiences. In my study, seven participants were living with post-stroke communication impairments. The fact that both KMa and I had undertaken training for supported communication in healthcare and research strengthens this study. We were able work closely with individuals to adapt our methods of communication to best suit their needs.

My findings also suggest that the supervised component of the intervention contributed to participant enjoyment and encouraged attendance. With most participants, a one-to-one ratio of participant to exercise professional was required. This ratio was found to be crucial to the delivery of the intervention, in order to facilitate movement patterns, assist in transfers and to maintain compliance to the dose of exercise that day. In a study of 12 community-dwelling stroke survivors, authors highlighted that participants relied on exercise instructors to support them whilst exercising (60). Likewise, White et al. (392) also found that encouragement by exercise professionals was advantageous and a source of motivation to improve and for participants be "pushed". Research has therefore demonstrated that interpersonal relationships, not just with other stroke survivors, but also with facilitators, promoted post-stroke exercise engagement (61). Supported activity in this way has implications for promoting and maintaining motivation. This relationship can influence adherence and should be considered when designing future exercise interventions for stroke survivors.

Throughout the delivery of exercise interventions, I was able to personalise exercise programmes and promote autonomy by including goal setting and where possible, their own choice of exercises during each session. However, I found it quite restrictive to remain within the remit of one 'type' of exercise intervention group. For some of the participants, their goals or exercise choices did not

always fit the remit of the intervention group they were allocated too, particularly for aerobic and strength training in isolation. This findings supports combining aerobic exercise and strength training within exercise after stroke programmes to best suit the needs and goals of stroke survivors (62). The protocol for The EXERCISES Study stated that exercise programme were centred, as far as possible, on the participant's goals. However, in the design of future studies, parameters must be set to determine the level and scope of individualisation related to goal setting so as not to confound treatment effects of intervention groups.

In relation to goal setting, participants in my study commented that they did not feel the intervention was long enough to achieve their goals. Participants articulated feelings of 'loss' when The EXERCISES Study came to an end and they wished there was more time available to achieve their goals. Interventions in previous studies have ranged from four weeks (7) to six-months (14). Although these authors also found the length of these interventions to be feasible, there was no qualitative component to address acceptability from the perspective of participants; including whether the length of intervention was sufficient for them to achieve their goals.

The frequency and length of an exercise intervention will directly impact the extent to which physiological adaptations to exercise occur (63). In the present study, I am unable to infer the extent to which a 6-week exercise intervention can affect outcome measures such as heart rate, blood pressure and maximal aerobic capacity. This is due to the nature of the feasibility study design. However, visual interpretations of descriptive statistics may be sought to inform the design of future studies.

The visual representation of resting pre-exercise systolic blood pressure presented in figure 28 suggests that the majority of participants sit within the pre-hypertension range (120 to 140 mmHg (64)). Secondary prevention of recurrent stroke has an anti-hypertensive focus, in which aerobic exercise is an intervention found to improve systolic blood pressure (65). Visual interpretations also suggest that there is a slight trend to indicate a reduced resting pre-exercise systolic blood pressure, over the 12 exercise sessions. Exercise interventions can produce significant reductions in systolic blood pressure among stroke survivors (66). In a meta-analysis of 12 studies including 606 stroke

survivors, aged 52 to 69 years, reductions in systolic blood pressure were most pronounced among studies that initiated exercise within 6-months of stroke onset or transient ischemic attack (65). Previous work involving stroke survivors, supported by the present study, encourage further research to explore the impact of aerobic and strength exercise on systolic blood pressure. Furthermore, this proposed work would be in line with recurrent stroke prevention guidelines which promote reductions in systolic blood pressure to reduce recurrent stroke risk (67).

For the majority, participants' pre-exercise resting heart rate measures pre-exercise were within normative ranges for adults aged 55 to 65 years (70 to 75 beats per minute). A higher resting heart rate is associated with a greater risk of mortality (68-70). However, there is variation within these data. The large range reported (62.00 beats per minute) may be attributed to the prescription of medications such as beta-blockers, to individuals pre-morbid and/or their current cardiorespiratory fitness levels, or due to the small sample size. Moving forwards into a pilot or full-scale randomised controlled trial, it is important that demographics are adequately reported and parameters are controlled for in prospective analyses. Resting heart rate is also an indicator of cardiovascular adaptations to aerobic exercise (71-73). Although this study was not designed to statistically test for differences between groups or changes over time, descriptive statistics and visual interpretations of graphs suggests there was little difference in pre-exercise resting heart rate between intervention groups, nor over the six-week exercise intervention. This is consistent with previous work with stroke survivors (71, 73).

Post-exercise session, resting heart rate was recorded within approximately 5 minutes of a participant's cool-down. In contrast, previous studies have reported values of heart rate recovery, which defines the rate of decline in heart rate with the cessation of exercise (74, 75). In a study of 128 chronic stroke survivors, 12 weeks of progressive aerobic cycling favourably modified heart rate reserve (76). In the EXERCISES Study, I did not record heart rate recovery, but on reflection, it would have been an interesting variable to report, as greater values are associated with cardiovascular disease and are known predictors of all-cause mortality (75). Stroke survivors often experience impaired cardiac regulation and autonomic function which is clinically presented as heart rate and

blood pressure abnormalities (77, 78). It is therefore important that future studies consider reporting and analysing parameters related to cardiac regulation and autonomic function as they are useful in predicting gains in cardiovascular fitness.

Repeated measures of peak heart rate during each exercise allowed me to monitor adherence to exercise prescription and progress exercise intensity where appropriate (37, 79). Highest values were observed in the aerobic intervention group. The combination intervention group was found to have the lowest mean peak heart rate over the intervention, attributed to alternating aerobic and strength exercises, which served as an active recovery period. As this was a feasibility study, the intervention groups were not equated for the amount of exercise performed done. There was variation in the training principles (i.e., intensity and time), both at an individual level and between groups. Future studies may consider holding some parameters of exercise prescription constant, such as time, so that a true comparison of the impact an exercise intervention may be sought.

Based on peak heart rate data, participants achieved the recommended amount of exercise intensity for stroke survivors (80). This contrasts with previous work, as adherence to exercise intensity as per clinical guidelines, is limited across the evidence-base (50). A systematic review of 28 studies (81), found that the dose of exercise prescribed to stroke survivors, did not meet the daily recommended amount of exercise for adults (82). This highlights the need for research to focus on the fidelity of exercise prescription (83).

Peak heart rate and peak maximal aerobic capacity values obtained during CPET informed exercise prescription (i.e., intensity) for individual participants. This method of exercise prescription is in line with Billinger et al. (84). There is increasing evidence to support the use of CPET for exercise prescription among clinical populations (85). However, pragmatically, it was challenging to monitor exercise heart rate ranges due to technical issues with the heart rate monitors used and the amount of adaptation/support required during each exercise. I therefore became increasingly reliant on the use of RPE to monitor and progress exercise intensity.

The RPE reported by participants in the EXERCISES study ranged from 11 to 14, which sits within lower ranges of what was originally prescribed for this intervention. A subjective rating of exercise

intensity may be a better indication of effort and provide more precise information required for intensity progression, in comparison to heart rate. In cardiac rehabilitation, RPE is recommended as a method of monitoring exercise intensity and progression (86). A study involving stroke survivors, found the Borg 6 to 20 RPE scale to be feasible in progressing the exercise intensity of functional and upper limb strength training (87). Similar to CPET, peak RPE values were recalled after the activity. Most participants found it challenging to interpret the Borg 6 to 20 RPE scale while exercise. Walking, cycling and other exercise activities are already complex tasks, requiring a greater demand on higher order cognitive processes (88). The addition of a dual-task, such as interpreting the Borg 6 to 20 RPE scale while exercising, may be challenging for stroke survivors (89-91). For example, research has shown changes in parameters of gait, such as decreases in gait speed, stride length and cadence; are associated with concurrent cognitive tasks (92, 93). This may also be applicable to other exercise activities.

Furthermore, the aforementioned studies do not consider the challenges those with post-stroke communication impairments would experience while using the Borg 6 to 20 RPE scale. In my study, just under half of participants were living with a post-stroke communication impairment. In order to collect RPE data, I had to recognise certain physical cues during exercise e.g., increased respiratory rate, sweating; and then provide a narrower range of scores from participants with post-stroke communication impairments to choose from. Although I aimed to be as consistent as possible in reporting, some mismatches in RPE and heart rate values may be attributed to this.

A further challenge in using the RPE scale came with the exercise intervention group allocation. The RPE scale is designed to correspond with heart rate and feelings of breathlessness (51). The application of this makes it more acceptable for use with aerobic exercise. However, there are challenges when applied to strength training, when muscular effort, tension and fatigue are the focus for monitoring intensity. It may be that tools such as the Borg 1-10 scale (94) is more suitable for future studies that explore combined aerobic and strength training as other indicators of exercise intensity may be monitored. In addition, when reflecting on the use of the Borg scale in The EXERCISES Study, the Borg 1-10 scale (94) may also be more appropriate for stroke survivors

with communication impairments and should therefore be a consideration for future studies and a feature of PPI activities.

From the interview data and anecdotal conversations with participants, it may be that the intensity of the exercise could have been higher. Participants expressed that they "could have been pushed a bit more". Differences between perceived exertion and qualitative findings further support the combined use of the Borg 6 to 20 RPE scale and peak heart rate for exercise prescription and intensity monitoring during exercise for stroke survivors. Quantitative data such as peak heart rate and peak RPE guides our understanding of the population's ability to exercise and may be used to inform future exercise prescription. Participant feedback highlights the importance of employing mixed methods as an approach to research design. The combined approach to data collection and analysis provides opportunity to elaborate on any previously conflicting findings, enhance understanding on optimal dose and seek clarification in results.

7.4.2 Adaptations

Reporting exercise adaptations was in line with the CERT tool (appendix 17) for reporting interventions (95). Sharing creativity in adaptation and modifications is important for the development and replication of future exercise after stroke programmes (95). Reporting in this way also contributes to understanding the fidelity of an exercise intervention.

Modifications to exercise equipment were introduced to adapt to participants' needs. This was consistent with published evidence which advocated the need to adapt exercise training according to physical ability (84, 96-98). For example, the seat and slide mechanism on the rowing machine was detached so that participants were able to remain seated in their wheelchair or on a chair, with their feet strapped into the feet rests of the rowing machine. The arm rests of the wheelchair were also removed so that the rowing technique was not restricted. I modified equipment to assist performance such as a wrist cuff to support grip when holding on to apparatus. In addition, I found that equipment, with easy modifications to suit participants' movement ability and exercise capacity, needed to be readily available. For example, Thera bands, hand or wrist cuffs, varied step heights, non-slip floor mats. However, individualisation and adaptation to exercises during sessions

to better suit this population may challenge the fidelity of interventions. Future research should therefore define parameters and the scope to which adaptations to exercise activities may occur.

Although participants acknowledged movement impairments and the lack of adaptation to be a barrier to formal exercise training, the qualitative sub-study revealed that participants' aspirations to continue taking part in formal exercise training. Participants were interested in how such modifications or movement adaptations could be applied to exercising at home or within other exercise facilities, outside of a research laboratory setting. I was able to provide this advice to participants by visiting them at home following the intervention to demonstrate activities with them. This information should be easily accessible to stroke survivors following formal exercise after stroke programmes if they wish to continue in alternative settings.

7.6 Evaluation of outcome questionnaires

One objective of this study was to evaluate the use of the outcome measures for a future trial; including their responsiveness to change and their potential for floor and ceiling effects. The outcome measures of this study were chosen with a view to explore the influence of exercise on cardiorespiratory fitness and therefore, cognitive health.

My findings suggest that the MoCA was not an appropriate outcome measure to assess global cognitive health among this sample of stroke survivors. To accommodate communication challenges, I provided pen and paper to those who found expressing an answer or interpretation difficult, so they could either write a word down or draw a picture to support their response. However, there was still a substantial proportion of missing data. Similar challenges were noted when administering the SSQoL questionnaire and Barthel Index.

Similar studies exploring the use of the MoCA with stroke survivors highlighted that the occurrence of non-completed scales, may be attributed to refusal, neglect, dysphagia and aphasia (77). Authors also found that those who did not complete the MoCA were more likely to be older, to have had a recurrent stroke and were within the chronic stages (up to six years post-stroke (77). Although this

was the first stroke for participants in the EXERCISES study, both participant's mean age and time since stroke was comparable to Cumming et al. (77).

It is estimated that 17% to 38% of the stroke population are aphasic (43). My sample is representative of this, as 39% were living with post-stroke communication impairments. Although some research suggests the MoCA is not suitable for severely aphasic patients (44), one study found around three quarters of stroke survivors with severe aphasia were, in fact, able to complete the MoCA (42). With conflicting evidence around the suitability of the MoCA for those with aphasia, it is important that further research is undertaken. Alternatively, other tools such as the Oxford Cognitive Screen may be more appropriate, and may overcome limitations related to issues of aphasia and neglect experienced when using the MoCA (45). The Oxford Cognitive Screen was primarily designed to be inclusive and unconfounded by aphasia and visuospatial neglect (46). The tool measures five cognitive domains: attention and executive function, language, memory, number processing, and praxis, as well as visual field deficits. Assessment using the Oxford Cognitive Screen provides a 'snapshot' of stroke survivors' cognitive status and can contribute to the design of a rehabilitation programmes. For each domain of cognition, separate cut off points for each task allows researchers and clinicians to define cognitive strengths and weaknesses of individual stroke survivors. In comparison to the MMSE, the Oxford Cognitive Screen has been shown to detect a higher incidence of stroke-specific cognitive impairment (46). In the same study, The Oxford Cognitive Screen detected high incidences of stroke-specific cognitive impairments, not detected by the MMSE. For example, it was found that visuospatial neglect was present in 31% of patients, who were found to be unimpaired on the MMSE (46). Furthermore, when compared to the MoCA, the Oxford Cognitive Screen also had greater sensitivity, in that approximately 10% more participants were found to have had at least one cognitive impairment when assessed by the Oxford Cognitive Screen (47). The use of the Oxford Cognitive Screen instead of the MoCA was considered in the development of The EXERCISES study, however, due to the nature of this project and its funding source, the study was ineligible for free licensing and additional funds for its use were unavailable. To my knowledge, the sensitivity of the Oxford Cognitive Screen detecting changes in

cognition in response to exercise training among stroke survivors is yet to be investigated. This will contribute to the rationale and design of the next phase of my research beyond The EXERCISES Study.

7.7 Limitations of the feasibility study

One primary limitation of my study was the small sample size, which may limit the interpretation of quantitative findings, specifically outcome questionnaires. Geographical and socio-economic factors related to participants should also be considered when generalizing findings.

There were challenges with recruitment, including travel burden and challenges with the original recruitment strategy via the Early-Supported Discharge Team at the local NHS health and care trust. However, the ability to adapt recruitment strategies for optimal reach of prospective participants highlights the benefit of adopting a feasibility study design for this phase of research and may therefore be a strength of this study.

There were limitations in the qualitative sub-study used to gather this feedback from participants. Six-weeks may not have been long enough for individuals to formulate robust opinions of the exercise intervention. It may be assumed that individuals who took part in the exercise intervention had predisposed characteristics to enjoy exercise training. Participants may have already valued exercise training as part of their lifestyle this may therefore have influenced the outcomes of the interviews. Inherent enjoyment of exercise may also affect adherence and attrition rates. It could be assumed that with enjoyment and value in exercise training, individuals are less likely to drop-out of research studies.

Some participants may have had different experiences of the intervention, depending on at what time point they were recruited to the EXERCISES study. For some participants, particularly in the beginning and end phases of recruitment, they would have exercised independently. But for others, they would have exercised as a group with up to three other participants in a circuit. This may have resulted in different experiences among participants who were interviewed.

The perceptions of stroke survivors who declined to take part have not been addressed. Purposive sampling in future studies may be a useful method to explore the perceived barriers and reasons

for non-participation to community-based exercise trials. However, this type of research is challenging, as those who decline to take part, may also be likely to decline to participate in research exploring reasons for non-participation.

I chose not to offer respondent validation in my study. Instead, I presented the findings of the EXERCISES study as a whole to all participants who took part. This presentation included an overview of both qualitative and quantitative findings and explained what these findings may mean in the development of future exercise after stroke research. Findings of the qualitative sub-study were emphasised and encouraged participants to share any other thoughts or opinions they had regarding their experience of the exercise intervention. This provided participants with the opportunity to comment on my interpretation of what was captured from interview data. However, although a summary of overall findings was presented to participants, without respondent validation, the credibility and trustworthiness of qualitative findings may be limited.

7.8 Strengths of the feasibility study

The EXERCISES study extends previous work by including those who have more severe movement impairments. Exercise prescription was in line with best practice guidance (91) with the aim of reducing variation in the exercise after stroke studies.

The use of a mixed methods is a strength of this study. A mixed methods approach to data collection captured both potential physiological changes to, and the subjective responses to exercise training and testing, thus maximizing the study's rigor. This is also one of the first studies to include a qualitative component exploring participant's experience of CPET.

This feasibility study was strengthened by preparatory work completed prior to the start of the study. Working with service users was beneficial in the design of participant information sheets and the creation of the information video. Piloting CPET procedures with healthy volunteers was a helpful practice pertaining to the development of the EXERCISES study. I was able to identify potential barriers to the inclusion of stroke survivors, related to CPET and exercise intervention delivery.

Exploratory testing of the three types of interventions (aerobic exercise, strength training and a combination of aerobic exercise and strength training) was of value in understanding the implementation of complex interventions. The flexibility in the delivery of the intervention strengthened this study as exercise prescription and adaptations were tailored specifically to the individual.

7.9 Summary of chapter

Overall, the EXERCISES study found that CPET and a six-week exercise-based intervention of either aerobic exercise, strength training or a combination of aerobic exercise and strength training, was safe and feasible for chronic stroke survivors with moderate to severe movement impairments. The EXERCISES study was acceptable and satisfactory to participants. This was primarily attributed to enjoyment, increases in confidence and a felt sense of community among other participants.

Important findings regarding recruitment and adherence were reported and may be used in the design of future studies. A flexible approach to intervention delivery, equipment modification and movement adaptations should be employed, to best suit the needs and abilities of stroke survivors with moderate to severe movement impairments. Suitable tools to measure cognitive health needs to be further explored, in response to exercise training. It may be that an exercise intervention of this nature has the potential to benefit cognitive health among stroke survivors living with the long-term consequences of a severe stroke.

Chapter 8

Conclusions, Recommendations and Reflections

8.1 Introduction

The final chapter of this thesis integrates and discusses the findings of the systematic review and the EXERCISES study in relation to the original aim of this thesis. Implications for clinical practice, recommendations for future research and my reflections on the research process are described.

8.2 Overview of thesis and key findings

The background and literature review (chapter 2) established that:

- Exercise after stroke is recommended for improving cardiorespiratory fitness and reducing the risk of a recurrent stroke (90). However, there is variation in the training parameters of exercise (i.e. the FITT principle) across clinical guidelines.
- Stroke survivors with moderate to severe movement impairments are underrepresented in the literature (11, 12).
- There appears to be limited research to support the use of CPET in exercise after stroke services for both safety screening and for exercise prescription.
- There is some evidence in support of aerobic exercise after stroke to benefit cognitive health (43, 184-190). The extent to which outcomes of aerobic exercise, for example cardiorespiratory fitness, mediates improvements in cognitive health, is yet to be established among stroke survivors.

A number of previously unexplored, but important areas of research were highlighted:

- The feasibility of exercise interventions, with a view to maintain cognitive health, for stroke survivors with moderate to severe movement impairments;
- The feasibility of CPET and exercise training for stroke survivors with moderate to severe movement impairments;
- The nature of the association between cardiorespiratory fitness and cognitive health among stroke survivors;

- Optimal feasibility parameters of studies exploring the optimal dose of aerobic exercise to maintain cognitive health.

As a result of these gaps in the evidence, this thesis set out to explore the influence of exercise after stroke on cardiorespiratory fitness, with a view to maintain cognitive health.

In chapter 3, a systematic review of the literature was conducted, to explore the research question, *What is the nature of the relationship between cardiorespiratory fitness and cognitive health, among stroke survivors?*

The objectives of the systematic review were to systematically identify relevant literature to be included in this systematic review; and to quantify an estimate of the association, if any, between cardiorespiratory fitness and cognitive functioning among stroke survivors, by means of a meta-analysis where appropriate.

Eight studies were included in the review and the key findings were:

- There was little primary evidence available to quantify and describe the nature of the relationship between cardiorespiratory fitness (VO_2) cognitive function among stroke survivors.
- A meta-analysis was not undertaken as a result of heterogeneity in the methodology of studies was found, as well as variation in the tools used to measure exposure (VO_2) and outcome (cognitive function).
- Global cognitive function is measured sporadically across the exercise after stroke literature. It is often used to describe the prevalence of mild cognitive impairment among the sample, as opposed to defining the impact of an exercise intervention on cognitive function.

The EXERCISES study (chapters 5 to 7) investigated the feasibility, and safety, of delivering two methods of CPET modes (1) treadmill with BWS, and (2) cycle ergometry; and the feasibility, and safety, of delivering exercise-based interventions to people with moderate to severe movement impairments as a result of stroke.

