The ATAS Trial

Full trial title:

Aerobic exercise training in acute ischaemic stroke: A single-centre, single-blinded, randomised, controlled feasibility study of an aerobic exercise training intervention versus standard care conducted in the acute phase of stroke.

Short trial title and acronym:

Aerobic Exercise Training in Acute Ischaemic Stroke (ATAS)

Research reference numbers

Sheffield Teaching Hospitals (STH) project reference:	STH21298
Sheffield Hallam University Research Ethics Committee reference:	ER25055563
NHS Research Ethics Committee reference:	20/YH/0285
IRAS project ID:	280320
Clinical trials registration number:	NCT04742686
Protocol version and date:	3 – 14.12.2020

Protocol amendment history

Protocol		Amendments			
Version no.	**Date (dd/mm/yy)**	**Amendment no.**	**Protocol section/page number(s)**		**Summary of key changes from previous version**
2	18/11/20	1	7.2	23	Added: • Patients will be provided with a participant information sheet and will be politely asked to contemplate the information and make a decision within 48 hours of the initial discussion. This is due to the time-sensitive nature of the research. Deleted: • Patients will be given at least 24 hours to consider the information.
2	18/11/20	2	7.5	24	Added following items to exclusion criteria: • Pain during mobilisation of lower-limbs. • Lower-limb spasticity or contracture which impairs ability to cycle. .
2	18/11/20	3	9	33-35	Within '**Table 3 - Schedule of investigations and outcome measures'**, the tick colour representing SOC activities has been changed from black to orange. The remaining black ticks represent research activities that are additional to SOC.
2	18/11/20	4	10	46	Added **'Section 10 – COVID-19 contingency plan'.**

2	18/11/20	5	10	46-48	Added '**Table 5 – COVID-19 contingency plan'.**

Declaration

The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the UK Policy Framework for Health and Social Care Research, Good Clinical Practice (GCP) guidelines, the Sponsor's and Site's standard operating procedures, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay, an honest accurate and transparent account of the trial will be given, and any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

Trial Sponsor:

Signature: Date:

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Name (please print):

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Position:

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Principal Investigator:

Signature: Date:

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Name (please print):

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Position:

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i. Abbreviations

Abbreviation	Meaning
AE	Adverse event
ASU	Acute stroke unit
ATAS	Aerobic exercise training in acute ischaemic stroke
AWRC	Advanced Wellbeing Research Centre
BDNF	Brain-derived neurotrophic factor
BHRU	Beech Hill Rehabilitation Unit
CBF	Cerebral blood flow
CO_2	Carbon dioxide
CPET	Cardiopulmonary exercise test
EQ-5D	EuroQol Quality of Life Index
FSS	Fatigue Severity Scale
GAD-7	Generalised Anxiety Disorder
GCP	Good Clinical Practice
GPAQ	Global Physical Activity Questionnaire
HASU	Hyper acute stroke unit
HR	Heart rate
HRmax	Maximum heart rate
HRR	Heart rate reserve
mBDNF	Mature brain-derived neurotrophic factor
MoCA	Montreal Cognitive Assessment
mRS	Modified Rankin Scale
NHS	National Health Service
NIHSS	National Institutes of Health Stroke Scale
PHQ-9	Patient Health Questionnaire
PI	Principal Investigator
PPI	Patient and public involvement
RCT	Randomised controlled trial
REC	Research Ethics Committee
RHH	Royal Hallamshire Hospital
rLOT	Revised Life Orientation Test
RoFS	Rating of Fatigue Scale
RPE	Rating of perceived exertion
SAE	Serious adverse event
SHU	Sheffield Hallam University
SPPB	Short physical performance battery
STH	Sheffield Teaching Hospitals
TMG	Trial Management Group
$\dot{V}O_2$	Oxygen consumption

ii. Trial summary

Trial title	Aerobic exercise training in acute ischaemic stroke: A single-centre, single-blinded, randomised, controlled feasibility study of an aerobic exercise training intervention versus standard care in the acute phase of stroke	
Internal ref. no. (or short title)	Aerobic Exercise Training in Acute Ischaemic Stroke (ATAS).	
Clinical phase	II	
Trial design	A single-centre, single-blinded, two-arm parallel group, randomised, controlled feasibility trial	
Trial participants	Acute ischaemic stroke patients (1-7 days post stroke)	
Planned sample size	30	
Intervention duration	5 working days	
Trial duration per participant	3 months	
Estimated total trial duration	21 months	
	Objectives	**Outcome Measures**
Primary	To determine the feasibility of conducting a randomised controlled trial (RCT) to assess the effects of an aerobic exercise intervention on stroke outcomes.	• safety • recruitment rate • exclusion rate • consent rate • dropout rate • participant fidelity to intervention • acceptability • completeness of data
Secondary	To identify potential primary outcomes for a subsequent definitive RCT.	For example: • physical function/disability • health-related quality of life • cognitive function • mood • fatigue

	To develop mechanistic knowledge of the intervention.	• physical activity levels • Cerebral blood flow velocity • Mature brain-derived neurotrophic factor
Type of intervention	Power-assisted aerobic exercise training.	
Intervention components	A 10-30 minute session of low-moderate aerobic interval exercise conducted once per day for 5 working days. Exercise type: semi-recumbent power-assisted in-bed cycling.	

iii. Funding and support in kind

Funder(s)	**Financial and non-financial support given**
Sheffield Hallam University Tel: 0114 225 5044 Email: HWB-DoctoralAdmin@shu.ac.uk	Vice Chancellor's PhD Scholarship: £15,009 per annum salary for PhD student for 3 years (£45,027) £1,500 per academic year for research-related costs including consumables, patient transport and research dissemination (£4,500) Total = £49527
Sheffield Teaching Hospitals NHS Foundation Trust, Department of Neurosciences. Tel: 0114 2711768 Email: ali.ali9@nhs.net	Transcranial Doppler ultrasound device provided in kind. Cycle ergometer provided in kind.

iv. Role of Sponsor and Funder

Sheffield Hallam University (SHU) is both the Sponsor and Funder of the ATAS trial. Some SHU equipment has been funded by the European Regional Development Fund. SHU holds professional indemnity insurance (Royal & Sun Alliance; policy no. RKK856067) to meet the potential legal liability of the Sponsor and employees for harm to participants arising from the design and management of the research. The professional indemnity insurance policy is due for renewal in July 2021; policy details will be updated accordingly. Indemnity to meet the potential legal liability of Investigators for harm to participants arising from the conduct of the research is provided by the NHS indemnity scheme or through professional indemnity.

Both the research team and the Sponsor are responsible for:

- The trial design
- The trial conduct
- Data analysis and interpretation
- Manuscript writing
- Dissemination of results

v. Trial Management Group

This is a small-scale study which will only include a Trial Management Group (TMG). The TMG will comprise of the PI, the Study Doctor and all Co-Investigators. The Sponsor will have no representation on the TMG but will be kept updated of progress.

vi. Expertise and protocol contributions

Dr Simon Nichols is a senior research fellow in clinical exercise physiology with expertise in conducting exercise-based cardiovascular rehabilitation trials in clinical populations. Dr Nichols is also the scientific chair for the British Association for Cardiovascular Prevention and Rehabilitation and the academic lead for physiology at the Advanced Wellbeing Research Centre at SHU. In addition, Dr Nichols is the co-principal investigator for the ongoing ESCAPE trial (STH20750) which is a proof of concept study investigating the safety and feasibility of a single bout of aerobic exercise during the acute phase of stroke. Dr Nichols has provided strategic guidance on the design and conduct of this research and will be the Principal Investigator for this trial.

Dr Ali Ali is a consultant physician specialising in stroke and geriatrics with extensive experience in recruiting patients to clinical trials. Dr Ali is also a senior honorary lecturer at the University of Sheffield and the research lead for the Integrated Geriatric and Stroke Medicine Directorate at STH NHS Foundation Trust. In addition, Dr Ali is the co-principal investigator and study doctor for the ESCAPE trial (STH20750). Dr Ali has provided clinical expertise and guidance on logistical and practical aspects of conducting the research at The Royal Hallamshire Hospital. Dr Ali will oversee the medical safety aspects of this trial.