The key findings were:

- Cardiopulmonary exercise testing is feasible for stroke survivors with moderate to severe movement impairments. Participants were able to undertake CPET safely, with no adverse events.
- Cycle ergometry was found to be more appropriate compared with the treadmill with BWS as a CPET mode for pre-exercise safety screening.
- Combined aerobic exercise and strength training in line with previous clinical guidance (91), is feasible for chronic stroke survivors with moderate to severe movement impairments.
- The exercise intervention was well-received by participants, who emphasised their enjoyment as a result of the social interaction with others, a new-found confidence and from the recognition of their own achievements.
- There were limitations with the tools chosen to measure cognitive health and quality of life; primarily a result of post-stroke communication impairments.

8.3 Implications of findings

The intention of the systematic review (chapter 3) was to explore the nature of the relationship between cardiorespiratory fitness and cognitive function. However, there was not the available data to quantify an estimate. Further research is therefore needed to explore the nature of the relationship between cardiorespiratory fitness and cognitive function. With this, it may be that clinical practice can be tailored with a view to maintain cognitive health. For example, an increase in VO_2 by a particular amount may produce clinically meaningful changes in cognitive health, such as the threshold criteria of mild cognitive impairment.

As a feasibility study, findings of the EXERCISES study have limited application to clinical practice and policy. However, there were important learnings regarding the inclusivity of stroke survivors who are living with moderate to severe movement impairments. Those who have experienced a severe stroke and therefore have more severe impairments have typically been excluded from exercise-based research and within exercise after stroke services. The EXERCISES study highlighted that there were a number of ways in which exercise may be adapted to account for the physical

impact of a severe stroke. With further research, findings may contribute to the tailoring of exercise guidelines for the more severely disabled.

With new knowledge about the feasibility of CPET for stroke survivors with moderate to severe movement impairments, clinical practice may look towards using CPET to risk stratify those with complex medical histories, confirming their safety to participate in exercise. Clinicians and stroke survivors could therefore both be confident that they are safe to undertake exercise training. Physiotherapists or other healthcare professionals may also use CPET findings to prescribe exercise intensities, based on an individual's exercise tolerance. Confidence in the knowledge that they are safe to participate in exercise after stroke is important for stroke survivors themselves. For some individuals, undertaking CPET prior to an exercise after stroke programme may be a way in which apprehension or nervousness regarding engaging in exercise may be eased.

Overall, findings of the EXERCISES study has implications for informing the design of a future definitive randomised controlled trial. Recommendations for future research are presented in the following section.

8.4 Recommendations for future research

I envisage the research undertaken in this thesis to be the first phase in a programme of research designed to explore the potential benefits of exercise after stroke for cognitive health. Based on learnings from the EXERCISES study, the next phase of research will be to design a pilot study, aiming to consider the efficacy of exercise for cognitive health among larger samples of stroke survivors with moderate to severe movement impairments. This is in line with the MRC framework for the development, evaluation and implementation of complex interventions (234), as described in the methodology of the EXERCISES study (chapter 5). The subsequent research will work toward assessing effectiveness, understanding the change process and assessing the cost-effectiveness of such intervention (figure 29).

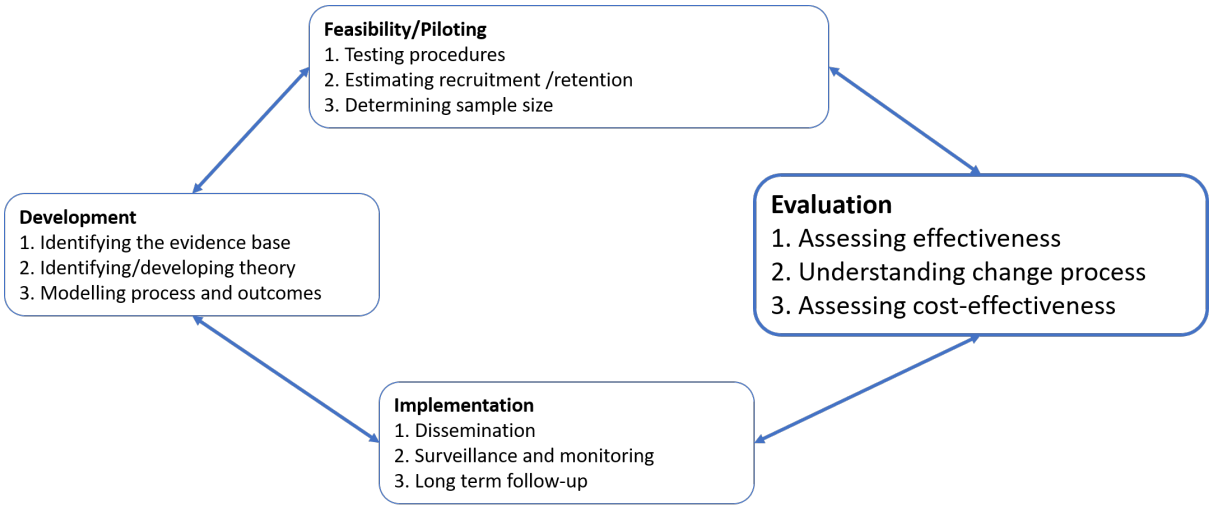

Figure 33: Key elements of the development and evaluation process (234)

In the development of this future research, areas of interest include:

- The production of high-quality research to explore the dose-response relationship between cardiorespiratory fitness and cognitive health, aiming to determine the optimal dose of exercise to maintain cognitive health;
- Explore sustainable ways of implementing community-based exercise interventions for chronic stroke survivors with severe movement impairments; including, home-based, leisure and community centre-based programmes;
- The randomisation of participants and a comparison of exercise training with a control group, e.g. cognitive training, social group or usual care;
- Further exploratory work of the feasibility of exercise training among those with varying degrees of cognitive and communication impairment;
- To explore the impact of exercise training across multiple domains of cognition, including language and other domains that may be a specific risk factor to vascular dementia.

For the development of accurate and suitable outcome measures, other areas of interest for future research include:

- Establishing a valid cycle ergometry CPET protocol for stroke survivors living with moderate to severe movement impairments;
- Further qualitative investigation of participants' experiences of CPET;

- The use of cognitive tools that are adapted and suitable for those living with post-stoke communication impairments including an exploration of the sensitivity of the Oxford Cognitive Screen to detect changes in response to exercise training.

It is important that in the design of the next phase of research (a pilot study), service users are consulted, not only on the overall scope and design of the research but are also involved in activities related to the selection of outcome measures. Service users should have the opportunity to share their views and experiences and identify domain that are meaningful to them. For example, within research priority setting for life after stroke, stroke survivors and caregivers identified several outcomes that were of significance to themselves, including cognition, aphasia, confidence and avoiding subsequent stroke (99). Although activities of daily living is not specifically defined in Pollock et al. (99) as a research priority, difficulty in performing activities of daily living is likely to predict reduced physical fitness, worse mobility and poorer quality of life, and therefore constitute an important area for continued research. However, for chronic stroke survivors with severe movement impairments, significant change in activities of daily living may be unexpected, given the type of activity and the level of impairment (and/or disability) stroke survivors are living with. The inclusion of PPI activities may allow service users to identify activities that are meaningful and possibly achievable for them, as well as to ascertain domains or aspects that bear little relevance to them and are therefore redundant. For example, in The EXERCISES Study, there was a significant amount of missing data for the 'stairs' item on the Barthel Index. This learning suggests that some domains may be redundant for the target population. Undertaking PPI activities related to the selection of outcome measures prior to The EXERCISES Study may have pre-emptied this, and thus should be advocated in the design of future studies.

In the present study, participants found the Stroke Specific Quality of Life Scale particularly challenging to complete, owing to the language used and the corresponding five-point Likert-scale response categories. Participant feedback of this nature may inform the design of future studies, in that researchers may look towards supporting participants one-to-one or provide a video and/or audio, to guide participants through the questionnaire; or, the use of a different measure of quality

of life, such as the EuroQoL-5, may be more appropriate (100, 101). Further learning from The EXERCISES Study suggest that more specific aspects of quality of life, such as depression may be more advantageous to explore, following an exercise-based intervention. Post-stroke depression affects up to 64% of stroke survivors and is associated with poor cognitive functioning (33, 102). There is accumulating evidence that aerobic exercise is an effective intervention to improve symptoms of depression and is therefore advocated as an area of interest for future research (103). Tools such as the Beck Depression Inventory (104, 105) Hospital Anxiety and Depression Scale may be used (106).

Undertaking PPI activities allows service users to address the accessibility of questionnaires or tools. It may be that work needs to be undertaken to modify the formatting of tools to suit the needs of service users, based on their views and experience. The modification of data collection methods based on population needs is particularly important for people post-stroke, given the prevalence of post-stroke communication impairments. For example, in The EXERCISES Study, I modified the format of the Stroke Specific Quality of Life Scale to be in Ariel font, bold text and size 14, based on feedback from stroke survivors living with aphasia. Similar considerations should be made for other data collection methods, such as interviews or focus groups (107). For example, closed-questions and the use of pen and paper.

As well as PPI, it is important that research teams seek expertise from clinical teams and encompass their views and experience in the selection of outcome measures and tools. For example, consultations with an occupational therapist with expertise in cognitive function ensures evidence-based and clinically relevant tools are used. It is also important that in future studies, outcome measure tools are responsive to COVID-19 and can possibly be adapted to support online or virtual versions or that they can be completed independently, given potential restrictions on face-to-face activities.

In a study of this nature, researchers should be mindful of participant burden, due to numerous questionnaires or tools to complete, in addition to the time commitment of an exercise intervention.

In future work, I endeavour to work closely with stroke survivors to decide an appropriate number of tools and outcome measures. Basing research design on service user recommendations may promote the desirability to take part in research studies and may reduce participant burden, and therefore potential withdrawals in future studies.

With regards to this research, the current health crises of COVID-19 has provided me with the opportunity to reflect on the design of future exercise after stroke research. Future studies will need to consider how social distancing may be accounted for and the introduction of safety measures for the delivery of exercise interventions. More than ever, the need to include service users from the initial planning phases of research is paramount. Many stroke survivors may be defined as clinically vulnerable due to additional health concerns, thus may be 'shielding' or in self-isolation (460, 461). Members of PPI groups would be able to provide insight as to how future research can continue to be inclusive of an already hard to reach population safely. With COVID-19, a large proportion of stroke survivors will be at a considerably greater risk of the long-term effects of cardiovascular deconditioning. It is known that the implications of cardiovascular deconditioning exacerbates the risk of secondary events and other cardiorespiratory complications (462). Therefore, physiotherapy and exercise after stroke services should be responsive to the physiological consequences of 'lock-down' and the reduced access to stroke services during this time.

8.5 Reflections

The purpose of this section is to share the reflections I have made throughout my period of study for this PhD. Reflection is a relatively new practice to me, and I have found it challenging, yet informative and rewarding. The ability to reflect is an important feature of professional practice. It involves engagement in retrospection, self-evaluation and re-orientation, based on our own experiences (463, 464). Critical reflection is often used in clinical practice in order to improve the delivery of care and enhance patient experiences (465, 466). In research, reflection is usually adopted in the form of reflexive practice as a means to ensure rigor and trustworthiness in qualitative research. But, in terms of the research process as a whole, reflection is important for

interpreting experiences, supporting decision making and for evaluation. Towards the end of my doctoral studies, it has been an important practice to demonstrate what I have learnt and what existing knowledge I have expanded with new approaches. Overall, I have developed my skills as a researcher, increasing my knowledge of research design, implementation and evaluation. Over the four years, my supervisory team have encouraged me to undertake other academic activities, such as lecturing and research associate posts, in order to broaden and strengthen my academic skills.

I have learnt about physiotherapy practice for stroke and neurorehabilitation and worked to apply my existing knowledge of exercise physiology within this context. My supervisory team often challenged my ideas and provided the opportunity for us to have academic discussions. As a result, I have developed in confidence and I can demonstrate ownership of my work.

Writing this thesis throughout the COVID-19 global pandemic was a unique experience. I had to adapt my own learning styles and methods of writing to suit a home-working environment. Here, I learnt I can be resilient and still be driven, despite such challenging circumstances and demonstrate largely autonomous initiative in a complex and unpredictable situation.

The reflections I have made when writing this thesis are linked to four 'themes': study development, inclusion, participants expectations of research and the 'unexpected' benefits of taking part. Each are described in the subsequent sections.

8.5.1 Study development

One of the challenges I faced early on in my studies was the ethical approval process. Although I had some experience of applying to NHS ethics for my MRes degree, the application and approval processes had changed considerably. The time in which ethical approval was granted, took much longer than anticipated; from original submission to receiving final approval from the relevant bodies took nine months.

The research ethics committee commented on the scientific design and the conduct of the study. This enabled important learning of research design, requiring me to justify aspects of the study design and as a result, strengthened the project as a whole. There were some components of the study I had to rethink to ensure procedures were robust and safe for participants. For example, with my supervisory team, I produced a protocol for identifying and reporting adverse events that

occurred outside of the centre (section 5.8.4). This is now included in the MoveEx Lab risk assessment and standard operating procedures for use in future research studies. As such, the ethical approval process was a valuable learning experience and I have gained a greater appreciation of ethical considerations within research.

Working with service users in a PPI capacity from the start of this project was crucial to ensuring an inclusive design. The service users were able to offer advice, on not only on the development of supporting documents, but also in being pragmatic in the set-up of the MoveEx Lab. This, in addition to the small proof-of-concept study, were helpful practices in finding the optimal set-up of the MoveEx Lab and the procedures I carried out. I learnt the importance of considering how the environment may impact accessibility and the ability to communicate, for example, background noise, harsh lighting, and de-cluttering spaces. With this learning, potential participants were always offered an initial visit to the MoveEx Lab, prior to their baseline assessment. This was offered with the aim of reducing any apprehension of visiting a new place, trialling travel arrangements and journey time. First impressions of the environment and ease of access would have most definitely affected decisions to take part and overall adherence to the study.

8.5.2 Inclusion

During my MRes and other relevant work experience, I had some experience of working with vulnerable people. However, this was my first time working solely with people who had experienced a stroke. Despite some volunteering with community support groups at the beginning of my studies, I was still surprised at the extent to which stroke impacts all aspects of life. As people with stroke may present with a number of different problems, I quickly had to become knowledgeable about possible and the differences in stroke presentation, including both physical and cognitive changes. I had originally underestimated the extent to which communication impairments would impact engagement in exercise. However, my work with service users and the training in supported communication I undertook was invaluable. I learnt ways to adapt my methods of communication to suit the needs of participants. The implications communication impairments have on inclusion is something that has resonated with me and became an important aspect of this thesis. Adapting

communication for optimal inclusion and for participation in exercise, has now become a particular interest of mine. I would like to continue researching ways in which exercise after stroke programmes may be adapted to be more inclusive of stroke survivors with communication impairments.

I learnt that individuals' exercise training had to take an even more holistic approach than previously anticipated. Despite planning exercise programmes and activities in advance, sessions often had to be modified on the day, in order to manage pain, changes in muscular tone and symptoms of fatigue. I had to rapidly become familiar with physiotherapy practices such as stabilising joints to facilitate a movement, managing other musculoskeletal issues and muscular relaxation techniques. Exercise sessions also had to be responsive to emotionalism, memory problems and sometimes frustration from participants. To manage these, I introduced regular rest-breaks during sessions, time for refreshments and allowed plenty of time to just talk about life after stroke. I also learnt that this time was equally as important for relatives who also attended the exercise sessions along with participants.

Throughout this research, I particularly enjoyed building relationships with participants and their relatives. I felt my relationship with participants was an important part of the group dynamic and for maintaining engagement throughout the intervention. For me, it was a real privilege to share this experience with participants. I was able to provide participants with opportunities they may not have had otherwise, such as being able to cycle again or providing dedicated time to practice walking, both in a safe environment with healthcare professionals. I felt delivering the intervention was exceptionally rewarding. I was able to share many 'first times' with participants; for example, stepping on to a step. Seeing how participants improved and changed in various ways over the course of the intervention was particularly rewarding for me.

Learning from The EXERCISES Study suggested that multiple methods of recruitment is required for optimal inclusion of stroke survivors. The recruitment strategy employed in the present study presented several challenges. To summarise, challenges in recruitment were related to:

- The rurality of Norfolk where the study was set and therefore travel burden;

- Those residing in a care or nursing home were unable to participate, due to difficulties in travel arrangements and a lack of care staff to accompany them to the MoveEx Lab;
- There was a reported lack of time from clinical teams to discuss opportunities to talk part in research, once the clinical needs of the patient had been addressed;
- The inclusion criteria for this study did not optimally define the population I was aiming to capture. At patient's six-month review meetings, the clinical team felt a significant proportion of patients were either sufficiently recovered or presented with disabilities that were too severe for the study inclusion criteria.

Part way through The EXERCISES Study, I amended the recruitment strategy to extend invitations to those attending community support groups, in an attempt to overcome some the challenges I was faced with. If I was to undertake this feasibility study again, or when planning a pilot study of a similar nature, I would be sure to adopt more than one avenue of recruitment from the outset. This would include using community support groups and national charities, such as The Stroke Association as gatekeepers, in addition to clinical recruitment pathways, such as community rehabilitation teams. I would endeavour to optimally define the inclusion criteria to overcome the anecdotal evidence from the clinical team regarding finding the optimal 'window of time' to recruit stroke survivors. Finding the optimal 'window of time' may be based on PPI and service user experience of their time 6-months post-stroke and their perception of when the most appropriate time to initiate exercise training might be. In the design of future research studies, it will be important to converse with care and/or nursing homes to discuss potential methods of promoting the inclusion of residents. This may be achieved by securing funding for travel and supervision, or by tailoring the research design to explore the feasibility of exercise interventions being delivered at a care and/or nursing home.

8.5.3 Participant's expectations of research

It was interesting to reflect on participants expectations of the exercise intervention. Seemingly, some participants perceived this research project to be an extension of their formal stroke rehabilitation. I felt some expected a different type of service, such as further physiotherapy,

followed by some form of quantitative feedback on stroke-specific outcomes. I thought this may be attributed to the involvement of healthcare professionals.

As part of the feasibility study, I administered the Montreal Cognitive Assessment. I was always mindful about explaining the purpose of the assessment to participants. I explained the assessment was for research purposes, not diagnostic purposes i.e. 'we are not testing you, we are testing the test'. Despite this, it emerged that there was some perception among participants that they assumed they were being formally assessed for cognitive impairment or dementia. For one participant and their relative, undertaking the Montreal Cognitive Assessment was a particularly emotionally distressing experience and I ended up stopping the assessment. This again highlighted the devastating impact of stroke to me and I provided support where I could. From this experience, I learnt that it is important to continually remind participants of the purpose of all activities being carried out throughout the research project.

As with any type of feasibility work, there are elements of flexibility and some trial and error. Due to this, I felt some participants were disappointed with the delivery of exercise sessions. I sensed some were disappointed they were unable to receive any formal feedback post-intervention, due to the nature of my study. In an attempt to overcome this, I opened up the conversation for them (and their relatives) to reflect on what they felt they had improved on. I provided a subjective summary of how they progressed in terms of their exercise ability, for example, *"in week one, you pedalled only for two minutes. But by week 3 you could do five and in week 6, you cycled for almost 10 minutes".* Here, I learnt the significance of sharing how participants are working towards or are attaining their goals and what this actually means to participants. Feedback on performance and recognition for achieving goals is an important part of behaviour change and adopting long-term adherence to exercise or physical activity (467-469). Therefore, in my future research, I intend to include formal feedback post-intervention as part of the study design.

8.5.4 Unexpected benefits of participation

For participants, taking part in a structured exercise intervention, if adhered to, may have improved general health and fitness. In addition, I observed several unexpected benefits of participation. I learnt that for participants, attending the MoveEx Lab was much more than just a place to exercise.

They had the opportunity to socialise and meet others who had shared-experiences – some had even previously been on the same acute stroke ward. Several formed friendships and now attend community stroke support groups together.

The MoveEx Lab is a research active site, with a number of on-going projects. Participants were aware of other projects and where appropriate, had the opportunity to request information about taking part. Some participants also expressed an interest in being involved in the development of future projects in a PPI capacity.

Anecdotally, I noted that participants who were six-months to one-year post-stroke, had several unmet needs. The research team was made up of a stroke consultant and a physiotherapist with neuro-expertise, this provided a platform for participants and their relatives to ask questions. We were able empathise, spend time problem-solving and signpost participants to the relevant services. Here, I learnt the importance of a multi-disciplinary research team to support the ongoing needs of participants.

Whilst stroke survivors exercised, it was initially expected that relatives would use this time as respite. However, almost all stayed to observe the exercise sessions. It was clear that relatives also benefitted from peer support and the social elements of the research study. For example, they were able to share personal experiences of caring for those who experienced a stroke, talk about home renovations, applications for personal independence payments and offer recommendations of private physiotherapy practices. Relatives were able to observe how participants responded to the exercise intervention and perhaps note some level of perceived improvement. For example, increased confidence and willingness to try new activities.

Where appropriate and safe, relatives were able to be involved in the delivery of exercises, so we could explore ways in which activities may be further adapted to be completed at home. For example, one participant purchased a stationary bike for home use, thus I demonstrated to their relative how they can facilitate pedalling by stabilizing the knee.

8.6 Participant vignettes

As described in the results of the EXERCISES study, participants expressed their intentions to continue engaging in exercise. Once participants had completed the EXERCISES study, some have been pleased to share what exercise they had recently been participating in either at home, or at local facilities. Included below are some vignettes that participants have shared with me. It appears that taking part in the EXERCISES study provided participants with the confidence that they are safely able to exercise. These vignettes are examples of the implications this research has for stroke survivors. They demonstrate the impact taking part in the EXERCISES study has had on their longer-term adherence to exercise training.

Figure 34: Participant vignette 1

Margaret (pseudonym) after completing the EXERCISES study, joined a local CrossFit® gym. She now attends they gym once a month, due to costs and transport, and takes part in a one-to-one adaptive CrossFit® session.

Figure 35: Participant vignette 2

Before his stroke, Steve (pseudonym) was heavily involved in the local hockey league and has coached at various levels. Steve said that taking part in the EXERCISES study gave him the confidence and improved mobility to return to coaching, albeit from mostly sitting down!

Figure 36: Participant vignette 3

Stuart (pseudonym) now regularly works with a personal trainer, both at home and at local facilities. He and his wife suggested that taking part in the EXERCISES study gave them the inspiration and the motivation to continue with formal exercise training.

Once the EXERCISES study had come to an end and I had analysed the data, I invited all participants to a 'reunion'. This took place at a local gym, a not-for-profit organisation that provides fitness opportunities to children and adults with learning and physical disabilities. Although the primary aim of the 'reunion' was to reconnect with participants and to share my findings, it was also an opportunity to showcase the facilities available for exercise after stroke and for participants to experience adaptive boxing. Since the reunion, I know of one participant who has been attending classes there regularly.

Figure 37: Participant vignette 4

Photographs taken at the EXERCISES study reunion. Individuals were able to have a go at adaptive boxing, with the exercise instructors and physiotherapists based at the local gym.

8.7 Summary of chapter

This thesis set out to explore the influence of exercise after stroke on cardiorespiratory fitness, with a view to maintain cognitive health. The research undertaken in this thesis has fulfilled this aim, by providing evidence relating to the acceptability of exercise after stroke. Findings of the systematic review (chapter 3) indicated there is currently a lack of evidence available to quantify and describe the nature of the relationship between cardiorespiratory fitness and cognitive function among stroke survivors. Future researchers are encouraged to explore this association at an individual level within well-designed studies, before the magnitude of this relationship may be described for the stroke population. Findings of the EXERCISES study (chapters 5 to 7) demonstrated inclusive adaptations for CPET and exercise training for stroke survivors with moderate to severe movement impairments. It is hoped that based on the learnings of the feasibility study, further research may determine optimal methods for implementing exercise after stroke interventions, with a view to maintain cognitive health.

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Appendices

1. Functional Ambulation Category

Appendix—Description of Functional Ambulation Category (FAC)

FAC	Ambulation Description	Definition
0	Nonfunctional ambulation	Subject cannot ambulate, ambulates in parallel bars only, or requires supervision or physical assistance from more than one person to ambulate safely outside of parallel bars
1	Ambulator-Dependent for Physical Assistance Level II	Subject requires manual contacts of no more than one person during ambulation on level surfaces to prevent falling. Manual contacts are continuous and necessary to support body weight as well as maintain balance and/or assist coordination
2	Ambulator-Dependent for Physical Assistance Level I	Subject requires manual contact of no more than one person during ambulation on level surfaces to prevent falling. Manual contact consists of continuous or intermittent light touch to assist balance or coordination
3	Ambulator-Dependent for Supervision	Subject can physically ambulate on level surfaces without manual contact of another person but for safety requires standby guarding on no more than one person because of poor judgment, questionable cardiac status, or the need for verbal cuing to complete the task.
4	Ambulator-Independent Level Surfaces only	Subject can ambulate independently on level surfaces but requires supervision or physical assistance to negotiate any of the following: stairs, inclines, or non-level surfaces.
5	Ambulator-Independent	Subject can ambulate independently on nonlevel and level surfaces, stairs, and inclines.

2. Systematic review search strings

Searches ran: Tuesday 22nd October 2019

Allied and Complementary Medicine Database (AMED)

	Search Terms	Results
S4	S1 AND S2 AND S3	8
S3	(MM "Cardiorespiratory Fitness") OR "cardiorespiratory fitness" OR (MM "Physical Fitness+") OR (MM "Exercise Test+") OR "maximal aerobic capacity"	284
S2	(MH "Cognition+") OR (MM "Mental Processes+") OR (MM "Executive Function") OR "cognitive function" OR "cognition"	5,048
S1	(MH "Stroke+") OR (MM "Brain Infarction+") OR (MM "Cerebrovascular Disorders+") OR (MH "Brain Ischemia+") or "stroke"	8,868

Cumulative Index to Nursing and Allied Health Literature (CINAHL

	Search Terms	Results
S4	S1 AND S2 AND S3	33
S3	(MM "Cardiorespiratory Fitness") OR "cardiorespiratory fitness" OR (MM "Physical Fitness+") OR (MM "Exercise Test+") OR "maximal aerobic capacity"	19,565
S2	(MH "Cognition+") OR (MM "Mental Processes+") OR (MM "Executive Function") OR "cognitive function" OR "cognition"	238,755
S1	(MH "Stroke+") OR (MM "Brain Infarction+") OR (MM "Cerebrovascular Disorders+") OR (MH "Brain Ischemia+") or "stroke"	126,862

Database of Research in Stroke (DORIS)

Search Terms	Results
Cognitive function AND maximal aerobic capacity	0
Cognition AND maximal aerobic capacity	0
Cognitive function AND fitness	7
Cognition AND cardiorespiratory fitness	1

E-Journals

	Search Terms	Results
S4	S1 AND S2 AND S3	4
S3	(MM "Cardiorespiratory Fitness") OR "cardiorespiratory fitness" OR (MM "Physical Fitness+") OR (MM "Exercise Test+") OR "maximal aerobic capacity"	3,568
S2	(MH "Cognition+") OR (MM "Mental Processes+") OR (MM "Executive Function") OR "cognitive function" OR "cognition"	107,570
S1	(MH "Stroke+") OR (MM "Brain Infarction+") OR (MM "Cerebrovascular Disorders+") OR (MH "Brain Ischemia+") or "stroke"	156,693

MEDLINE and MEDLINE Complete

	Search Terms	Results
S4	S1 AND S2 AND S3	7

S3	(MM "Cardiorespiratory Fitness") OR "cardiorespiratory fitness" OR (MM "Physical Fitness+") OR (MM "Exercise Test+") OR "maximal aerobic capacity"	76,749
S2	(MH "Cognition+") OR (MM "Mental Processes+") OR (MM "Executive Function") OR "cognitive function" OR “cognition”	1,536,840
S1	(MH "Stroke+") OR (MM "Brain Infarction+") OR (MM "Cerebrovascular Disorders+") OR (MH "Brain Ischemia+") or “stroke”	947,918

Physiotherapy Evidence Database (PEDro)

Search Terms	Results
Stroke AND cognitive function AND maximal aerobic capacity	0
Stroke AND cognition AND maximal aerobic capacity	0
Stroke AND cognitive function AND cardiorespiratory fitness	3
Stroke AND cognition AND cardiorespiratory fitness	3
Stroke AND cognition AND fitness training AND clinical trial	7

Occupational Therapy (OT) Seeker Database

Search Terms	Results
Stroke AND cardiorespiratory fitness AND cognition	1
Stroke AND cardiorespiratory fitness AND cognitive function	1
Stroke AND cardiorespiratory fitness	4
Stroke AND maximal aerobic capacity	0
Stroke AND cognitive function	32
Stroke AND cognition	23

PsychARTICLES and PsychINFO

	Search Terms	Results
S4	S1 AND S2 AND S3	5
S3	(MM "Cardiorespiratory Fitness") OR "cardiorespiratory fitness" OR (MM "Physical Fitness+") OR (MM "Exercise Test+") OR "maximal aerobic capacity"	848
S2	(MH "Cognition+") OR (MM "Mental Processes+") OR (MM "Executive Function") OR "cognitive function" OR “cognition”	270,649
S1	(MH "Stroke+") OR (MM "Brain Infarction+") OR (MM "Cerebrovascular Disorders+") OR (MH "Brain Ischemia+") or “stroke”	39,665

National Rehabilitation Information Centre (NARIC Rehabdata)

Search Terms	Results
Stroke AND cognitive function AND maximal aerobic capacity	1
Stroke AND cognition AND maximal aerobic capacity	1
Stroke AND cognitive function AND cardiorespiratory fitness	2
Stroke AND cognition AND cardiorespiratory fitness	2

SportDISCUSS

	Search Terms	Results
S4	S1 AND S2 AND S3	4
S3	(MM "Cardiorespiratory Fitness") OR "cardiorespiratory fitness" OR (MM "Physical Fitness+") OR (MM "Exercise Test+") OR "maximal aerobic capacity"	2,248
S2	(MH "Cognition+") OR (MM "Mental Processes+") OR (MM "Executive Function") OR "cognitive function" OR “cognition”	11,964
S1	(MH "Stroke+") OR (MM "Brain Infarction+") OR (MM "Cerebrovascular Disorders+") OR (MH "Brain Ischemia+") or “stroke”	19,783

Trip Medical Database

Search Terms	Results
Stroke AND cognitive function AND maximal aerobic capacity	177 Filtered to primary research = 3 exported
Stroke AND cognition AND maximal aerobic capacity	181 Filtered to primary research = 3 exported
Stroke AND cognitive function AND cardiorespiratory fitness	143 Filtered to primary research = 7 exported
Stroke AND cognition AND cardiorespiratory fitness	154 Filtered to primary research = 10 exported

3. Systematic review: excluded studies

Reference	Title	Reason for Exclusion
Rand et al. (10)	Feasibility of a 6 month exercise and recreation program to improve executive functioning and memory in individuals with chronic stroke.	No direct measure of VO_{2max}
Ji et al. (470)	Effect of yoga exercise on cognitive ability and motor function recovery in stroke patients	No direct measure of VO_{2max}
Lee et al. (471)	The effects of a motorized aquatic treadmill exercise program on muscle strength, cardiorespiratory fitness, and clinical function in subacute stroke patients: a randomized controlled pilot trial	No measure of cognition
Lee et al. (472)	Associations of arterial stiffness and cognitive function with physical fitness in patients with chronic stroke	No direct measure of VO_{2max}
Marzolini et al. (473)	Feasibility and Effects of Cardiac Rehabilitation for Individuals after Transient Ischemic Attack	Population did not adhere to inclusion criteria
Marzolini et al. (474)	Prescribing Aerobic Exercise Intensity without a Cardiopulmonary Exercise Test Post Stroke: Utility of the Six-Minute Walk Test	No direct measure of VO_{2max}
Potempa et al. (425)	Physiological outcomes of aerobic exercise training in hemiparetic stroke patients	No measure of cognition
Olivier et al. (292)	Maximal Cardiorespiratory Fitness Testing in Individuals with Chronic Stroke with Cognitive Impairment: Practice Test Effects and Test-Retest Reliability.	No measure of cognition
Stoller et al. (475)	Feedback-controlled robotics-assisted treadmill exercise to assess and influence aerobic capacity early after stroke: a proof-of-concept study.	Study design did not adhere to inclusion criteria
Pinter et al. (476)	Rehabilitation after stroke in older people.	Study design did not adhere to inclusion criteria
Blumenthal et al. (477)	Lifestyle and Neuro-cognition in Older Adults with Cardiovascular Risk Factors and Cognitive Impairment.	Population did not adhere to inclusion criteria

Dawes et al. (478)	The effect of a perceptual cognitive task on exercise performance: the dual-task condition after brain injury.	No direct measure of VO_{2max}
Steen et al. 2019 (479)	Effect of Home-Based High-Intensity Interval Training in Patients with Lacunar Stroke: A Randomized Controlled Trial.	No direct measure of VO_{2max}
Delistraty et al. (480)	Cardiovascular reactivity in Type A and B males to mental arithmetic and aerobic exercise at an equivalent oxygen uptake.	Population did not adhere to inclusion criteria
Pallesen et al. (481)	The effects of high-intensity aerobic exercise on cognitive performance after stroke: a pilot randomised controlled trial	No direct measure of VO_{2max}
Wolf et al. (482)	Combined Cognitive-Strategy and Task-Specific Training Affects Cognition and Upper-Extremity Function in Subacute Stroke: An Exploratory Randomized Controlled Trial	No direct measure of VO_{2max}
Bunketorp-Käll et al. (483)	Long-Term Improvements After Multimodal Rehabilitation in Late Phase After Stroke: A Randomized Controlled Trial	No direct measure of VO_{2max}
Ploughman et al. (224)	Does treadmill exercise improve performance of cognitive or upper-extremity tasks in people with chronic stroke? A randomized cross-over trial	No direct measure of VO_{2max}

Cardiorespiratory fitness and cognitive functioning following short-term interventions in chronic stroke survivors with cognitive impairment

Blanchet et al. (166)

Study design	Quasi-experimental, one-group pretest–posttest pilot study		
Inclusion criteria	A diagnosis of ischemic or haemorrhagic stroke; a cognitive deficit (Hachinski 2006); fluency in French; not currently receiving rehabilitation services; living at home; able to walk with an aid or independently; leg impairment score of 3 or more (Chedoke-McMaster Stroke Assessment)		
Sample size	14		
Participant characteristics (mean ± SD)	61.93 ± 9.90 years old 9 males, 5 females 51.50 ± 38.22 months since stroke		
	Aerobic Exercise (n = 7)	Aerobic Exercise and Cognitive Training (n = 7)	Control Group (n = 5)
Intervention characteristics			
Frequency	2 x week for 8 weeks	AE, plus: 1 x week for 8 weeks (plus, daily home programme)	No treatment
Intensity	60-70% of HRR	-	-
Type	AE (walking or cycling)	Cognitive computer training stimulating attention & working memory	-
Time	5 mins warm up/cool down, up to 30 mins	90 mins	-
Supervision	Exercise physiologist	Trained neuropsychologist	-
Setting	Research centre	Research centre and home	-
Measurement time points	Baseline, post-intervention (8 weeks) and 3 months follow up		
Outcome measures			

Cardiorespiratory fitness	Semi-recumbent ergometer; 10W/1 min, 60 rpm
Cognitive function	Episodic memory (Hopkins-revised verbal learning test), working memory (Brown-Peterson paradigm), attention (continuous performance test)
Findings	No significant findings were present for cardiorespiratory fitness, working memory, episodic memory (p = 0.18, p = 0.92 and p = 0.26, respectively). Attention was significantly improved at outcome (p = 0.01, 0.006) and in part at follow up (p = 0.03, 0.04).
Authors conclusions	Authors conclude that attention was significantly improved as a result of a structured intervention, however it is not known which intervention (aerobic exercise alone, or aerobic exercise and cognitive training combined) these benefits are attributed to. Given that changes in attention are present without any significant increase in cardiorespiratory fitness, the role in which this has in mediating changes to cognition and question what other potential mechanisms other than oxygen transportation or neurotransmitter transportation, may be responsible.

The effect of low-intensity aerobic training on cognitive functions of severely deconditioned subacute and chronic stroke patients: a randomized, controlled pilot study

Debreceni-Nagy (214)

Study design	Rater-blinded, randomized and controlled clinical study
Inclusion criteria	Ischaemic or haemorrhagic stroke more than three months ago; 18–75 years old; able to walk with or without devices; able to participate in CPET according to the Bruce protocol; mild or moderate stroke severity (according to the National Institutes of Health Stroke Scale (NIHSS); understanding the commands (according to Mini-Mental State Examination – MMSE test's complex command task) and having no dementia (MMSE sum of the points exceeding 23 points); ejection fraction over 40% without beta-blockers; blood pressure at rest 140/90 mmHg or less
Intervention	Control group

Sample size	19	16
Participant characteristics (median)	59 years 6 males, 13 females 12 ischemic strokes, 7 haemorrhagic strokes 10 months since stroke	62 years 5 males, 11 females 10 ischemic strokes, 6 haemorrhagic strokes 13 months since stroke
Intervention characteristics		
Frequency	1 x per day for 20 consecutive days	1 x per day for 20 consecutive days
Intensity	40-60% of HRR	-
Type	Conventional physiotherapy and cycle ergometry	Conventional physio- and occupational therapy
Time	60 mins and 20 mins	30 mins
Supervision	NR	NR
Setting	NR	NR
Measurement time points	Baseline and post-intervention (4 weeks)	
Outcome measures		
Cardiorespiratory fitness	Cycle ergometry; Bruce protocol	
Cognitive function	Functional independent measure cognitive sub-domain, working memory (digit span test), processing speed (coding subtest , symbol search)	
Findings	In-group analysis showed a significant improvement in study group patients regarding Coding subtest of Processing Speed domain (p = 0.003). Symbol Search subtest of Processing Speed showed significant improvements in both groups by the end of the programme (study group, p = 0.041; control group, p = 0.006). There were no significant changes in the FIM-cog and Digit Span task.	
Authors conclusions	Authors concluded that low intensity aerobic training in combination with conventional physical therapy is beneficial for domains of cognitive functions, specifically processing speed.	

Exercise and executive function in individuals with chronic stroke: a pilot study
Kluding et al. (211)

Study design	Single-group, pretest-posttest pilot
Inclusion criteria	Single stroke, ≥6 months prior; able to transfer from sitting position to a standing position; able to walk 30ft without assistance of another person; had received medical clearance from their primary physician; baseline score of MMSE >23
Sample size	9
Participant characteristics (mean ± SD)	63.7 ± 9.1 years old 5 males, 4 females 50.4 ± 37.9 months since stroke
Intervention characteristics	
Frequency	3 x week for 12 weeks
Intensity	50% of VO_{2max} or 11-14 RPE
Type	AE (TBRS) and RT (seated knee & ankle exercises with resistance bands)
Time	5 mins warm up/cool down; 20 minutes AE, 20 minutes RT
Supervision	NR
Setting	Academic medical centre
Measurement time points	Baseline and post-intervention (12 weeks)
Outcome measures	
Cardiorespiratory Fitness	Cycle ergometer; 10W/1 min, 60 rpm Total body recumbent stepper; 25 W, 40 W, 55 W, 70 W, 85 W, 100 W, 115 W, 130 W; 2 min 80 steps/min
Cognitive Function	Global cognition (MoCA), working memory (Digit Span Backwards Test), attention and executive function (Flanker Test), memory (Stroke Impact Scale)
Other	Walking endurance (6MWT), motor control (Fugl-Myer), gait speed (10WT), quality of life (Stroke Impact Scale)
Findings	Post-intervention, working memory, SIS total score and motor control was significantly improved (p=0.05, p=0.02, p=0.05 respectively). Strong trends towards improvements were noted for cardiorespiratory fitness, attention and executive function (p=0.06 and p=0.06, respectively). A significant association between improved cardiorespiratory fitness and improved identification of incongruent arrangements on the Flanker Test for attention and executive function (*r*=0.74, p=0.02).

Authors conclusions	The lack of improvement in cardiorespiratory fitness may be attributed to the short-term intervention and low level of training intensity. The diagnosis of diabetes mellitus in four out of nine participants may have confounded results of changes in cognition as a result of brain atrophy. Authors identified primary limitations to be a difficulty in recruitment and retention, and a small sample size leading to the increased risk of type II error.

The effects of an aerobic and resistance exercise training program on cognition following stroke
Marzolini et al. (212)

Study design	Pretest-posttest design
Inclusion criteria	≥10 weeks post-stroke, Chedoke McMaster motor impairment score of <7, able to ambulate ≥10 meters independently with or without an assistive device, no significant limitation from pain, other neurological condition or contraindication to maximal exercise testing.
Sample size	41
Participant characteristics (mean ± SD)	63.6 ± 13.5 years old 30 males, 11 females 27 ischemic strokes, 12h haemorrhagic strokes, 1 unknown 18.5 ± 33.6 months since stroke
Intervention characteristics	
Frequency	1 x supervised session per week for 6 months; recommended 4 additional AE session and 1-2 RT sessions a week
Intensity	AE: 40-70% of VO_{2max} or 11-16 RPE RT: ≥50% of 1RM or 13-14 RPE
Type	AE: walking, stationary recumbent/upright cycling; RT: task specific strengthening exercises with dumbbells, resistance bands or body weight
Time	20-60 mins
Supervision	NR
Setting	Community and home-based
Measurement time points	Baseline and post-intervention (6 months)
Outcome measures	
Cardiorespiratory fitness	Recumbent/upright bicycle ergometer or treadmill; 8.3 or 16.7 W/1 min
Cognitive function	Montreal Cognitive Assessment (MoCA)
Other	Gas exchange anaerobic threshold (CPET), body composition (DXA), muscular strength (1RM), motor impairment score (Chedoke McMaster), depression (CES-D scale), walking endurance (6MWD)
Findings	Significant improvements were noted in both global cognition (p=<0.001) and VO_{2max} (p=<0.001). There was a significant positive association between change in attention/concentration domains of the MoCA and changes in oxygen uptake at ATge (B=0.383), P=>0.001), independent of age, sex, time from stroke, change in fat

	mass and baseline or change in depression score. Change in ATge accounted for 40.9% of the variance in change in attention/concentration score.
Authors conclusions	Following a 6 month combined AT and RT exercise intervention, there was a 44.5% reduction in the proportion of participants meeting the threshold criteria for mild cognitive impairment (MCI), as measured by the MoCA (a score of <25 indicates MCI). Despite the absence of a control group, the magnitude of physiological changes following the intervention, may infer some efficacy for combined AT and RT to improve cognition, in particular memory and attention. Authors recommend further research to be conducted into the use of resistance training as a mediator in improving cognitive function, given the demonstration of positive associations between cognitive performance and fat free mass.