Dr Tom Maden-Wilkinson is a senior research fellow in clinical exercise physiology specialising in neuromuscular physiology and resistance training interventions to promote healthy ageing. Dr Maden-Wilkinson is the academic lead for imaging at the Advanced Wellbeing Research Centre at SHU. In addition, Dr Maden-Wilkinson is a co-investigator for the ESCAPE trial (STH20750). Dr Maden-Wilkinson has provided strategic guidance on the design and conduct of this research.

Dr Helen Speake is a research fellow in exercise psychology specialising in user-centred design and participatory approaches to physical activity interventions. In addition, Dr Speake is a co-investigator for the ESCAPE trial (STH20750). Dr Speake has provided expertise on the design and conduct of this research, particularly patient and public involvement (PPI) events and qualitative evaluation of the exercise intervention.

Mr Nikolaus Kudiersky is undertaking a PhD in clinical exercise physiology. Mr Kudiersky is a recipient of the SHU Vice Chancellor's PhD Scholarship and has a research focus on exercise-based rehabilitation for clinical populations. Mr Kudiersky is a co-investigator for the ESCAPE trial (STH20750) and provides technical support to the RICFAST trial (STH19508) where his role is to conduct cardiopulmonary exercise tests for people affected by stroke (>6 weeks post-stroke).

vii. Patient and public contributions

We have facilitated three PPI events which were used to gather feedback from people affected by stroke, and healthcare practitioners. For the first two PPI events, the topic of interest was the acceptability of our proposed exercise protocol and overall research design. Adjustments to the research protocol have been made based on feedback from the events (see ATAS - Patient and Public Involvement. January 2020). In response to a suggestion at this PPI event, we created an aphasia-friendly participant information sheet (ATAS - Aphasia-Friendly Participant Information Sheet. Version 2. 25.08.2020) using the Stroke

Association guidelines for accessible information. This document has been reviewed by Ms Jenni Crisp (Speech and Language Therapist, and Patient and Public Involvement Research Coordinator for Integrated Stroke and Geriatric Medicine, Sheffield) who has stated that the document is well-designed and provides sufficient information for individuals with aphasia to make an informed decision.

In October 2020, we hosted an online PPI event which was attended people affected by stroke and aphasia, and Ms Jenni Crisp. The purpose of this event was to review the style and content of visual aids that we intend to use to facilitate participant engagement in the research. These visual aids have been designed using the Stroke Association guidelines for accessible information. The PPI feedback was generally positive, and some minor amendments were made based on the PPI panel's suggestions (Aphasia-Friendly Visual Aids. V1 – 23.10.2020).

We will deliver a final PPI event after the data collection period. The purpose of this event is to seek the support of study participants and the wider stroke population to determine the most appropriate ways to translate and disseminate our findings to people affected by stroke. This will be held at a community venue with accessible parking and facilities for people with disabilities. Travel expenses will be paid to PPI participants for this event.

viii. Keywords

ATAS, acute ischaemic stroke, aerobic exercise, feasibility, stroke rehabilitation.

1. Main research question

Is a full-scale randomised controlled trial (RCT) (to test the hypothesis that aerobic exercise training initiated in the acute phase of stroke leads to better clinical outcomes compared to standard care) feasible?

2. Abstract

Ischaemic stroke is a leading cause of death and long-term disability which affects over 100,000 people per year in the UK. The condition involves the blockage of a cerebral blood vessel which restricts blood supply to part of the brain and results in brain tissue death.

Despite major advances in stroke care in recent decades, over half of stroke survivors suffer with a long-term disability and have a reduced quality of life. This poses a major burden on stroke survivors and their support network, as well as health and social care services. Early-initiated aerobic exercise training is a promising, novel intervention which may enhance recovery from stroke and thereby improve stroke survivors' level of independence and quality of life.

The purpose of this study is to determine whether it is feasible to conduct a RCT to test the hypothesis that aerobic exercise training initiated in the acute phase of ischaemic stroke (1-7 days post-stroke) results in better clinical outcomes than standard care alone. The proposed mode of aerobic exercise is power-assisted cycling which enables people with hemiplegia or hemiparesis to exercise whilst remaining in their hospital bed. The study will focus on feasibility outcomes including recruitment, safety and acceptability. Exploratory outcomes will also be measured to advance mechanistic knowledge of the intervention and to identify suitable outcome measures for a full-scale clinical trial.