Effects of community exercise therapy on metabolic, brain, physical and cognitive function following stroke

Moore et al. (167)

Study design	Randomised controlled trial	
Study setting	Community, leisure centre	
Inclusion criteria	≥50 years old, ≥6 months post-stroke, able to complete 6MWT with or without a stick, living at home, completed all NHS physiotherapy, not already undertaking regular exercise.	
Sample size	40	
	Intervention group	Control group
Participant characteristics (mean ± SD)	68.0 ± 8.0 years old 18 males, 2 females 19 ischemic strokes, 1 haemorrhagic stroke 21.0 ± 34.0 months since stroke	71.0 ± 11.0 years old 16 males, 4 females 18 ischemic strokes, 2 haemorrhagic stroke 16.0 ± 12.0 months since stroke
Intervention characteristics		
Frequency	3 x week for 19 weeks	3 x week for 19 weeks
Intensity	40-80% of HR_{max}	NR
Type	Combined programme of stretching, functional strength, balance, agility and fitness training	Home stretching program
Time	45-60 mins	45-60 mins
Setting	NR	Home-based
Measurement time points	Baseline and post-intervention (19 weeks)	
Outcome measures		
Cardiorespiratory fitness	Recumbent bicycle ergometer; 10W/1 min at 50 rpm	
Cognitive function	Global cognition (Addenbrooke's Cognitive Examination)	
Other	Glucose control (HOMA), grey matter atrophy, cerebral blood flow and regional metabolism (MR imaging), resting blood pressure, lipid profile, body composition, walking endurance (6MWT), gait speed (10MWT),	

	balance (Berg balance test), quality of life (Stroke Impact Scale)
Findings	The study found significant increases in both VO_{2max} (p = <0.01) and global cognition as measured by the Addenbrooke's Cognitive Examination (ACE-R) (p = <0.01). Following the intervention, no change nor group-differences, were noted in glucose control, cerebral metabolism or cerebral tissue volume. The exercise group saw a significant increase in medial temporal lobe CBF (p = 0.05). Body composition remained unchanged, however, there was a within group improvement in HDL-C following the exercise intervention. Significant within-group improvements were only made in the exercise group in global cognitive function (p = <0.01) and quality of life (p = 0.03). Significant between-group differences were demonstrated in favour of the exercise intervention in walking endurance (p = <0.01), walking speed (p = <0.01) balance (p = <0.01), cognition (p = <0.01), mood (p = 0.02), and overall stroke recovery (p = <0.01).
Authors conclusions	Moore at al. conclude that short-term benefits in metabolism, physical function, cognition and quality of life are present following a 19 week community-delivered exercise intervention. Authors recommend future research to be undertaken with increased sample sizes, a more representative sample and an investigation of the long-term effects exercise may elicit on stroke recurrence, cardiovascular health and disability.

Synergistic benefits of combined aerobic and cognitive training on fluid intelligence and the role of IGF-1 in chronic stroke

Ploughman et al. (262)

Study design	Block-randomized, single-blinded pilot trial			
Inclusion criteria	Aged 18 years and over; ischemic or haemorrhagic stroke more than 6 months ago; self-reported cognitive problems related to stroke, interfering with daily functioning; ability to perform 2-step instruction; ambulation with/without aid ≥10 m; negative high-risk screening; agreement to refrain from aerobic exercise outside of the intervention; time commitment for the study.			
	Aerobic exercise & cognitive training	Aerobic exercise & games	Activity & cognitive training	Activity & games
Sample size	12	13	15	12
Participant characteristics (mean ± SD)	62.1 ± 14.2 years old 7 males, 5 females 9 ischemic strokes, 3 haemorrhagic strokes 40.9 ± 33.8 months since stroke	58.4 ± 11.7 years old 9 males, 4 females 12 ischemic strokes, 1 haemorrhagic strokes 36.0 ± 53.4 months since stroke	63.9 ± 8.5 years old 12 males, 3 females 11 ischemic strokes, 4 haemorrhagic strokes 35.2 ± 33.9 months since stroke	69.7 ± 8.9 years old 8 males, 4 females 8 ischemic strokes, 4 haemorrhagic strokes 53.9 ± 37.4 months since stroke
Intervention				
Frequency	3 x week for 10 weeks	3 x week for 10 weeks	3 x week for 10 weeks	3 x week for 10 weeks
Intensity	60-80% VO_{2peak}	NR	NR	NR
Type	Treadmill walking with BWS & computerized dual-n-back training	Treadmill walking with BWS & computer-based games	Therapeutic activity & computerized dual-n-back training	Therapeutic activity & computer-based games
Time	20-30 minutes	20-30 minutes	20-30 minutes	20-30 minutes
Supervision	HCP	HCP	HCP	HCP

Setting	Laboratory	Laboratory	Laboratory	Laboratory
Measurement time points	Baseline, post-intervention (10 weeks) and 3 month follow-up			
Outcome measures				
Cardiorespiratory fitness	Treadmill (with 10-15% BWS), 2.5% incline increase/2 mins; or total body recumbent stepper, 20W/2 mins			
Cognitive function	Fluid intelligence (Raven's Progressive Matrices Test), global cognition (MoCA)			
Other	Walking speed, serum levels of neurotrophins (brain-derived neurotropic factor and insulin-like growth factor)			
Findings	At follow-up, fluid intelligence scores significantly improved compared to baseline in the Aerobic + COG and Activity + COG groups; however, only the Aerobic + COG group was significantly different (+47.8%) from control (Activity + Games −8.5%). Greater IGF-1 response to exercise at baseline predicted 40% of the variance in cognitive improvement. There was no effect of the interventions on resting BDNF or BDNF response to exercise; nor was BDNF predictive of the outcome.			
Authors conclusions	Aerobic exercise combined with cognitive training improved fluid intelligence by almost 50% in patients >6 months post-stroke who were presumed to have reached their recovery plateau. Participants in the Aerobic + COG group also experienced gains in aerobic fitness and walking speed. Levels of serum IGF-1 in response to acute exercise at baseline (IGF-1response) significantly predicted improvements in fluid intelligence among the groups receiving cognitive training.			

Aerobic exercise improves cognition and motor function post-stroke
Quaney et al. (196)

Study design	Randomised clinical pilot study	
Study setting	NR	
Inclusion criteria	A single ischemic stroke ≥6 months, residual hemiparetic deficits in either the upper or lower limb, MMSE score of ≥23 and adequate cardiac function	
	Intervention group	Control group
Sample size	19	19
Participant characteristics (mean ± SD)	64.10 ± 12.30 years old 10 males, 9 females 19 ischemic strokes 55.44 ± 38.52 months since stroke	58.96 ± 14.68 years old 7 males, 12 females 19 ischemic strokes 61.32 ± 42.36 months since stroke
Intervention		
Frequency	3 x week for 8 weeks	3 x week for 8 weeks
Intensity	70% of HR_{max}	NR
Type	Aerobic exercise – cycling	Upper and lower extremity stretching activities
Time	45 mins	45 mins
Supervision	Physiotherapist & exercise physiologist	Home-based
Measurement time points	Baseline, post-intervention (8 weeks) and retention (+8 weeks)	
Outcome measures		
Cardiorespiratory fitness	NR	
Cognitive function	Global cognition (MMSE), learning (WCST), reaction time (Stroop test), reaction time (SRTT), attention (TMT)	
Findings	Significant improvements were noted in reaction time (measured by the Serial Timed Reaction Test) (p= 0.024) and VO_{2max} (p = 0.040), but not in attention or learning domains of cognition.	
Authors conclusions	This study provides evidence that the benefits of aerobic exercise training may be extended to not only improving the cognitive function of stroke survivors, but also sensorimotor learning.	

High and low intensity exercise do not improve cognitive function after stroke
Tang et al. (263)

Study design	Randomised controlled trial	
Study setting	Research centre	
Inclusion criteria	≥1-year post-stroke, able to walk ≥5m, free form stroke from aneurysm, tumour or infection or significant health conditions that would preclude participation in in exercise.	
Sample size	47	
	Intervention	Control
Participant characteristics (mean ± SD)	65.9 ± 6.4 years old 14 males, 11 females 3 lacunar strokes, 7 ischemic strokes, 9 haemorrhagic strokes, 6 unknown 51.6 ± 34.8 months since stroke	66.9 ± 7.8 years old 15 males, 10 females 4 lacunar strokes, 12 ischemic strokes, 7 haemorrhagic strokes, 2 unknown 48 ± 36 months since stroke
Intervention		
Frequency	3 x week for 6 months	3 x week for 6 months
Intensity	40-80% HRR	<40% HRR
Type	Combined programme of stretching, functional strength, balance, agility and fitness training	Low-intensity balance and flexibility
Time	60 mins	60 mins
Supervision	Physiotherapist, occupational therapist & exercise instructor	NR
Measurement time points	Baseline and post-intervention (6 months)	
Outcome measures		
Cardiorespiratory fitness	Cycle ergometry; 10 or 20W/1 min, 60 rpm	
Cognitive function	Global cognition (MoCA), working memory (DSBT), attention (TMT and Stroop test)	
Findings	Following 6 months of an individually tailored exercise programme, there were no significant improvements apparent in measures of cognition, with the exception of working memory in which both groups presented significant improvements over time (p= 0.04).	

Authors conclusions	Authors recommend that future studies should explore the development of optimal training parameters and examine potential mediators of such changes in cognition and cardiovascular function.

5. Quality appraisal tool: effective public health practice project

QUALITY ASSESSMENT TOOL FOR QUANTITATIVE STUDIES

EPHPP
Effective Public Health Practice Project

COMPONENT RATINGS

A) SELECTION BIAS

(Q1) Are the individuals selected to participate in the study likely to be representative of the target population?

1 Very likely
2 Somewhat likely
3 Not likely
4 Can't tell

(Q2) What percentage of selected individuals agreed to participate?

1 80 - 100% agreement
2 60 – 79% agreement
3 less than 60% agreement
4 Not applicable
5 Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

B) STUDY DESIGN

Indicate the study design

1 Randomized controlled trial
2 Controlled clinical trial
3 Cohort analytic (two group pre + post)
4 Case-control
5 Cohort (one group pre + post (before and after))
6 Interrupted time series
7 Other specify _____
8 Can't tell

Was the study described as randomized? If NO, go to Component C.

No Yes

If Yes, was the method of randomization described? (See dictionary)

No Yes

If Yes, was the method appropriate? (See dictionary)

No Yes

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

1

C) CONFOUNDERS

(Q1) Were there important differences between groups prior to the intervention?

1 Yes
2 No
3 Can't tell

The following are examples of confounders:

1 Race
2 Sex
3 Marital status/family
4 Age
5 SES (income or class)
6 Education
7 Health status
8 Pre-intervention score on outcome measure

(Q2) If yes, indicate the percentage of relevant confounders that were controlled (either in the design (e.g. stratification, matching) or analysis)?

1 80 – 100% (most)
2 60 – 79% (some)
3 Less than 60% (few or none)
4 Can't Tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

D) BLINDING

(Q1) Was (were) the outcome assessor(s) aware of the intervention or exposure status of participants?

1 Yes
2 No
3 Can't tell

(Q2) Were the study participants aware of the research question?

1 Yes
2 No
3 Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

E) DATA COLLECTION METHODS

(Q1) Were data collection tools shown to be valid?

1 Yes
2 No
3 Can't tell

(Q2) Were data collection tools shown to be reliable?

1 Yes
2 No
3 Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

F) WITHDRAWALS AND DROP-OUTS

(Q1) Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group?

1 Yes
2 No
3 Can't tell
4 Not Applicable (i.e. one time surveys or interviews)

(Q2) Indicate the percentage of participants completing the study. (If the percentage differs by groups, record the lowest).

1 80 -100%
2 60 - 79%
3 less than 60%
4 Can't tell
5 Not Applicable (i.e. Retrospective case-control)

RATE THIS SECTION	STRONG	MODERATE	WEAK	
See dictionary	1	2	3	Not Applicable

G) INTERVENTION INTEGRITY

(Q1) What percentage of participants received the allocated intervention or exposure of interest?

1 80 -100%
2 60 - 79%
3 less than 60%
4 Can't tell

(Q2) Was the consistency of the intervention measured?

1 Yes
2 No
3 Can't tell

(Q3) Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?

4 Yes
5 No
6 Can't tell

H) ANALYSES

(Q1) Indicate the unit of allocation (circle one)

community organization/institution practice/office individual

(Q2) Indicate the unit of analysis (circle one)

community organization/institution practice/office individual

(Q3) Are the statistical methods appropriate for the study design?

1 Yes
2 No
3 Can't tell

(Q4) Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actual intervention received?

1 Yes
2 No
3 Can't tell

GLOBAL RATING

COMPONENT RATINGS
Please transcribe the information from the gray boxes on pages 1-4 onto this page. See dictionary on how to rate this section.

A	**SELECTION BIAS**	**STRONG**	**MODERATE**	**WEAK**	
		1	2	3	
B	**STUDY DESIGN**	**STRONG**	**MODERATE**	**WEAK**	
		1	2	3	
C	**CONFOUNDERS**	**STRONG**	**MODERATE**	**WEAK**	
		1	2	3	
D	**BLINDING**	**STRONG**	**MODERATE**	**WEAK**	
		1	2	3	
E	**DATA COLLECTION METHOD**	**STRONG**	**MODERATE**	**WEAK**	
		1	2	3	
F	**WITHDRAWALS AND DROPOUTS**	**STRONG**	**MODERATE**	**WEAK**	
		1	2	3	Not Applicable

GLOBAL RATING FOR THIS PAPER (circle one):

1	STRONG	(no WEAK ratings)
2	MODERATE	(one WEAK rating)
3	WEAK	(two or more WEAK ratings)

With both reviewers discussing the ratings:

Is there a discrepancy between the two reviewers with respect to the component (A-F) ratings?

No Yes

If yes, indicate the reason for the discrepancy

1	Oversight
2	Differences in interpretation of criteria
3	Differences in interpretation of study

Final decision of both reviewers (circle one):

1	**STRONG**
2	**MODERATE**
3	**WEAK**

6. Quality appraisal tool: quality assessment components and rating

Components	Strong	Moderate	Weak
Selection bias	Very likely to be representative of the target population and greater than 80% participation rate	Somewhat likely to be representative of the target population and 60–79% participation rate	All other responses or not stated
Design	RCT and CCT	Cohort analytic, case-control, cohort, or an interrupted time series	All other designs or design not stated
Confounders	Controlled for at least 80% of confounders	Controlled for 60–79% of confounders	Confounders not controlled for, or not stated
Blinding	Blinding of outcome assessor and study participants to intervention status and/or research question	Blinding of either outcome assessor or study participants	Outcome assessor and study participants are aware of intervention status and/or research question
Data collection methods	Tools are valid and reliable	Tools are valid but reliability not described	No evidence of validity or reliability
Withdrawals and dropouts	Follow-up rate of >80% of participants	Follow-up rate of 60–79% of participants	Follow-up rate of <60% of participants or withdrawals and dropouts not described

Faculty of Medicine and Health
School of Health Sciences
University of East Anglia

Participant Information Sheet

Exercise to Improve Brain Health in People Following Stroke

IRAS reference number: 227602
Project Lead Investigators:
Alison C. Welsh, Dr. Kathryn Mares & Prof. Antony Arthur
Project Lead Clinician: Dr. Kneale Metcalfe
Project Site: University of East Anglia

You are being invited to take part in a research study looking at **how exercise and can improve your brain health.**
Before you decide, it is important for you to understand **why the research is being done and what it will involve.**
Please take time to **read the following information carefully and discuss it with others** if you wish.
Please ask if there is anything that is not clear or if you would like more information.

Thank you for reading this information and for considering taking part.

What is the purpose of this study?

The purpose of this study is to **find out what you think about carrying out an exercise test and taking part in an exercise training programme**. We want to know what works well, and what doesn't, so

that the information may **inform the design of future studies** looking at **exercise after stroke**.

Why do we need to do this study?

Exercise rehabilitation after a stroke aims to improve one's fitness levels, hoping to make daily activities less challenging. Regular exercise has also been shown to improve our memory and attention. However, we are not sure whether people who have had been diagnosed with a stroke, are willing to participate in both exercise testing and training.

Why have I been given this information?

You have been offered this information because we are hoping to work with those who had a stroke six or more months ago and are over 18 years old. You may have been identified by the community team you have been receiving care from, received information from a stroke survivor support group, or seen information on social media platforms.

What will happen if I participate?

If you decide to take part in the study, you will be asked to sign a **consent form**. We hope that you will be able stay with us throughout the whole duration of the study, which will **last for 6-8 weeks,** but we will work with you to make sure it will best fit your lifestyle. We will also need to **let your GP know that you are taking part** in our research project.

We would like to see how your brain health improves with exercise. So to do this, we ask that one of our researchers may visit you at home to **ask you some questions about your brain health, quality of life and daily activities.** We will contact you in advance to arrange a time and date that suits you best. Or if you would prefer to meet us elsewhere, such as a public place or a friend/relative's house, just let us know. This visit will take no more than an hour.

As exercise is the main part of this study, **we will invite you to the University of East Anglia (UEA) to meet a Stroke Consultant**/

Physician. This is will be in our Movement and Exercise Laboratory, also known as the MoveEx Lab. **The Stoke Consultant/Physician will carefully screen you to make sure you are safe to exercise**. They will have a chat with you about your current health, look at some previous medical notes, and check your heart rate and blood pressure. You will have the opportunity here to ask the Stroke Consultant/ Physician any questions you may have.

Once the Stroke Consultant/Physician is happy with your participation in exercise, we would like you complete a **short, gentle exercise test** so we can see what your current fitness levels are like. The exercise test may be done on a **stationary bike or a treadmill, with a body-weight supported harness, and will only take around 5 minutes to complete**. Two or three members of our research team, and a Stroke Consultant/Physician will be on hand during the test. Before you visit the MoveEx Lab for the exercise test, we do ask that you **avoid alcohol, tobacco and caffeine for at least 3 hours before**. This **visit will take up to 1 hour and a half** and refreshments will be provided.

Once we know what your current fitness levels are like, we **will create your own personal exercise programme with you that is tailored**

to your needs and abilities. We would like you to come back to UEA to do your exercise programme and this will be in the same room as you did your exercise test. You will have the opportunity to exercise when best suits you as we will offer 3 or 4 different days and times throughout the week – it doesn't have to be the same day/time each week. **Each session will be for one hour and there may be up to 8 other people also doing their own programme alongside you.** Ideally, we would like you to do your exercise programme **twice a week, for up to six-weeks**. However, we know you may have other commitments so will work with you to see how we can best fit your schedule.

When you come to the end of your exercise programme, we hope that your fitness levels will have improved, so to check this, we would like you do **another short, gentle exercise test.** We would also like to **arrange another time to meet to ask you the same questions about brain health, quality of life and daily activities**. Again, this can be done in your home, at UEA or another venue of your choice. Exercise testing and training in this way is a relatively new thing for those people post-stroke, so your views and opinions about it are really important to us. **You may have the opportunity to be invited to be interviewed by a member of our research team**. We would like to ask you about your experience of participating in the study, your likes and dislikes, your exercise preferences and any suggestions or improvements we can make for the future. **The interview may last for up to an hour** and are happy to visit you at home or other venue of your choice. With your permission we would record this interview with a voice recorder.

Do I have to take part?

No, taking part is entirely voluntary. If you decide not take part, your care will not be affected in any way. You are **free to withdraw from the study at any time**. **If you do decide to withdraw, it will**

not affect your level of care. Although it would be **helpful to know the reason why you withdrew**, you are under no obligation to tell us. Any data that we may have collected from you before you withdrew, will used in the final analysis, unless you tell us you do not want it to be used. Remember that your identity will be kept a secret.

What are the possible benefits of me taking part?

Taking part in a supported, structured exercise programme, if adhered to, **may improve your overall fitness and health**.

Travel expenses, including taxi fares, up to £100 per participant will be reimbursed for travel to and from UEA. Refreshments will be provided at the sessions. Car parking is very close to the MoveEx Lab.

Are there any possible disadvantages or risk if I take part?

Participating in **exercise can make you more tired than usual** and you **may feel a little achy in the muscles you have used**. Any achiness or light muscle soreness will be short-lived and you should **recover well within a day or two**. There is a relatively small risk of adverse events for all people participating in exercise. However, you will have been **thoroughly screened by a Stroke Consultant**/ **Physician** to make sure you are safe to participate. All of the research team are trained in first aid, intermediate life support and manual handling.

All exercises will be tailored to you and will be reviewed each week. It is very important that you talk to the research team if are experiencing any pain or discomfort as a result of any of the exercises.

If at any point during the study you feel uncomfortable, too tired to continue or just had enough, you are free to stop and continue another at another time or day. Or of course, you are free to withdraw from the study completely.

What if something goes wrong?

All exercise sessions and tests are extremely controlled and there will be a number of healthcare professionals on hand, so we expect that the risk of anything going wrong to be minimal.
However, if something does go wrong, or you have a complaint about the study in any respect, our research team will do our best to address the problem appropriately. You can contact the study leads of this study, Alison Welsh or Dr. Kathryn Mares – their details are at the bottom of this sheet. However, if you wish to talk to someone who will not be dealing with you directly, or you want your feedback to be anonymous, you can contact Prof. Valerie Pomeroy, who is the Director of Research in the School of Heath Sciences, here at the UEA. Compensation arrangements for negligent harm are covered by normal NHS and UEA Indemnity.

Prof. Valerie Pomeroy
Director of Research School of Health Sciences
Email: V.Pomeroy@uea.ac.uk
Tel: (01603) 591668

You may also contact the UEA Research and Enterprise Services or if any issues arise:

Research & Enterprise Services
The Registry (Floor 1)
University of East Anglia,
Norwich Research Park,
Norwich,
NR4 7TJ
Email: rin.reception@uea.ac.uk
Tel: 01603 591574

As a patient of the NHS, you also have the right to pursue a complaint through the usual NHS process. To do so, you can submit a written complaint to:

Patient Liaison Manager,
Complaints Office,
NCH&C NHS Trust,
Norwich Community Hospital,

Bowthorpe Road,
Norwich,
NR2 3TU
Email: complaints@nchc.nhs.uk
Tel: 01603 697381

Note that the NHS has no legal liability for non-negligent harm. However, if you are harmed and this is due to someone's negligence, you may have grounds for a legal action against NCH&C but you may have to pay your legal costs.

Will my taking part in the study be kept confidential?

All information collected about you during the course of the research will be kept strictly confidential. If you agree to take part, your medical records will be looked at by Stroke Consultant/Physician - they may also be looked at by staff from regulatory bodies to check that the study is being carried out properly. Data collected from the exercise test, exercise session, interviews and questions, will be stored on password protected university computers; and if they are hand written, stored in locked filing cabinets at UEA.

Who is organising the study?

The study is being **organised by Alison Welsh, a PhD student UEA**, along with her supervisors Dr. Kathryn Mares, Prof. Antony Arthur and Dr. Rebekah Hill. They are working alongside NNUH and the 6 month review team. The study is being conducted as part of a PhD.

What will happen with the results of the research?

The results will be written up in a thesis and submitted to UEA. We hope we can also submit the results to a scientific journal and present them at a number of scientific and medical conferences and other academic meetings. If you like, we can send you a copy of the results.

Who has reviewed this project?

The study has been reviewed by the Heath Research Authority and the Research and Development Committees at Norwich Community Hospital and Norfolk and Norwich University Hospital.

Whom may I contact for further information?

If you have any further questions, or feel you want just a little more information, please don't hesitate to get in contact with any of the research team. If you wish, **you can also contact us to arrange a day and time to visit the MoveEx Lab here at UEA** so you can see the set-up of the room.

Alison Welsh
PhD Student, UEA
a.welsh@uea.ac.uk
Tel: (01603) 593093

Dr. Kath Mares
PhD Supervisor; Lecturer in Physiotherapy
k.mares@uea.ac.uk
Tel: (01603) 593099

Prof. Antony Arthur
PhD Supervisor; Senior Lecturer
antony.arthur@uea.ac.uk
Tel: (01603) 591094

Dr. Rebekah Hill
PhD Supervisor; Lecturer in Adult Nursing
rebekah.hill@uea.ac.uk
Tel: (01603) 597051

Thank you for taking the time to read this information sheet – we hope that you will consider taking part.

Faculty of Medicine and Health
School of Health Sciences
University of East Anglia

Participant Information Sheet for Exercise

Exercise to Improve Brain Health in People Following Stroke

IRAS reference number: 227602
Project Lead Investigators:
Alison C. Welsh, Dr. Kathryn Mares & Prof. Antony Arthur
Project Lead Clinician: Dr. Kneale Metcalfe
Project Site: University of East Anglia

Thank you for agreeing to take part in above study. This information sheet will tell you all you need to know about the exercise test and the exercise sessions.

Also in this pack:

- Exercise session timetable
- UEA campus map
- Research team contact details

Don't hesitate to get in contact with any of our research team if you have any questions – our details are included in this pack on a separate sheet.

The Exercise Test

Why do I need to do an exercise test?

The purpose of the exercise test is to determine your overall fitness levels. For some people post-stroke, feelings of tiredness, shortness of breath and low mood may be common – and increasing fitness levels has been shown to improve these. However, we are still uncertain of the best way to measure a stroke-survivors' fitness –

either on a stationary bike or a treadmill with body-weight support – therefore we would like you to complete the tests and tell us about your experiences.

How will I be tested?

To discover your overall fitness, **we will ask you to do a little bit of exercise, either cycling on a stationary bike or walking on a treadmill with a body-weight supported harness, for around 5 minutes, or as much as you can manage.** The speed will start off extremely slow and then we will begin to make the speed a little faster each minute you are walking or cycling for. We do **ask that you wear a facemask so that we are able to analyse the air you breathe in and out.** There are two options of facemasks, so you can choose which one you prefer best. We also **ask that you will wear an ECG monitor so that we are able to monitor your heart rate**. This will involve having 6 stickers on your chest which has wires leading to a small belt. Ladies – please wear an appropriate sports top or vest; and gents – you may want to shave the area to reduce any pain when removing the stickers! There are private areas for changing to apply the stickers.

How will you decide which test I will do?

We would like to find out which of the exercise testing modes you prefer, so we hope that will complete both – one at the beginning of your exercise training programme and then the other one after you have completed your programme. To decide which one you do first, **one of our research team will randomly allocate you** to either the stationary bike or treadmill –as easy as flipping a coin.

What will I have to do in the test?

Stationary Bike:

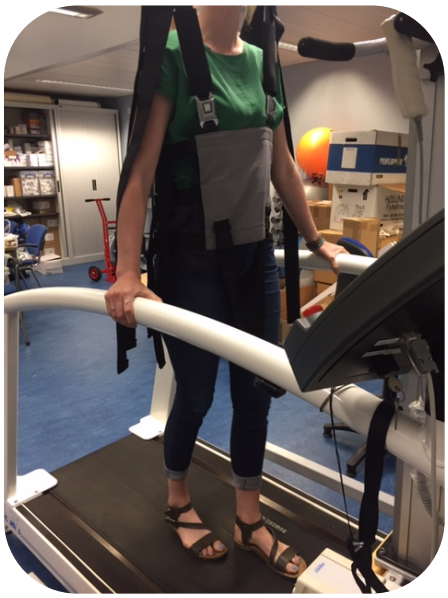
We will set you up on the stationary bike so that the handlebars and seat are at comfortable heights. If required, we do have access to a hoist to make your transition onto the bike easier and more comfortable. You will have a chance to pedal on a free wheel for a few

minutes so you are able to get used to the cycling motion. Then, when you are ready, we will begin to increase the resistance a tiny bit for every minute you are pedalling. It is really important to let us know when you are ready to stop cycling for whatever reason. We would like to record your reason for stopping, but let us know if you do not want us to. We'd guess that you'll be cycling for around 5 minutes – but any more or less time is fine.

Body-Weight Supported Treadmill:

For the treadmill test, we will fit you into a body-weight supported harness whist seated. The harness is very similar to a rock climbing harness with padding around the legs and inner thighs. You will then stand and step on to the treadmill and we will clip the harness in over-head. The harness will lift you up slightly so you are able to walk comfortably and feel safely supported. Holding on to the handrails will increase your stability. You will have some time to get used to walking on the treadmill and when you are ready, we will start the test by increasing the speed slightly, every minute or so. We expect you to be

walking for around 5 minutes – it very important to let us know when you wish to stop, for whatever reason.



How long will it take?

We expect the **whole visit to take up to an hour and a half**. However, the exercise test itself is very short – you will probably be **cycling or walking for only about 5 minutes**.

What do I need to wear?

Please wear **comfortable sports clothes and trainers**. A baggy t-shirt and thick tracksuit bottoms are recommended. There will be **private areas to change** if need be.

Who will be with me when I do the test?

During the test, **a stroke consultant or physician will be present, as well as two or three members of our research team.** You are welcome to bring your spouse, family member or a friend with you too.

Is there anything I need to do before the test?

Before you come to the Movement and Exercise Laboratory, also known as the MoveExLab, make sure you have taken all your medications as normal, are hydrated and had something light to eat.

We would like you to **please avoid alcohol, tobacco and caffeine for at least 3 hours before** you join us.

Do I need to bring anything with me?

Please bring a **bottle of water** with you, but don't worry too much if you forget, as refreshments will be provided. You may wish to also bring a **small exercise towel**.

You MUST bring with you any required medications, such as inhalers, epi-pens or angina sprays. If you forget them, unfortunately, you will not be allowed to exercise – however we will have the opportunity to arrange the test to another time that suits you.

Where do I go for the test?

The MoveExLab is located in the **Medical Building**, on Chancellors Drive, at the UEA main campus. On the map, it is **building number 43, grid number K17**. There is plenty of room for a taxi drop-off directly outside the building, or if you are driving, you will be able to park in the UEA main visitor's car park (pay and display) (grid number N29) or the Central visitor's car park (pay and display) (grid number K18). Both car parks are very close to the Medical Building. You will be reimbursed up to £100 for travel expenses (including taxi fares) and parking fees.

What happens after the test?

Directly after the test we will would like you **sit and relax in the MoveExLab for up to 20 minutes** so we can monitor your heart rate until it returns to normal. During this time, we will ask you a few questions about what you want out of your upcoming exercise training programme. We want to tailor it to your needs as much as possible so we value your input. Tea, coffee and refreshments will also be provided afterwards.

After the test, you may notice that you feel a little more tired than usual, so is best not to do much more physical activity the rest of the day. You may also feel thirstier or have more of an appetite afterwards, so make sure you drink and eat well.

The Exercise Sessions

How will you make my training programme?

The researchers working on this study are looking at three different types of exercise training after stroke to see which one may be best. You will be allocated to one exercise type. We want to make sure you get the most out of your exercise programme, so we will be working closely with you to develop it, according to your needs and exercise goals.

What do I have to do?

Ideally, we would like you to do your exercise programme **twice a week, for up to six-weeks**. However, we know you may have other commitments so will work with you to see how we can best fit your schedule. You will need to come to MoveExLab for your sessions – in this pack is a timetable of when the MoveExLab will be open for sessions.

How long is a session?

The exercise **sessions will be for one hour.** We do ask that you arrive in plenty of time before the session to get changed if need be and put on heart rate monitors.

Where do I go for the sessions?

The sessions will be held in the same place as your exercise test.

How will you monitor me?

To consistently make sure you are exercising safely, we will provide and ask you to wear a heart rate monitor. The monitor is a belt that will go around your middle, just above your ribs under your t-shirt. It then connects wirelessly to a watch that you will wear on your wrist. The researcher that is running your exercise session will record your heart rate during each of the exercises you do. They will also show you an exertion scale so we know how hard you feel you are working.

Who will be with me during the sessions?

The sessions will be run by the study organiser, Alison Welsh. Also in the MoveExLab will be one or two others from the research team. All members of the research team are training in first aid, intermediate life support and manual handling. During the sessions, other participants of the study will also be there completing their exercise programme. The session will be ran as a circuit class so you will exercise and rest at the same time.

What do I need to wear?

Please wear **comfortable sports clothes and trainers**. A baggy t-shirt and tracksuit bottoms are recommended. There will be **private areas for you to change** if need be.

You MUST bring with you any required medications, such as inhalers, epi-pens or angina sprays. If your forget them, unfortunately, you will not be allowed to exercise.

What will happen after the session?

Directly after the sessions, we will would like you **sit and relax in the MoveEx Lab for up to 20 minutes** so we can monitor your heart rate until it returns to normal. Tea, coffee and refreshments will also be provided afterwards.

After the test, you may notice that you feel a little more tired than usual, so is best not to do much more physical activity the rest of the

day. You may also feel thirstier or have more of an appetite afterwards, so make sure you drink and eat well.

What do I do if I cannot attend my next session?

If you cannot attend your next session for whatever reason, please let us know as soon as you can. You will be able to rearrange your session.

If you become unwell after one of the sessions and think it may be a result of the exercise, or if you are experiencing any prolonged pain/fatigue, again, please let us know at your earliest convenience.

University of East Anglia

Consent Form

Exercise to Improve Brain Health in People Following Stroke

IRAS reference number: 227602
Project Lead Investigators:
Alison C. Welsh, Dr. Kathryn Mares & Prof. Antony Arthur
Project Lead Clinician: Dr. Kneale Metcalfe
Clinical Trial Site: University of East Anglia

Name of Participant: _____

Participant Identification Number: _____

NB. *If the potential participant is unable to write, please find an independent witness who may complete this form as verbal consent is given by the potential participant. The independent witness should read each of the items to the potential participant and if the participant agrees, the independent witness should initial each of the boxes.*
The purpose of the independent witness is to physically complete this consent form on the instruction of a participant in the instance that the participant cannot do so for him or herself due to a physical inability to hold and or use a pen, or in the instance in which attempting to do so would or appears to cause distress to the participant. The independent witness cannot provide consent on behalf of a participant.
An independent witness must not be part of the research team and not be managed by a member of the research team.
One original copy of this form should be completed. The original should be stored in the investigator site file.
A photocopies should be made of the original and given to the participant.

	Initial Box
1. I confirm that I have read and understood the information sheet (version 4, dated 12/10/2018) received for the above study.	☐
2. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
3. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
4. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the University of East Anglia, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
5. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers (subject to relevant approvals being in place).	☐
6. I understand that the information held and maintained by the Health and Social Care Information Centre the University of East Anglia and other central UK NHS bodies may be used to help contact me or provide information about my health status.	☐
7. **I agree to take part in the above study.**	☐

Signature of **Participant**	Name of **Participant**	Date
Signature of **Witness** (in cases of oral consent)	Name of **Witness**	Date
Signature of **Researcher**	Name of **Researcher**	Date

When completed: 1 for participant; 1 for researcher site files; 1 (original) to be kept in medical notes.

10. Interview consent

University of East Anglia

Audio Recording Consent Form

Exercise to Improve Brain Health in People Following Stroke

IRAS reference number: 227602
Project Lead Investigators: Alison C. Welsh, Dr. Kathryn Mares & Prof. Antony Arthur
Project Lead Clinician: Dr. Kneale Metcalfe
Clinical Trial Site: University of East Anglia

This agreement is to be signed by the person who has agreed to be audio recorded as the principal party to, or as part of, an interview carried out within the University of East Anglia, or at the participants' home. The purpose of this agreement is to seek consent for this audio recording to be taken, subsequently transcribed and anonymised, and then used primarily within a doctoral thesis and other publications. The University of East Anglia in turn, offers a commitment to only allow audio recordings to be used appropriately and sensitively.
By signing this agreement, I hereby agree that:

1) The University of East Anglia shall record my interview in audio format.
2) I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason.
3) I, the undersigned, consent to the use of my personal data being processed for the purposes of this recording and subsequent publishing. My personal data will be processed in accordance with the provisions of the Data Protection Act 1998. I understand that my image and/or recordings will be used for educational purposes only and that copyright in the recordings will be retained by The University of East Anglia.
4) I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers (subject to relevant approvals being in place).

Signature of **Participant**	Name of **Participant**	Date
Signature of **Witness**	Name of **Witness**	Date
Signature of **Researcher**	Name of **Researcher**	Date

11. Letter to GP

University of East Anglia

Post-Graduate Research Office, Queens Building,
University of East Anglia, Norwich Research Park,
Norwich, NR4 7TJ.

Email: a.welsh@uea.ac.uk
Tel: 01603 593093
Twitter: @alliecwelsh

Aerobic Exercise to Improve Cognitive Function within Stroke Survivors

IRAS reference number: 227602
Project Lead Investigators: Alison C. Welsh, Dr. Kathryn Mares & Prof. Antony Arthur
Project Lead Clinician: Dr. Kneale Metcalfe
Clinical Trial Site: University of East Anglia

Dear Dr. _____

Re: Your Patient: _____

Date of Birth: _____

NHS Reference Number: _____

Address: _____

Your patient has kindly agreed to take part in the above research project. The project is being conducted in fulfilment of a PhD at the University of East Anglia. The objective of the project will be to explore the feasibility of delivering a 6 week exercise intervention with the aim of improving cognitive function and cardiovascular fitness in patients' 6 months or more post-stroke. We will also be investigating the safety and feasibility of different cardiovascular fitness testing modes.
A Stroke Consultant/Physician at the Norfolk and Norwich University Hospital has carefully screened your patient to ensure their eligibility to participate in exercise.
Your patient has been provided with an information sheet for the study (copy enclosed) which explains why s/he has been approached to take part in the trial, that the participation is entirely voluntary, and emphasises that they are free to withdraw from the trial at any time without prejudicing their future medical care.
If you have any concerns regarding your patients' participation, or would like any more information, please do not hesitate to get in contact with any of the research team. Their details are included on the enclosed participant information sheet.
Yours faithfully,
Alison Welsh BSc(Hons), MRes
PhD Student | Associate Tutor

12. Researcher screening form

Consent

Has informed consent been obtained for participation in this study? Yes / No (circle)

Date of consent: _____ / _____ / _____ (DD/MM/YY)

Participant characteristics

Date of Birth: _____ / _____ / _____ (DD/MM/YY) Gender: M / F (circle)

Medical history

For most recent stroke:

Date of stroke: _____ / _____ / _____ (DD/MM/YY)

Type of stroke: Ischaemic / Haemorrhagic (circle)

More paretic side of the body: Left / Right (circle)

Side of brain lesion: Left / Right (circle)

Residual disabilities: _____

_____

_____

Controlled hypertension? Yes / No (circle)
Comments: _____

Controlled hyperlipidaemia? Yes / No (circle)
Comments: _____

Diagnosis of diabetes? Yes / No (circle)
Comments: _____

Diagnosis of asthma? Yes / No (circle)
Comments: _____

Diagnosis of CVD? Yes / No (circle)
Comments: _____

Recent hospitalisations? Yes / No (circle)
Comments: _____

Musculoskeletal problems? Yes / No (circle)
Comments: _____

Skin allergies (or other)? Yes / No (circle)
Comments: _____

Smoking? Current? Yes / No (circle)
If currently, how many each day? _____
Comments: _____

Alcohol Consumption? Yes / No (circle)
How often? _____
Number of units? _____

Exercise history

Describe your current physical activity/exercise levels:

Sedentary *Light* *Moderate* *Vigorous* *(circle)*

Frequency (number of sessions per week): _____

Duration (minutes per session): _____

Do you use the stairs? Yes / No (circle)

Do you do light household activities? E.g. dusting, folding laundry, washing up

Yes / No (circle)

If yes, how often? _____

Do you do heavy household activities? E.g. vacuuming, gardening, moving boxes

Yes / No (circle)

If yes, how often? _____

Do you do any leisure activities? E.g. gym, swimming, walking, golf, boules

Yes / No (circle)

if so, please describe: _____

When you exercise, do you experience any of the following symptoms?

Chest discomfort Yes / No (circle)

Unreasonable breathlessness Yes / No (circle)

Dizziness, fainting or blackouts Yes / No (circle)

Before your stroke, what were your physical activity/exercise levels?

Sedentary *Light* *Moderate* *Vigorous* *(circle)*

Before your stroke, did you do any leisure activities? E.g. gym, swimming, walking, golf, boules

if so, please describe: _____

Current status:

	Comments:
Affected side:	
Medications:	
Pain Status:	
Range of Motion:	

Muscle Tone:	
Balance:	
Gait:	
Visuospatial problems:	
Communication:	
Transferring:	
Goals:	

After your stroke, can you describe what kind of physiotherapy you received?

_____

After your stroke, did you complete any community rehabilitation programme?

_____

After your stroke, did you/do you attend any stroke survivor groups?

_____

Eligibility Criteria

	Yes	No*
Informed consent has been provided		
Aged >18 years		
Are >6 months post-stroke		
Score 3-5 on the Functional Ambulation Category		
Can follow 1-stage command i.e. sufficient communication/orientation for interventions in the trial		
Are not attending any other exercise rehabilitation programmes for stroke		
Have been cleared by a physician to participate in exercise See physician screening form and exercise test data collection sheet		

*If answer is NO to any of the above questions, participant is NOT eligible to continue in the trial.
Is the participant eligible to participate in the trial? Yes / No (circle)

If no, describe reasons:

_____

_____

Person completing form:

Name (print):_____

Signature: _____

Date: _____ / _____ / _____ (DD/MM/YY)

Physician screening for CPET

Date: _____ / _____ / ____ (DD/MM/YY)

Participant ID Number: Ex_____

ABSOLUTE CONTRAINDICATIONS TO EXERCISE	Yes*	No
A recent significant change in the resting ECG suggesting significant ischaemia, recent myocardial infarction (within 2 days) or other acute cardiac event		
Unstable angina		
Uncontrolled cardiac dysrhythmias causing symptoms or hemodynamic compromise		
Symptomatic severe aortic stenosis		
Uncontrolled symptomatic heart failure		
Actuate pulmonary embolus or pulmonary infarction		
Acute myocarditis or pericarditis		
Suspected or know dissecting aneurysm		
Acute systematic infection, accompanied by fever, body aches or swollen lymph glands		

*If any item is marked YES, participant is **not** eligible to partake in the trial.

RELATIVE CONTRAINDICATIONS TO EXERCISE	Yes*	No
Left main coronary stenosis		
Moderate stenotic heart disease		
Electrolyte abnormalities e.g. hypokalaemia, hypo-magnesia		
Severe arterial hypertensions i.e. systolic BP of >200mmHg and/or diastolic BP of >110mmHg at rest		
Tachydysrthythmia or bradydsrhythmia		
Hypertrophic cardiomyopathy and other forms of outflow tract obstruction		
Neuromuscular, musculoskeletal or rheumatoid disorders that are exacerbated by exercise		
High-degree atrioventricular block		

Ventricular aneurysm		
Uncontrolled metabolic disease e.g. diabetes, thyrotoxosis or myxedemia		
Chronic infectious diseases e.g. mononucleosis, hepatitis, AIDs		
Mental or physical impairment leading to inability to exercise adequately		

*If any item is marked YES, participant will only take part in the trial under physicians' discretion.

This patient (Participant ID Number: Ex_____) is

To participate in an **exercise test** under the supervision of a stroke physician and a Health and Care Professions Council (HCPC) registered physiotherapist.

Name of physician completing screen: _____

Signature of physician completing screen: _____

Date: _____/_____/_____ (DD/MM/YY)

CPET data collection sheet

Date: _____ / _____ / ____ (DD/MM/YY)
Participant ID Number: Ex_____
Height:_____(m) Weight: _____(kg)

Beta-Blockers? Yes / No (circle) Dose: _____mg

Pre-CPET

Heart Rate:

1. _____ bpm
2. _____ bpm
3. _____ bpm

Blood Pressure:

1. _____ mmHg
2. _____ mmHg
3. _____ mmHg

Oxygen saturation: _____%

Predicted HR_{max}: _____bpm
(220 – (0.7 x age)) or (164 – (0.7 × age)) for beta-blocker medication
80% Predicted HR_{max}: _____bpm

Predicted VO_{2max}:

Absolute = _____mL/kg/min

(15.3) HRmax/HRresting

Relative = _____mL/min

absolute x body mass (kg)

CPET

Exercise Mode:

Treadmill ☐ Cycle Ergometer ☐

Weight on treadmill: _____ Seat Height: _____

BW x 0.9 = _____

Approx. % displaced: _____

Rating of Perceived Exertion			
Time	Stage	RPE	Heart Rate

Post-CPET

CPET data saved? Yes ☐ No ☐

Reason for stopping the test? _____

Other comments: _____

Heart Rate:	Blood Pressure:
4. _____ bpm	4. _____ mmHg
5. _____ bpm	5. _____ mmHg
6. _____ bpm	6. _____ mmHg

Adverse Events

Did any adverse events occur during the exercise test? Yes / No (circle)
If yes, please give details: _____

_____

_____

This patient (Participant ID Number: Ex_____) is

To participate in an **exercise intervention** under the supervision of a Health and Care Professions Council (HCPC) registered physiotherapist.

Name of supervising physician: _____

Signature of supervising physician: _____

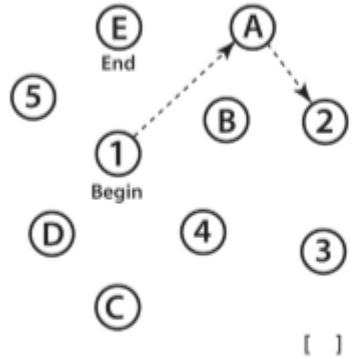
Date: _____/_____/_____ (DD/MM/YY)

14. Montreal Cognitive Assessment

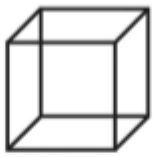
MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube



[ ] [ ]

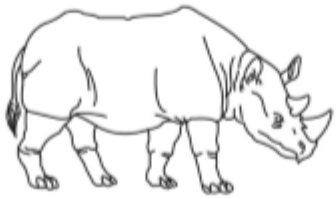
Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

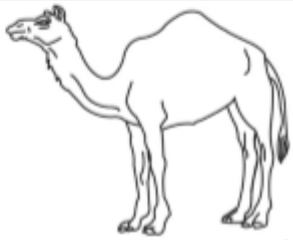
__/5

NAMING

[ ]



[ ]



[ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

__/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words **WITH NO CUE**	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

© Z.Nasreddine MD www.mocatest.org Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

15. Stroke Specific Quality of Life Scale

Scoring: each item shall be scored with the following key Scoring: each item shall be scored with the following key

Total help - Couldn't do it at all - Strongly agree - 1
A lot of help - A lot of trouble - Moderately agree - 2
Some help - Some trouble - Neither agree nor disagree - 3
A little help - A little trouble - Moderately disagree - 4
No help needed - No trouble at all - Strongly disagree - 5

Energy

1. I felt tired most of the time. ____
2. I had to stop and rest during the day. ____
3. I was too tired to do what I wanted to do. ____

Family Roles

1. I didn't join in activities just for fun with my family. ____
2. I felt I was a burden to my family. ____
3. My physical condition interfered with my personal life. ____

Language

1. Did you have trouble speaking? For example, get stuck, stutter, stammer, or slur your words? ____
2. Did you have trouble speaking clearly enough to use the telephone? ____
3. Did other people have trouble in understanding what you said? ____
4. Did you have trouble finding the word you wanted to say? ____
5. Did you have to repeat yourself so others could understand you? ____

Mobility

1. Did you have trouble walking? (If patient can't walk, go to question 4 and score questions 2-3 as 1.) ____
2. Did you lose your balance when bending over to or reaching for something? ____
3. Did you have trouble climbing stairs? ____
4. Did you have to stop and rest more than you would like when walking or using a wheelchair? ____
5. Did you have trouble with standing? ____
6. Did you have trouble getting out of a chair? ____

Mood

1. I was discouraged about my future. ____
2. I wasn't interested in other people or activities. ____
3. I felt withdrawn from other people. ____
4. I had little confidence in myself. ____
5. I was not interested in food. ____

Personality

1. I was irritable. ____
2. I was inpatient with others. ____
3. My personality has changed. ____

Self-care

1. Did you need help preparing food? ____
2. Did you need help eating? For example, cutting food or preparing food? ____
3. Did you need help getting dressed? For example, putting on socks or shoes, buttoning buttons, or zipping? ____
4. Did you need help taking a bath or a shower? ____
5. Did you need help to use the toilet? ____

Social roles

1. I didn't go out as often as I would like. ____
2. I did my hobbies and recreation for shorter periods of time than I would like. ____
3. I didn't see as many of my friends as I would like. ____
4. I had sex less often than I would like. ____

5. My physical condition interfered with my social life. ____

Thinking

1. It was hard for me to concentrate. ____
2. I had trouble remembering things. ____
3. I had to write things down to remember them. ____

Upper extremity function

1. Did you have trouble writing or typing? ____
2. Did you have trouble putting on socks? ____
3. Did you have trouble buttoning buttons? ____
4. Did you have trouble zipping a zipper? ____
5. Did you have trouble opening a jar? ____

Vision

1. Did you have trouble seeing the television well enough to enjoy a show? ____
2. Did you have trouble reaching things because of poor eyesight? ____
3. Did you have trouble seeing things off to one side? ____

Work/productivity

1. Did you have trouble doing daily work around the house? ____
2. Did you have trouble finishing jobs that you started? ____
3. Did you have trouble doing the work you used to do?

16. Barthel Index

THE BARTHEL INDEX

Patient Name: _____
Rater Name: _____
Date: _____

Activity	Score
FEEDING 0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent	_____
BATHING 0 = dependent 5 = independent (or in shower)	_____
GROOMING 0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)	_____
DRESSING 0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)	_____
BOWELS 0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent	_____
BLADDER 0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent	_____
TOILET USE 0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)	_____
TRANSFERS (BED TO CHAIR AND BACK) 0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent	_____
MOBILITY (ON LEVEL SURFACES) 0 = immobile or < 50 yards 5 = wheelchair independent, including corners, > 50 yards 10 = walks with help of one person (verbal or physical) > 50 yards 15 = independent (but may use any aid; for example, stick) > 50 yards	_____
STAIRS 0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent	_____
TOTAL (0–100):	_____

Provided by the Internet Stroke Center — www.strokecenter.org

17. Consensus on Exercise Reporting Template

CERT ✓ *C*onsensus on *E*xercise *R*eporting *T*emplate

A Checklist for what to include when reporting exercise programs

Section/Topic	Item #	Checklist item	Location **	
			Primary paper (page, table, appendix)	† Other (paper or protocol, website (URL)
WHAT: materials	1	Detailed description of the type of exercise equipment (e.g. weights, exercise equipment such as machines, treadmill, bicycle ergometer etc)		
WHO: provider	2	Detailed description of the qualifications, teaching/supervising expertise, and/or training undertaken by the exercise instructor		
HOW: delivery	3	Describe whether exercises are performed individually or in a group		
	4	Describe whether exercises are supervised or unsupervised and how they are delivered		
	5	Detailed description of how adherence to exercise is measured and reported		
	6	Detailed description of motivation strategies		
	7a	Detailed description of the decision rule(s) for determining exercise progression		
	7b	Detailed description of how the exercise program was progressed		
	8	Detailed description of each exercise to enable replication (e.g. photographs, illustrations , video etc)		
	9	Detailed description of any home program component (e.g. other exercises, stretching etc)		
	10	Describe whether there are any non-exercise components (e.g. education, cognitive behavioural therapy, massage etc)		
	11	Describe the type and number of adverse events that occurred during exercise		

WHERE: location	12	Describe the setting in which the exercises are performed		
WHEN, HOW MUCH: dosage	13	Detailed description of the exercise intervention including, but not limited to, number of exercise repetitions/sets/sessions, session duration, intervention/program duration etc		
TAILORING: what, how	14a	Describe whether the exercises are generic (one size fits all) or tailored whether tailored to the individual		
	14b	Detailed description of how exercises are tailored to the individual		
	15	Describe the decision rule for determining the starting level at which people commence an exercise program (such as beginner, intermediate, advanced etc)		
HOW WELL: planned, actual	16a	Describe how adherence or fidelity to the exercise intervention is assessed/measured		
	16b	Describe the extent to which the intervention was delivered as planned		

***It is recommended that this checklist is used in conjunction with the Explanation and Elaboration Statement which is a guide each item in the CERT Checklist**

The CERT Checklist is designed for reporting details of an exercise intervention. The CERT Checklist should be used in conjunction with a reporting checklist appropriate for the study type e.g. the CONSORT Statement (www.consort-statement.org) for randomised controlled trials, the SPIRIT Statement (www.spirit-statement.org) for a clinical trial protocol. For further guidance regarding reporting guidelines please consult the EQUATOR network (www.equator-network.org)

** Authors – please use N/A if an item is not applicable Reviewers – please use "?" if information is not provided or not/insufficiently reported

† If the information is not provided in the primary paper that is under consideration, please provide details of where this information is available e.g. in a published protocol, published papers (provide citation details) or on a website (provide the URL).

18. Example exercise programme

Week 1 Session 1				**Week 1 Session 2**			
	Heart Rate		**Blood Pressure**		**Heart Rate**		**Blood Pressure**
Pre	91		133/84	**Pre**	89		135/84
Exercise	**Time**	**HR**	**RPE**	**Exercise**	**Time**	**HR**	**RPE**
Recumbent bike (level 5)	15 mins	118	13	Recumbent bike (level 5)	15 mins	111	13
Superman	3 x 8 reps	110	15	Superman	3 x 8 reps	107	
Rotators (2kg)	1 x 10 reps each side	121	-				
Rower (level 10)	-	108	-	Rower (level 10)	10 mins	105	11
				Shoulder press (1kg) (on large ball)	1 x 10	102	17
				Chest press (1kg) (on large ball)	1 x 10 each arm	95	17
Post	101		129/89	**Post**	104		157/86

Week 2 Session 1				**Week 2 Session 2**			
	Heart Rate		**Blood Pressure**		**Heart Rate**		**Blood Pressure**
Pre	89		132/85	**Pre**	96		133/80
Exercise	**Time**	**HR**	**RPE**	**Exercise**	**Time**	**HR**	**RPE**
Rower (level 10)	5 mins	-	13	Recumbent bike (level 5)	15 mins	117	13
Upright bike	20 mins	117	13	Upper back (green band)	2 x 10 reps	106	-
				Step ups	3 x 10 each leg	100	13
				Russian twists	2 x 10 each side	100	13
Post	88		138/79	**Post**	95		130/85

Week 3 Session 1				**Week 3 Session 2**			
	Heart Rate		Blood Pressure		Heart Rate		Blood Pressure
Pre	102		147/82	**Pre**	100		123/82
Exercise	**Time**	**HR**	**RPE**	**Exercise**	**Time**	**HR**	**RPE**
Recumbent bike (level 4)	20 mins	121	11	Rower (level 9)	10 mins	112	11

Arm circuit (2kg) (seated on large ball)	3 sets	112	15	Bicep curls	2 x 10 each arm	101	-
				Squats	3 x 5 reps	104	-
				Hip raises	3 x 5 reps (both feet on floor 2 x 5 each leg raised	102	-
				Upright bike	15 mins	120	13
Post	104		137/87	**Post**	-		-

Week 4 Session 1				**Week 4 Session 2**			
	Heart Rate		**Blood Pressure**		**Heart Rate**		**Blood Pressure**
Pre	101		104	**Pre**	101		129/87
Exercise	**Time**	**HR**	**RPE**	**Exercise**	**Time**	**HR**	**RPE**
Rower (level 10)	10 mins	-	13	Recumbent bike (level 5)	10 mins	-	-
Tricep dips	6 x 5 reps	116	15	Recumbent bike (level 6)	5 mins	122	13
Leg extensions (2kg ankle weight & blue band)	2 x 20 reps each leg	107	11	Seated row (2kg)	2 x 10 reps	107	13
Upright bike	15 mins	120	13	Seated flies (2kg)	2 x 10 reps	105	13
				Upright bike	10 mins	117	13
Post	127/87		128/95	**Post**	103		120/92

Week 5 Session 1				**Week 5 Session 2**			
	Heart Rate		**Blood Pressure**		**Heart Rate**		**Blood Pressure**
Pre	91		133/81	**Pre**	94		129/81
Exercise	**Time**	**HR**	**RPE**	**Exercise**	**Time**	**HR**	**RPE**
Upright bike	-	118	12	Upright bike	10 mins	120	12
Shoulder press (2kg) (seated on large ball)	2 x 10 reps	105	15	Hula (seated on large ball)	2 x 5 both directions	106	16
Bicep curls (2kg) (seated on large ball)	2 x 10 reps	-	15	Overhead press (1kg) (seated on large ball)	5 x 3 reps	105	15
Tricep dips	2 x 10 reps	-	15	Forward punches	-	101	13

				(1kg) (seated on large ball)			
Sit to stands	-	89	13	Recumbent bike (level 6)	10 mins	120	13
Recumbent bike (level 5)	-	115	12	Sit to stand	3 x 10 reps	104	13
Post	104		135/90	**Post**	103		135/87

Week 6 Session 1				**Week 6 Session 2**			
	Heart Rate		**Blood Pressure**		**Heart Rate**		**Blood Pressure**
Pre	99		128/85	**Pre**	91		141/87
Exercise	**Time**	**HR**	**RPE**	**Exercise**	**Time**	**HR**	**RPE**
Upright bike	15 mins	130	13	Upright bike	-	120	14
Hula (seated on large ball)	2 x 5 both directions	110	11	Overhead press (1kg) (seated on large ball)	2 x 10 reps	109	14
Overhead press (1kg) (seated on large ball)	5 x 3 reps	103	14	Sit to stand	-	107	12
Forearm rotators	-	103	13	Tricep dips	-	112	15
Sit to stand	2 x 10 reps	103	11	Recumbent bike (level 7)	10 mins	126	15
Calf raises	-	100	11				
Recumbent bike (level 6)	10 mins	120	14				
Post	107		132/85	**Post**	106		133/83

19. Interview topic guide

Topic	Questions/probes
Introduction sentence: *"I'd first like to talk about your general experiences of exercise and physical activity."*	
Past experience of exercise, before the stroke event	Can you tell me about what kind of exercise or physical activity you used to do before your stroke? Probe (1): Was exercise quite a big part of your life then, before your stroke? Probe (2): How did you find it? Probe (3): What were your reasons for doing *activity/exercise*? Probe (4): How did it make you feel when you exercised, or didn't exercise? Probe (5): You said you didn't really do much exercise or physical activity, why was that?
Past experience of exercise, after stroke event	Can you tell me about what physical activity or exercise you have been doing after your stroke, (other than the recent programme at UEA)? Probe (1): What kind of exercise did you do with the physios? Probe (3): Did you take part in any exercise referral schemes?
Barriers and facilitators of exercise participation	What barriers do you now come across, after your stroke, when participating in exercise or physical activity? Prompts: Travel, co-morbidities, cost, fatigue, time Do you now have any specific motivators, or something that spurs you on, to do exercise or physical activity? Prompts: Goals, socialisation, recovery
Summary of topic's main statements if necessary, followed by transition sentence: *"I'd now like to talk about the exercise tests that you did. Do you remember coming to the UEA when you met Dr. Metcalf, and you firstly exercised on the bike/treadmill, then the treadmill/bike a blue mask over your mouth and nose?"*	
CPET	
Perceptions of exercise testing before attending	Before you completed the first exercise test, what did you expect to happen, or it to be like? Probe (1): Was it different about it to the information video you watched? Prompts: Perceived fear, environment, people, level of difficulty
Experience of exercise testing modes Photographs of both modalities were used here as a memory prompt	Can you tell me about your experience of completing the exercise test you did right at the start on the *treadmill/bike*?

	And what about the other test you did, the *treadmill/bike*, at the end of your exercise programme? Prompts: Comfort of seat/harness/pedals, staff, level of difficulty Is there anything we could have done to improve your experience of the test on the *bike/treadmill*? Out of the two, is there a CPET mode that you preferred?
Summary of topic's main statements if necessary, followed by transition sentence: *"After you did the test, we created you an exercise programme and you visited us twice a week for six-weeks…"*	
Exercise intervention	
3a. Experience of intervention Show exercise programme card as a reminder of activities completed	Can you tell me about your experience of the exercise programme you have just completed? Probe (1): Were your previous expectations of the programme different to what you experienced? Probe (2): How did you find it? What things in particular do you remember about it?
Factors influencing intervention attendance	You attended *number* of sessions, what were some of the things that helped you, or motivated you to come to the exercise sessions? What about things that may have prevented you from coming?
Summary of topic's main statements if necessary, followed by transition sentence: *"We hope that we can develop and improve this programme for stroke survivors in the future and so I would like to know if you have suggestions…"*	
Suggestions to improve the suitability and acceptability of exercise testing and training	Was there anything we could have done to improve your experience? Prompts: Time, travel, exercising in a group
Summary of topic's main statements if necessary, followed by transition sentence: *"We hope that you have got some benefit from participating in this exercise programme and so I am interested to hear about whether you think you have improved…"*	
Perceptions of perceived outcomes	In terms of your overall fitness levels, do you think you have improved because of the exercise training? Probe (1): For example, do you feel less breathless? Do you feel stronger? Is your balance better? In terms of your cognitive function, meaning your memory and attention, do you feel like it has improved? Overall, do you think your quality of life has improved because of doing the exercise?

	Now you know how to complete some exercises safely, do you think you will continue exercising at home or perhaps join a gym?
Interviewer to paraphrase and summarise participants' all responses to ensure correct interpretations. *"We are now coming to the end of this interview, is there anything else you would like add or expand upon that we haven't yet covered?"*	
Closing statement: *"That now brings us to the end of this interview. Thank you very much for your time. I will be transcribing and analysing the information you have given me and if you like, I can send you a copy for your records. Thank you again for your time."*	

20. Consolidated criteria for reporting qualitative research (COREQ)

No	Item	Guide questions/description
Domain 1: Research team and reflexivity		
Personal characteristics		
1.	Interviewer/facilitator	Which author/s conducted the interview or focus group?
2.	Credentials	What were the researcher's credentials? *E.g. PhD, MD*
3.	Occupation	What was their occupation at the time of the study?
4.	Gender	Was the researcher male or female?
5.	Experience and training	What experience or training did the researcher have?
Relationship with participants		
6.	Relationship established	Was a relationship established prior to study commencement?
7.	Participant knowledge of the interviewer	What did the participants know about the researcher? e.*g. personal goals, reasons for doing the research*
8.	Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. *Bias, assumptions, reasons and interests in the research topic*
Domain 2: study design		
Theoretical framework		

No	Item	Guide questions/description
9.	Methodological orientation and Theory	What methodological orientation was stated to underpin the study? *e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis*
Participant selection		
10.	Sampling	How were participants selected? *e.g. purposive, convenience, consecutive, snowball*
11.	Method of approach	How were participants approached? e*.g. face-to-face, telephone, mail, email*
12.	Sample size	How many participants were in the study?
13.	Non-participation	How many people refused to participate or dropped out? Reasons?
Setting		
14.	Setting of data collection	Where was the data collected? e*.g. home, clinic, workplace*
15.	Presence of non-participants	Was anyone else present besides the participants and researchers?
16.	Description of sample	What are the important characteristics of the sample? *e.g. demographic data, date*
Data collection		
17.	Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?
18.	Repeat interviews	Were repeat interviews carried out? If yes, how many?

No	Item	Guide questions/description
19.	Audio/visual recording	Did the research use audio or visual recording to collect the data?
20.	Field notes	Were field notes made during and/or after the interview or focus group?
21.	Duration	What was the duration of the interviews or focus group?
22.	Data saturation	Was data saturation discussed?
23.	Transcripts returned	Were transcripts returned to participants for comment and/or correction?
Domain 3: analysis and findings		
Data analysis		
24.	Number of data coders	How many data coders coded the data?
25.	Description of the coding tree	Did authors provide a description of the coding tree?
26.	Derivation of themes	Were themes identified in advance or derived from the data?
27.	Software	What software, if applicable, was used to manage the data?
28.	Participant checking	Did participants provide feedback on the findings?
Reporting		
29.	Quotations presented	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? e.*g. participant number*

No	Item	Guide questions/description
30.	Data and findings consistent	Was there consistency between the data presented and the findings?
31.	Clarity of major themes	Were major themes clearly presented in the findings?
32.	Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?

21. The EXERCISES study: ethical approval – REC favourable opinion

NHS
Health Research Authority

East of England - Cambridge Central Research Ethics Committee
Royal Standard Place
Nottingham
NG1 6FS

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

19 April 2018

Miss Alison C Welsh
Post-Graduate Research Office, Queens Building
University of East Anglia
Norwich Research park
NR47TJ

Dear Miss Welsh

Study title:	**Aerobic Exercise and Cognitive Function within Stroke Survivors, a Feasibility Study.**
REC reference:	**17/EE/0409**
IRAS project ID:	**227602**

Thank you for your letter of 23 February 2018, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [UEA Insurance and Indemnity Letter]	1	19 September 2017
GP/consultant information sheets or letters [Letter to GP]	1	06 June 2017
Interview schedules or topic guides for participants [Interview Schedule]	1	06 June 2017
IRAS Application Form [IRAS_Form_22122017]		22 December 2017
Laboratory Manual [UEA VO2max Testing Risk Assessment]	1	08 August 2017
Laboratory Manual [UEA MoveEx Lab Risk Assessment]	1	12 December 2017
Letters of invitation to participant [Invitation Letter and Consent to Contact]	1	31 August 2017
Other [NNUH/UEA SOP 206 dentifying, Recording and Reporting Adverse Events for Healthcare Research Studies that are not CTIMPS]	1	20 December 2017
Other [NNUH/UEA AE/SAE Reporting Form]	1	20 December 2017
Other [Ethics Response Letter]	1	20 December 2017
Other [Ethics Response Letter]	2	12 February 2018
Participant consent form [Consent Form]	2	20 December 2017
Participant information sheet (PIS) [Participant Information Video Outline]	1	21 September 2017
Participant information sheet (PIS) [Participant Information Sheet]	2	20 December 2017
Participant information sheet (PIS) [Participant Information Sheet]	3	12 February 2018
Participant information sheet (PIS) [Participant Information Sheet for Exercise]	3	12 February 2018
Referee's report or other scientific critique report [Val Pomeroy Peer Review 040517]	1	04 May 2017
Referee's report or other scientific critique report [Kneale Metcalfe Peer Review 081117]	1	08 November 2017
Research protocol or project proposal [Protocol]	3	12 February 2018
Summary CV for Chief Investigator (CI) [CI Alison Welsh CV]	1	19 September 2017
Summary CV for student [Alison Welsh]	1	18 September 2017
Summary CV for supervisor (student research) [Kathryn Mares]	1	15 September 2017
Summary CV for supervisor (student research) [Antony Arthur]		17 July 2017
Summary CV for supervisor (student research) [Rebekah Hill]	1	03 July 2017
Summary CV for supervisor (student research) [Niki Wyatt]	1	03 July 2017

Summary CV for supervisor (student research) [Kneale Metcalf]	1	18 September 2017
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Study Flow Chart]	1	06 June 2017
Validated questionnaire [Montreal Cognitive Assessment]	1	
Validated questionnaire [Stroke Specific Quality of Life Scale]	1	19 September 2017
Validated questionnaire [Barthel Index]	1	18 September 2017

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at
http://www.hra.nhs.uk/hra-training/

17/EE/0409	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely

pp. S. O'Neil

Revd Dr Derek Fraser
Chair

Email:NRESCommittee.EastofEngland-CambridgeCentral@nhs.net

Copy to: *Ms Tracy Moulton*
Ms Laura Haper, Norfolk and Norwich University Hospitals NHS Foundation Trust

22. The EXERCISES study: HRA ethical approval

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Miss Alison C Welsh
Post-Graduate Research Office, Queens Building
University of East Anglia
Norwich Research park
NR47TJ

Email: hra.approval@nhs.net

19 April 2018

Dear Miss Welsh

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Aerobic Exercise and Cognitive Function within Stroke Survivors, a Feasibility Study.**
IRAS project ID:	**227602**
REC reference:	**17/EE/0409**
Sponsor	**University of East Anglia**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?
You should now provide a copy of this letter to all participating NHS organisations in England and Wales*, as well as any documentation that has been updated as a result of the assessment.

Following the arranging of capacity and capability, participating NHS organisations should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "*summary of assessment*" section towards the end of this letter.

You should provide, if you have not already done so, detailed instructions to each organisation as to how you will notify them that research activities may commence at site following their confirmation of capacity and capability (e.g. provision by you of a 'green light' email, formal notification following a site initiation visit, activities may commence immediately following confirmation by participating organisation, etc.).

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

IRAS project ID	227602

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA/HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA/HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?
The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?
You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Name: Ms Tracy Moulton
Tel: 01603 591482
Email: t.moulton@uea.ac.uk

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **227602**. Please quote this on all correspondence.

IRAS project ID	227602

Yours sincerely

Juliana Araujo
Assessor
Email: hra.approval@nhs.net

Copy to: *Sponsor Representative: Ms Tracy Moulton, University of East Anglia*
Lead NHS R&D Office Representative: Ms Laura Haper, Norfolk and Norwich University Hospitals NHS Foundation Trust

23. Researcher safety checklist

Project Title: Aerobic Exercise and Cognitive Function within Stroke Survivors **Chief Investigator: Alison Welsh**			
Action	**Notes on Project Specific Arrangements**	**Who's Responsibility**	**Completed?**
Organisational			
Obtain UEA ID and NHS honorary contract/research passport	Alison Welsh (AW), the chief investigator of the study has a UEA ID as a full-time doctoral student. AW has obtained an NHS honorary contract.	AW	
Attend and complete appropriate training: e.g. good clinical practise (GCP), manual handling, intermediate life support (ILS), information governance (IG)	AW has completed the relevant training: • GCP: 18/01/2017 • Manual Handling: 13/04/2017 • First Aid: 12/04/2017 • IG: 26/07/2017	AW	
Risk assessments for research design	General risk assessments of the study design were considered when the study was designed by AW and supervisory team, Kathryn Mares (MK) and Anthony Arthur (AA)	AW, KM & AA	
Confirm indemnity insurance for researchers	As the sponsor of the study, UEA indemnity/insurance arrangements for the management, design and conduct of the study will apply	UEA Research Enterprise Network (REN)	
Create incident/adverse event reporting systems	AW, KM & AA have agreed upon a system for incident/adverse events reporting	AW, KM & AA	
Organise team meeting to agree on general level of risk, systems and responsibilities	AW, KM & AA have discussed researcher health and safety within a supervisory meeting	AW, KM & AA	
Operational (site visit for outcome assessments)			
Review participant notes and comments from clinical team to identify any potential risk	Participants of the study will have been under the care of the stroke team for >6 months, thus the clinical team will be aware of any potential risk and will be able to pass on any relevant information regarding the participant/site	AW & clinical team	
Contact participant to arrange visit time/day	Following consent, phone participant to arrange	AW	

	appropriate day and time to visit and carry out assessments		
Visit site prior to assessment visit	Visiting the site prior to assessment visit may facilitate in identifying any potential risks in the neighbourhood/local area. The clinical team may also be able to pass on any relevant information regarding location/potentially dangerous animals	AW (& clinical team)	
Carry out assessment in participants home	1. Plan route in advance and decide on appropriate transport; bearing in mind parking/time of day and journey distance 2. Notify primary supervisor (KM) or allocated PGR student of the visit including expected return time 3. Leave itinerary in PGR office (see home visiting book) 4. Carry UEA identity card, mobile phone, torch & personal alarm 5. Be aware – if necessary make an excuse and leave 6. Do not enter unless the patient is present. 7. On entry, note exits 8. If necessary, ask to have animals removed. 9. Be aware of changes in patient's mood. 10. Try to defuse situation, stay calm and distance self	AW/KM/Allocated PGR Student	

	11. If all else fails – get out. Use diversions, shouting or using personal alarm 12. Use code word in case of emergency (agreed with KM/PGR Student) 13. If necessary talk through any occurring incident with colleagues 14. Request patients, relatives and friends not to smoke during assessment 15. Only essential paperwork to be taken into patients home 16. Take minimal valuables 17. Dress appropriately		

24. Proof-of-concept study: ethics approval

Faculty of Medicine and Health Sciences Research Ethics Committee

University of East Anglia

Research & Innovation Services
Floor 1, The Registry
University of East Anglia
Norwich Research Park
Norwich, NR4 7TJ

Email: fmh.ethics@uea.ac.uk

Web: www.uea.ac.uk/researchandenterprise

Alison Welch
HSC

5/12/17

Dear Alison,

Project Title: Cardiopulmonary Exercise Testing in Healthy Adults
Reference: 2017/18 - 51

The submission of your above proposal has been considered by the Faculty Research Ethics Committee and we can confirm that your proposal has been approved.

Please could you ensure that any further amendments to either the protocol or documents submitted are notified to us in advance and also that any adverse events which occur during your project are reported to the Committee. Please could you also arrange to send us a report once your project is completed.

Yours sincerely,

Professor M J Wilkinson
Chair
FMH Research Ethics Committee

Physical Activity Readiness Questionnaire - PAR-Q (revised 2002)

PAR-Q & YOU

(A Questionnaire for People Aged 15 to 69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

YES	NO		
☐	☐	1.	**Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?**
☐	☐	2.	**Do you feel pain in your chest when you do physical activity?**
☐	☐	3.	**In the past month, have you had chest pain when you were not doing physical activity?**
☐	☐	4.	**Do you lose your balance because of dizziness or do you ever lose consciousness?**
☐	☐	5.	**Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?**
☐	☐	6.	**Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?**
☐	☐	7.	**Do you know of any other reason why you should not do physical activity?**

If you answered

YES to one or more questions

Talk with your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want — as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

DELAY BECOMING MUCH MORE ACTIVE:

- if you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better; or
- if you are or may be pregnant – talk to your doctor before you start becoming more active.

PLEASE NOTE: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed Use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

No changes permitted. You are encouraged to photocopy the PAR-Q but only if you use the entire form.

NOTE: If the PAR-Q is being given to a person before he or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

"I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction."

NAME _____

SIGNATURE _____ DATE _____

SIGNATURE OF PARENT or GUARDIAN (for participants under the age of majority) _____ WITNESS _____

Note: This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.

CSEP | SCPE

University of East Anglia

Participant Information Sheet

Cardiopulmonary Exercise Testing in Healthy Adults

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve.
Please take time to read the following information carefully.
Ask us if there is anything that is not clear or if you would like more information.

What is the purpose of the study?

The purpose of this study is to look at different ways of measuring your fitness levels. We are looking for eighteen volunteers to perform different types of exercise tests, on either a bike or treadmill. We wish to understand what works well, and what may not, when performing these exercise tests, with a view to invite volunteers who have been diagnosed with a stroke, to also perform a similar exercise test in the future.

Why do we need to do this study?

In the future, we are hoping do further research looking at exercise testing for stroke survivors. Currently, there are little guidelines or recommendations on how to do this. Therefore, we first need to do this study with healthy volunteers like yourself, so that we may be able to identify any practical issues or problems that someone diagnosed with stroke may come across when doing an exercise test. It is important to do this study so that can we see how long the test may take, understand different reasons for stopping the test and to understand the practicalities of undertaking each test.

What will happen if I participate?

If you decide you would like to participate, we will invite you to the Movement and Exercise Laboratory, located in the Medical Building, to complete your exercise test. We expect you will be there for up to one and a half hours. We recommend you wear something comfortable for exercising indoors, such as a T-shirt, shorts and trainers. We also ask that you avoid alcohol, tobacco and caffeine for at least 3 hours before. Your exercise test will be run by a PhD student and supervised by the MoveExLab technician. They both have first aid, manual handling and life support certifications.

Prior to your test, you will need to sign a consent form and complete a physical activity readiness questionnaire (PAR-Q) to ensure you are safe to exercise. Unfortunately, if you meet any of the contraindications listed within the questionnaires, we will not be able to invite you to participate in an exercise test. This includes things like long-term heart problems, severe asthma or severe muscle or joint injuries.

On the day of your test, we will ask you a few questions about your general health. We will also make sure you are well hydrated and have eaten enough. If the research team feel that your answers are not sufficient, we may ask you to rearrange the exercise test, or in some cases, decide you are no longer eligible to take part. If you have asthma, please make sure you have your inhaler with you, as you will not be allowed to exercise without it.
You will not be able to choose which type of exercise test you perform, as the research team will randomly assign you to one of two exercise modes: treadmill or cycle ergometry.

The research team will also randomly allocate which 'test phase' you will do. This may be an increase in speed, incline or resistance.

Fig 1. Cycle Ergometry

Fig 2. Treadmill

You will be fitted with a facemask, over your mouth and nose that will analyse your breathing as you exercise. You will also wear a heart rate monitor around your middle, under your t-shirt.

The test will include a 2 minute warm up, a test phase and a 2 minute cool down. For the test phase, we ask that you carry on exercising until you feel you cannot continue, or we tell you to stop. Within the test phase, the intensity of the exercise will increase over time – this may be in terms of speed, incline or resistance. You can stop the test at any time.
After your exercise test, there will be a cool down period and time and an area for you to relax. If you wish, we will also provide refreshments. You may want to bring a change of clothes for afterwards – there are shower facilities available. You may bring someone with you, but we will ask that they sit in the communal area just outside the MoveEx Lab during your exercise test.

There is a bus stop on Chancellors Drive, a short distance from the Medical Building, for Blue Line buses. Car parking is available in the Main and Central Car Parks and for those with a UEA permit the Edith Cavell Car Parking, located at the university hospital site, is an option. Please note that travel expenses will **not** be reimbursed.

Am I eligible to take part in this study?

To be able to take part in this study, you must be over the age of 18 and a UEA registered staff or student. You also must have no known medical conditions that may inhibit you from taking part in exercise and be able to speak adequate English, in order to understand the test instructions. If we receive a high volume of volunteers to take part, you may not be selected - recruitment will be on a first come-first served basis. In this case, we will write to you via email informing you of this situation and thanking you for your interest in the project.

Do I have to take part?

No, taking part is voluntary. Once you have expressed your interest, and you have received this information sheet, you will have up to 48 hours to decide if you would like to take part. You can also use this time to ask any further questions.
Even if you have decided to take part, you are able withdraw at any time, without giving a reason.

What are the possible benefits of taking part?

By taking part in this study, you will benefit from a full functional exercise test and you will be able to take away findings of your current fitness level. Your participation will contribute to our understanding of the practicalities of carrying out CPET testing. We will use this information to inform our future study with participants who have been diagnosed with stroke.

Unfortunately, we are unable to pay for any expenses incurred whilst participating in this study.

Are there any possible disadvantages of taking part?

Exercising can make you more tired than usual and you may feel a little achy in the muscles you have used. Any achiness or light muscle soreness will be short-lived and you should recover well within a day or two. There is a relatively small risk of adverse events such as fatigue or dizziness for people participating in exercise. However, you will have completed a PAR-Q, so we can assess whether you are safe to take part in exercise. All of the research team are trained in first aid, intermediate life support and manual handling. According to the health and safety protocol for the Movement and Exercise Laboratory, if we are concerned about your health then we will contact the appropriate medical services.

What if something goes wrong?

We expect that the risk of anything going wrong will be minimal. However if something does go wrong, or you have a complaint about the study in any respect, our research team will do our best to address the problem appropriately. You can contact the study leads, Alison Welsh or Dr. Kathryn Mares – their details are at the bottom of this sheet.
However, if you wish to talk to someone who will not be dealing with you directly, or you want your feedback to be anonymous, you can contact Prof. Valerie Pomeroy, who is the Director of Research in the School of Heath Sciences, here at the UEA. Normal UEA Indemnity covers compensation arrangements for negligent harm.

Prof. Valerie Pomeroy
Director of Research School of Health Sciences
V.Pomeroy@uea.ac.uk
Tel: (01603) 591668

Will my participation be kept confidential?

All information collected about you during the course of the research will be kept strictly confidential. Data collected from the exercise test will be anonymised and stored on password protected university computers; and if they are hand written, stored in locked filing cabinets at UEA. Any identifiable information, such as name, telephone number or email address used to arrange your exercise test appointment, will be kept separate to that of any other anonymised data.

Only authorised persons within the Research Team, who must follow strict ethical protocols in the handling and storage of all project data and observe the Data Protection Act (1998), will access the data.

Who is organising the study?

The study is being organised by Alison Welsh, a PhD student at UEA, along with her supervisors Dr. Kathryn Mares, Prof. Antony Arthur and Dr. Rebekah Hill. The study is being conducted as part of a PhD.

What will happen with the results off this study?

The results will be written up in a thesis and submitted to UEA. We hope to also submit findings to a scientific journal. If you would like, we can send you a copy of the results, just ask on the day of your exercise test or email/phone the research team.

After completion of the project, the data will be retained on the servers of UEA for any on-going analysis for a minimum of 15 years. All procedures for the handling, processing, storage and destruction of data are compliant with the Data Protection Act 1998.

Who has reviewed this project?

This study has been reviewed and approved by the Faculty of Medicine and Health Ethics Committee. The Research Ethics Committee is an independent group, which reviews research to protect the dignity, rights, safety and well-being of participants and researchers.

Whom may I contact for further information?

If you have any further questions, please do not hesitate to get in contact with any of the research team.

Alison Welsh
PhD Student, UEA
a.welsh@uea.ac.uk
Tel: (01603) 593093

Dr. Kathryn Mares
PhD Supervisor; Lecturer in Physiotherapy
k.mares@uea.ac.uk
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Thank you for taking the time to read this information sheet – we hope that you will consider taking part!

27. Proof-of-concept study: consent form

Consent Form: CPET STUDY

Name of Participant: _____

Participant Identification Number: _____

Signature of **Participant**	Name of **Participant**	Date

		Initial Box
8.	I confirm that I have read and understood the information sheet (version 1, dated 15/11/17) received for the above study.	☐
9.	I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
10.	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
11.	I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the University of East Anglia, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
12.	I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers (subject to relevant approvals being in place).	☐
13.	I understand that the information held and maintained by the Health and Social Care Information Centre the University of East Anglia and other central UK NHS bodies may be used to help contact me or provide information about my health status.	☐
14.	**I agree to take part in the above study.**	☐

Signature of **Researcher**	Name of **Researcher**	Date

When completed 1 for participant and 1 for researcher site files

28. Exercise intervention data

Table 40: Exercise intervention data, per participant, per session

	Exercise session	Pre-HR (bpm)	Pre-BP systolic/diastolic (mmHg)	Average exercise HR (bpm)	% of prescribed HR	Average exercise RPE (Borg 6-20)	% of prescribed RPE	Post-HR (bpm)	Post-BP systolic/diastolic (mmHg)
1	1	71	170/89	95	57%	11.66	80%	71	169/77
	2	62	144/75	102	62%	11	76%	65	138/70
	3	61	152/75	80.3	49%	11.33	78%	69	140/76
	4	71	135/88	-	-	13	90%	73	152/93
	5	78	154/91	82.66	50%	-	-	-	-
	6	65	128/79	80	48%	-	-	66	144/83
	7	64	149/73	92.25	56%	11.5	79%	66	142/72
	8	71	143/76	80	48%	-	-	75	139/88
	9	71	143/76	85.5	52%	10.25	71%	75	139/88
	10	67	120/79	-	-	12	83%	65	147/82
	11	65	136/71	83.66	51%	10.25	71%	66	140/73
	12	62	150/78	79.75	48%	11	76%	72	147/76
	Overall mean (SD)	67.3(5.10)	143.66(13.06) / 79.16(6.57)	86.11(7.71)	52%	11.33(0.86)	78%	69.36(3.98)	145.18(9.02) / 79.81(7.50)
2	1	80	133/65	90	52%	13	90%	78	139/78
	2	77	136/62	90.33	53%	13	90%	65	136/65
	3	91	116/59	98	57%	14	97%	85	125/72
	4	80	128/68	100	58%	15	103%	85	130/69
	5	80	-	89.66	52%	14	97%	80	131/60
	6	87	117/63	98.4	57%	15	103%	84	120/58
	7	88	109/61	103.66	60%	16	110%	87	136/62
	8	87	132/64	87	51%	17	117%	83	115/57
	9	79	128/60	89	52%	-	-	80	152/68
	10	83	131/60	91	53%	15	103%	82	127/62
	11	84	132/64	94	55%	12	83%	80	130/67
	12	87	126/59	98.5	57%	12	83%	86	124/73

	Exercise session	Pre-HR (bpm)	Pre-BP systolic/diastolic (mmHg)	Average exercise HR (bpm)	% of prescribed HR	Average exercise RPE (Borg 6-20)	% of prescribed RPE	Post-HR (bpm)	Post-BP systolic/diastolic (mmHg)
	Overall mean (SD)	83.58(4.39)	126.18(8.50) / 62.27(.2.83)	94.12(5.36)	55%	14.18(1.60)	98%	81.25(5.83)	130.41(9.68) / 65.91(6.44)
3	1	91	133/84	114.25	66%	14	0% 97%	104	129/89
	2	89	135/84	105.2	61%	13	90%	104	157/86
	3	89	132/85	116	67%	14	97%	88	138/79
	4	96	133/80	106	61%	13	90%	95	130/85
	5	102	147/82	116.5	68%	13	90%	104	137/87
	6	100	123/82	107.83	63%	11	76%	-	-
	7	101	127/87	115	67%	13	90%	104	128/95
	8	101	129/87	112.75	65%	13	90%	103	120/92
	9	91	133/81	106.75	62%	13	90%	104	165/90
	10	94	129/81	109.33	63%	13	90%	103	132/87
	11	99	128/85	109.85	64%	12	83%	107	132/85
	12	91	141/87	114.8	67%	14	97%	106	133/83
	Overall mean (SD)	95.33(5.06)	132.50(6.43) / 83.75(2.52)	111.18(4.15)	64%	13.17(0.88)	90%	102.00(5.54)	136.45(13.15) / 87.09(4.36)
4	1	80	125/68	148	86%	13	90%	79	130/70
	2	82	133/71	90.6	53%	13	90%	81	131/78
	3	80	127/67	91.5	53%	13	90%	83	129/72
	4	83	126/71	98	57%	13	90%	84	137/73
	5	78	141/66	89.75	52%	15	103%	80	128/62
	6	75	141/67	94	55%	14	97%	80	146/70
	7	70	129/60	90.25	52%	15	103%	72	137/72
	8	68	143/68	87.5	51%	14	97%	47	123/60
	9	77	123/63	94.5	55%	11	76%	84	125/58
	10	82	143/66	98.5	57%	12	83%	87	133/76
	11	87	121/57	102.33	59%	12	83%	91	121/57
	12	93	135/60	105.5	61%	13	90%	100	114/67
	Overall mean (SD)	79.58(6.84)	132.25(8.17) / 65.33(4.43)	99.20(16.29)	58%	13.52(1.20)	91%	80.66(12.65)	129.50(8.40) / 67.91(7.07)

	Exercise session	Pre-HR (bpm)	Pre-BP systolic/diastolic (mmHg)	Average exercise HR (bpm)	% of prescribed HR	Average exercise RPE (Borg 6-20)	% of prescribed RPE	Post-HR (bpm)	Post-BP systolic/diastolic (mmHg)
5	1	81	136/75	96	55%	13	90%	93	134/78
	2	85	131/88	120	69%	13	90%	104	143/90
	3	81	119/97	114	66%	11	76%	97	134/85
	4	80	131/83	-	-	13	90%	81	128/80
	5	101	119/82	106.66	61%	13	90%	94	132/82
	6	101	132/74	113	65%	13	90%	86	119/73
	7	89	136/84	117	67%	12	83%	89	132/87
	8	92	123/88	114.33	66%	12	83%	95	133/88
	9	89	133/85	152.66	88%	12	83%	97	124/84
	10	86	128/87	110	63%	11	76%	83	121/85
	11	86	131/87	125.25	72%	11	76%	87	136/85
	12	91	137/82	138	79%	11	76%	93	125/66
	Overall mean (SD)	88.50(7.01)	129.66(6.25) / 84.33(6.09)	118.80(15.43)	68%	12.41(0.77)	83%	91.58(6.59)	130.08(6.88) / 81.91 (6.82)
6	1	69	139/73	96.33	56%	13	90%	76	137/85
	2	76	146/82	95.33	56%	13	90%	72	125/69
	3	65	146/81	93.23	54%	12	83%	67	141/86
	4	75	145/84	103.25	60%	12	83%	75	136/84
	5	65	134/73	98.5	57%	11	76%	71	139/81
	6	72	138/87	110.5	64%	13	90%	79	129/86
	7	62	145/77	93	54%	11	76%	68	141/86
	8	73	150/83	113.22	66%	13	90%	82	123/85
	9	66	151/79	111	65%	12	83%	68	130/79
	10	80	129/70	113.5	66%	12	83%	86	129/67
	11	68	143/74	108.5	63%	13	90%	70	118/75
	12	75	136/84	112.75	66%	13	90%	78	127/86
	Overall mean (SD)	70.05(5.48)	141.83(6.67) / 78.75(5.52)	104.09(8.33)	61%	12.69(0.71)	85%	74.33(6.05)	131.25(7.49) / 80.75(6.87)

	Exercise session	Pre-HR (bpm)	Pre-BP systolic/diastolic (mmHg)	Average exercise HR (bpm)	% of prescribed HR	Average exercise RPE (Borg 6-20)	% of prescribed RPE	Post-HR (bpm)	Post-BP systolic/diastolic (mmHg)
7	1	70	168/90	89.8	51%	10	69%	73	141/88
	2	65	156/89	93.75	53%	13	90%	72	151/90
	3	73	164/82	108.75	62%	12	83%	87	146/88
	4	75	150/85	105.66	60%	11	76%	84	136/79
	5	68	158/80	108	61%	12	83%	87	131/82
	6	73	155/90	112.5	64%	19	131%	94	136/86
	7	61	155/78	-	-	12	83%	82	137/93
	8	66	152/82	117	67%	13	90%	94	143/77
	9	64	157/90	96.2	55%	13	90%	85	144/83
	10	67	139/80	107	61%	13	90%	93	128/86
	11	66	161/85	117	67%	11	76%	80	150/89
	12	65	150/85	106.66	61%	15	103%	84	149/86
	Overall mean (SD)	67.75(4.20)	155.41(7.46) / 84.66(4.33)	105.66(8.97)	60%	13.25(2.36)	89%	84.58(7.26)	141.00(7.49) / 85.58(4.62)
8	1	56	135/80	72	40%	11	76%	58	131/82
	2	55	141/77	73.66	41%	11	76%	55	139/77
	3	55	137/79	72	40%	15	103%	61	123/79
	4	56	131/76	68	38%	-	-	53	134/77
	5	56	134/82	74	41%	14	97%	57	148/79
	6	57	141/84	77	43%	14	97%	60	146/85
	7	54	133/81	-	-	12	83%	55	131/80
	8	58	143/83	74.5	42%	11	76%	-	-
	9	-	-	77	43%	12	83%	60	127/82
	10	57	131/83	-	-	14	97%	61	133/84
	11	60	157/86	-	-	11	76%	61	133/83
	12	53	138/88	74	41%	12	83%	63	120/76
	Overall mean (SD)	56.09(1.92)	138.27(7.43) / 81.72(3.63)	73.57(2.75)	41%	12.58(1.38)	86%	58.54(3.17)	133.18(8.62) / 80.36(3.04)
9	1	62	142/89	106.33	59%	12	83%	89	120/86

	Exercise session	Pre-HR (bpm)	Pre-BP systolic/diastolic (mmHg)	Average exercise HR (bpm)	% of prescribed HR	Average exercise RPE (Borg 6-20)	% of prescribed RPE	Post-HR (bpm)	Post-BP systolic/diastolic (mmHg)
	2	57	134/91	97	54%	13	90%	66	126/79
	3	57	137/83	120.66	67%	12	83%	75	123/70
	4	63	127/83	98.33	54%	13	90%	71	123/69
	5	61	126/70	100	55%	13	90%	70	134/84
	6	63	123/70	101.33	56%	13	90%	79	122/82
	7	57	123/92	80.33	44%	15	103%	69	128/88
	8	60	113/77	90	50%	13	90%	62	125/85
	9	58	118/82	82	45%	13	90%	63	131/75
	10	55	143/82	90.66	50%	14	97%	69	121/83
	11	57	135/80	107.33	59%	14	97%	82	131/73
	12	62	128/75	103	57%	14	97%	64	125/84
	Overall mean (SD)	59.33(2.80)	129.08(9.30) / 81.16(7.32)	89.08(25.60)	54%	13.40(0.84)	91%	71.58(8.32)	125.75(4.41) / 79.83(6.50)
10	1	-	-	-	-	-	-	-	-
	2	65	112/70	83	46%	13	90%	71	112/71
	3	65	114/70	83	46%	8	55%	72	104/72
	4	-	-	-	-	-	-	-	-
	5	74	118/67	99.33	55%	-	-	82	115/58
	6	65	124/61	99	55%	12	83%	87	108/66
	7	69	125/59	99.66	56%	12	83%	80	99/61
	8	84	114/68	103.33	58%	12	83%	100	131/73
	9	66	111/62	106.33	59%	12	83%	93	112/76
	10	58	117/70	84.66	47%	12	83%	89	122/60
	11	61	102/61	112.66	63%	13	90%	86	117/68
	12	61	107/64	99.33	55%	13	90%	80	106/66
	Overall mean (SD)	66.80(7.50)	114.40(7.07) / 65.20(4.28)	97.03(10.21)	54%	12.14(1.63)	82%	84.00(8.96)	112.60(9.28) / 67.10(6.02)
11	1	62	163/82	82	47%	-	-	62	156/83
	2	61	156/83	98.66	57%	12	83%	77	138/83

	Exercise session	Pre-HR (bpm)	Pre-BP systolic/diastolic (mmHg)	Average exercise HR (bpm)	% of prescribed HR	Average exercise RPE (Borg 6-20)	% of prescribed RPE	Post-HR (bpm)	Post-BP systolic/diastolic (mmHg)
	3	61	155/76	98.66	57%	11	76%	67	140/75
	4	60	154/80	131	75%	12	83%	75	147/84
	5	72	155/80	133	77%	-	-	87	146/77
	6	57	-	102	59%	12	83%	73	142/82
	7	67	144/67	120	69%	13	90%	76	143/75
	8	58	150/83	100	58%	11	76%	69	152/74
	9	60	146/75	108.33	62%	12	83%	70	144/74
	10	62	144/73	98.33	57%	12	83%	72	134/78
	11	62	125/67	118	68%	11	76%	82	141/75
	12	-	-	-	47%	-	-	-	-
	Overall mean (SD)	62.00(4.19)	149.90(10.16) / 76.60(6.09)	108.18(15.62)	62%	12.13(0.78)	81%	73.63(6.96)	143.90(6.22) / 78.18(4.02)
12	1	89	132/84	117	62%	13	90%	106	123/88
	2	-	-	-	-	-	-	-	-
	3	88	125/83	134	71%	-	-	95	131/72
	4	94	135/82	119.66	63%	12	83%	103	131/77
	5	87	134/81	119.66	63%	13	90%	104	129/82
	6	102	128/84	101.33	54%	13	90%	83	131/73
	7	96	128/85	121	64%	14	97%	94	126/75
	8	83	127/81	116.33	62%	15	103%	84	125/82
	9	86	135/72	111.33	59%	13	90%	88	118/76
	10	99	139/98	130	69%	15	103%	91	129/77
	11	87	122/75	143	76%	-	-	93	117/78
	12	87	124/78	106	56%	14	97%	104	118/75
	Overall mean (SD)	90.72(6.06)	129.90(5.41) / 82.09(6.64)	119.93(12.11)	64%	13.79(0.83)	93%	95.00(8.25)	125.27(5.53) / 77.72(4.64)
13	1	72	164/91	98	57%	-	-	88	139/85
	2	78	151/82	102.5	60%	10	69%	86	156/88
	3	86	164/92	102.5	60%	14	97%	91	126/79

	Exercise session	Pre-HR (bpm)	Pre-BP systolic/diastolic (mmHg)	Average exercise HR (bpm)	% of prescribed HR	Average exercise RPE (Borg 6-20)	% of prescribed RPE	Post-HR (bpm)	Post-BP systolic/diastolic (mmHg)
	4	86	157/84	112.66	66%	12	83%	91	122/81
	5	74	165/97	100	58%	-	-	79	140/81
	6	82	149/77	99.3	58%	-	-	84	112/74
	7	75	155/82	114.5	67%	14	97%	91	120/77
	8	80	139/92	-	-	-	-	92	130/76
	9	65	138/83	97.33	57%	12	83%	86	129/80
	10	68	163/92	94	55%	12	83%	91	126/82
	11	66	139/86	106	62%	11	76%	81	123/78
	12	79	137/87	101.66	59%	-	-	97	155/89
	Overall mean (SD)	75.91(7.20)	151.75(11.20) / 87.08(5.77)	102.58(6.29)	60%	12.53(1.33)	84%	88.08(5.10)	131.50(13.56) / 80.83(4.60
14	1	64	141/77	84	49%	-	-	70	131/80
	2	66	142/68	99.33	57%	10	69%	80	111/81
	3	65	127/77	99.33	57%	12	83%	73	134/76
	4	62	126/72	-	-	-	-	67	117/72
	5	66	135/71	78	45%	-	-	73	119/60
	6	69	135/74	-	-	13	90%	73	134/63
	7	71	144/72	96	55%	13	90%	94	119/72
	8	69	136/70	84.5	49%	-	-	77	130/72
	9	64	129/75	-	-	-	-	70	126/72
	10	68	121/84	-	-	10	69%	79	112/69
	11	64	133/72	99	57%	-	-	75	130/74
	12	65	131/71	87	50%	11	76%	85	132/68
	Overall mean (SD)	66.08(2.64)	133.33(6.94) / 73.58(4.25)	90.89(8.48)	53%	11.77(1.34)	79%	76.33(7.45)	124.58(8.51) / 71.58 (6.12)
15	1	41	158/82	78.99	45%	14	97%	51	129/74
	2	42	146/80	83	48%	-	-	50	134/73
	3	42	147/70	83	48%	12	83%	53	121/76
	4	48	143/70	73	42%	12	83%	73	129/68

	Exercise session	Pre-HR (bpm)	Pre-BP systolic/diastolic (mmHg)	Average exercise HR (bpm)	% of prescribed HR	Average exercise RPE (Borg 6-20)	% of prescribed RPE	Post-HR (bpm)	Post-BP systolic/diastolic (mmHg)
	5	46	149/70	77	44%	10	69%	53	134/75
	6	44	148/71	90.33	52%	12	83%	58	119/74
	7	47	115/65	86	49%	10	69%	62	118/77
	8	40	135/69	95.66	55%	-	-	64	115/70
	9	48	132/82	71	41%	11	76%	50	128/79
	10	41	136/71	84	48%	12	83%	53	120/61
	11	43	140/68	80	46%	13	90%	52	127/73
	12	41	135/82	63.5	36%	13	90%	59	121/63
	Overall mean (SD)	43.58(2.93)	140.33(10.94) / 73.33(6.25)	80.45(8.69)	46%	12.12(1.26)	82%	56.50(7.00)	124.58(6.37) / 71.91(5.48)
16	1	81	137/76	102	56%	13	90%	86	138/77
	2	82	129/81	132	72%	14	97%	82	127/77
	3	78	149/92	132	72%	14	97%	85	125/74
	4	92	142/92	126.5	69%	11	76%	87	132/75
	5	91	126/86	123.66	68%	14	97%	92	132/77
	6	87	143/73	105	58%	14	97%	92	161/98
	7	102	139/83	127.33	70%	14	97%	68	125/79
	8	77	130/62	124	68%	15	103%	88	124/80
	9	101	156/81	121.66	67%	14	97%	94	123/73
	10	83	155/87	124	68%	15	103%	86	139/82
	11	71	160/81	-	-	-	-	77	131/78
	12	78	143/70	120.5	66%	12.33	85%	95	137/84
	Overall mean (SD)	85.25(9.63)	142.41(11.04) / 80.33(8.90)	121.69(9.74)	67%	13.96(1.21)	94%	86.00(7.65)	132.83(10.49) / 79.50(6.62)
17	1	60	137/72	112.66	67%	13	90%	77	120/70
	2	82	178/96	130	77%		-	82	143/88
	3	70	154/71	130	77%	15	103%	83	149/77
	4	-	-	-		-		-	-
	5	77	137/64	119.66	71%	12	83%	73	140/69

	Exercise session	Pre-HR (bpm)	Pre-BP systolic/diastolic (mmHg)	Average exercise HR (bpm)	% of prescribed HR	Average exercise RPE (Borg 6-20)	% of prescribed RPE	Post-HR (bpm)	Post-BP systolic/diastolic (mmHg)
	6	66	155/80	82	49%	12	83%	71	139/71
	7	-	-	-	-	-	-	-	-
	8	-	-	-	-	-	-	-	-
	9	-	-	-	-	-	-	-	-
	10	-	-	-	-	-	-	-	-
	11	-	-	-	-	-	-	-	-
	12	-	-	-	-	-	-	-	-
	Overall mean (SD)	71.00(8.71)	152.20(16.87) / 76.60(12.23)	114.86(19.78)	68%	13.41(1.45)	90%	77.20(5.31)	138.20(10.89) / 75.00(7.90)
18	1	60	154/59	-	-	-	-		
	2	53	165/70	-	-	11	76%	53	170/71
	3	53	165/73	-	-	12	83%	54	146/66
	4	56	168/74	-	-	13	90%	53	163/77
	5	59	153/67	-	-	13	90%	54	151/79
	6	61	172/80	-	-	14	97%	60	163/73
	7	61	171/79	62	37%	11	76%	61	182/78
	8	66	130/61	73.66	44%	-	-	70	120/63
	9	55	171/76	67	40%	-	-	53	149/70
	10	60	158/73	-	-	13	90%	65	133/93
	11	58	153/68	72	43%	14	97%	59	167/74
	12	65	153/89	71.66	43%	14	97%	70	150/71
	Overall mean (SD)	58.91(4.18)	159.41(11.99) / 72.41(8.29)	69.26(4.75)	42%	13.02(1.17)	88%	59.27(6.63)	154.00(17.55) / 74.09(7.94)

Abbreviations
BP blood pressure **bpm** beats per minute **HR** heart rate **mmHg** millimetres of mercury **RPE** ratings of perceived exertion **SD** standard deviation

29. Interviewee characteristics

	Gender	Age	Time since stroke (months)	FAC score	Level of pre-stroke exercise	Number of exercise sessions attended	Randomisation order	Intervention group
Jane	Female	69	9	2	Vigorous	12	Treadmill with BWS / Cycle ergometer	Aerobic
John	Male	66	15	3	Vigorous	12	Treadmill with BWS / Cycle ergometer	Strength
Joe	Male	69	13	3	Moderate	12	Cycle ergometer / Treadmill with BWS	Aerobic
Paul	Male	58	51	3	Vigorous	12	Cycle ergometer / Treadmill with BWS	Strength
Mary	Female	54	193	3	Moderate	12	Treadmill with BWS / Cycle ergometer	Aerobic
David	Male	77	11	2	Light	12	Cycle ergometer / Treadmill with BWS	Combination

Abbreviations
BWS Body weight support **FAC** Functional ambulation category

30. Individual cardiopulmonary exercise test data

Participant	CPET Mode	Estimated Relative VO_2* (mL/kg/min)	Relative VO_2 (mL/kg/min)	Absolute VO_2 (kg/min)	RER	Exercise time (mins)	Reason for Stopping	Adverse Events
1	Cycle ergometer	17.56	13.50	896	1.06	2.23	Leg fatigue	None
	Treadmill with BWS	-	8.80	712	1.02	2.20	Harness discomfort	None
2	Treadmill with BWS	34.67	7.20	441	0.82	2.25	Unable to maintain speed	None
	Cycle ergometer	31.24	8.00	503	1.09	6.05	Fatigue in unaffected arm	None
3	Cycle ergometer	27.28	17.40	1690	1.04	15.32	Leg fatigue	None
	Treadmill with BWS	23.30	10.00	1018	0.94	12.57	Unable to maintain speed	None
4	Treadmill with BWS	31.77	12.60	880	0.93	4.59	Unable to maintain speed	None
	Cycle ergometer	35.68	11.60	837	1.10	5.10	Leg fatigue	None
5	Treadmill with BWS	34.40	8.70	1030	1.01	10.08	Unable to maintain speed	None
	Cycle ergometer	36.42	11.00	1345	1.11	7.26	Leg fatigue	None
6	Cycle ergometer	37.90	11.00	11182	1.29	8.51	Leg fatigue	None
	Treadmill with BWS	40.27	111.40	1243	1.09	8.16	Leg fatigue	None
7	Cycle ergometer	35.5	12.70	1178	1.16	8.38	Leg fatigue	None
	Treadmill with BWS	40.60	7.50	709	1.03	3.57	Unable to maintain speed	None
8	Cycle ergometer	46.83	12.40	1064	1.41	8.35	Leg fatigue	None
	Treadmill with BWS	52.57	9.50	815	1.04	8.38	Unable to maintain speed	None
9	Cycle ergometer	36.88	15.20	1433	1.29	13.57	Leg fatigue	None
	Treadmill with BWS	44.61	9.60	908	0.97	12.59	Unable to maintain speed	None

Participant	CPET Mode	Estimated Relative VO_2* (mL/kg/min)	Relative VO_2 (mL/kg/min)	Absolute VO_2 (kg/min)	RER	Exercise time (mins)	Reason for Stopping	Adverse Events
10	Cycle ergometer	41.58	13.80	1233	1.40	9.07	Leg fatigue	None
	Treadmill with BWS	43.56	18.20	1649	0.96	8.54	Leg fatigue	None
11	Treadmill with BWS	40.29	14.90	1211	1.02	5.32	Leg fatigue	None
	Cycle ergometer	-	-		-	-	-	-
12	Cycle ergometer	27.54	18.00	1183	1.46	3.10	Leg fatigue	None
	Treadmill with BWS	32.77	11.40	751	1.02	2.40	Unable to maintain speed	None
13	Treadmill with BWS	31.41	10.90	998	1.15	4.55	Leg fatigue	None
	Cycle ergometer	40.25	-		-	-	-	-
14	Treadmill with BWS	38.36	9.60	795	0.96	5.16	Harness	None
	Cycle ergometer	36.76	14.60	1217	1.19	11.27	Leg fatigue	None
15	Cycle ergometer	65.23	11.90	1125	1.35	6.50	Mask discomfort	None
	Treadmill with BWS	54.48	9.00	887	0.98	3.06	Unable to maintain speed	None
16	Treadmill with BWS	38.00	15.60	1054	0.96	10.10	Pain	None
	Cycle ergometer	42.84	17.60	1166	1.30	11.11	Breathlessness	None
17	Cycle ergometer	40.98	10.60	798	0.95	2.13	Leg fatigue	None
	Treadmill with BWS	39.70	10.00	722	0.96	6.55	Leg fatigue	None

Abbreviations

BWS Body weight support **CPET** Cardiopulmonary exercise test **kg** Kilograms **mL** millilitres **min** Minutes **RER** Respiratory exchange ratio **VO_2** Maximal aerobic capacity

*Estimated VO_{2max} equation: (15.5) x $HR_{max}/HR_{resting}$

End of thesis.