3. Background

Stroke is the primary cause of long-term disability worldwide (1). It is estimated that 50-65% of stroke survivors live with a long-term disability or depend on a caregiver (2,3). The emotional impact of stroke is also profound, with approximately 30% of stroke survivors living with depression (4). The total economic burden of stroke in the UK is £26 billion per year, and this figure is estimated to rise to £75 billion over the next 20 years due to improvements in stroke survival rates and an ageing population (5). 85% of stroke events are diagnosed as ischaemic stroke (6) which is defined as an episode of neurological dysfunction lasting longer than 24 hours, attributed to vascular occlusion (7). Following ischaemic stroke, a complex cascade of pathological events occurs. Briefly, depleted energy stores lead to ionic imbalance, excitotoxicity, oxidative stress, inflammation, blood brain barrier dysfunction, oedema and ultimately, infarction of the cerebral parenchyma (8). The extent of cell death and stroke-induced disability is dependent on the volume, location and duration of cerebral ischaemia (9). Surrounding the infarct core is a region of hypoperfused but potentially salvageable tissue called the ischaemic penumbra which is estimated to be viable for 24-48 hours post-stroke (10). The fate of the ischaemic penumbra is dependent on the speed of reperfusion relative to stroke onset, and the residual blood flow supplied by collateral blood vessels (11–13). In addition, after the initial ischaemic insult, a delayed cascade of pathological events occurs including vasogenic oedema, inflammation and programmed cell death. These events may lead to secondary infarct expansion up until ~4

days post-stroke (14,15). Currently, there are no medical treatments that mitigate delayed lesion expansion (9,16–18). Available treatment options are limited to reperfusion therapy (intravenous thrombolysis or mechanical thrombectomy) which can only be administered during a short time window after stroke (19). Further, 90% of stroke patients do not receive reperfusion therapy due to arriving at hospital after the licensed treatment timeframe, contraindications (e.g. high risk of bleeding), or lack of service provision (re: thrombectomy) (20,21). In addition, reperfusion therapy is not always successful and can exacerbate inflammation and oedema, inducing secondary cell death and possibly haemorrhagic transformation (22,23). As the incidence of stroke continues to rise, there is an urgent need to develop innovative treatments that enhance brain repair processes post-stroke and thereby reduce stroke-induced disability. Emerging evidence suggests that aerobic exercise training initiated in the acute phase of stroke (1-7 days post-stroke) may enhance brain repair, mitigate neurological deficit and augment neuroplasticity. However, this line of evidence is limited to rodent models of stroke. Research is required to attempt to translate these promising findings to the clinical setting (24–27).

4. Rationale

4.1. Acute aerobic exercise: proposed mechanisms

Aerobic exercise induces a variety of neurovascular stimuli which interact with reparative processes post-stroke. Two important mediating factors are neurotrophin concentration and cerebral blood flow (CBF). Mature brain-derived neurotrophic factor (mBDNF) is a neurotrophin which promotes neural cell survival (i.e. neuroprotection), the growth of new neurons (i.e. neurogenesis) and structural and functional neural adaptations in response to injury and environmental stimuli (i.e. neuroplasticity) (28). mBDNF is produced and stored in central and peripheral tissues. Its production is increased in response to neurological injury, neuronal activity and aerobic exercise (29). At the onset of aerobic exercise, activated cerebral neurons rapidly depolarise and release mBDNF from synaptic terminals. After which, mBDNF may exert its positive effects on local neurovascular tissues (29). The heightened metabolic rate of active cerebral neurons requires an increased supply of oxygen and glucose. Local blood vessels respond to this metabolic perturbation by increasing CBF to active regions in a process known as neurovascular coupling (30). In addition, aerobic exercise increases the metabolic rate of skeletal muscles which increases carbon dioxide (CO_2) production, blood pressure and cardiac output. Collectively, these integrated mechanisms contribute to a 10-30% increase in CBF during moderate-intensity exercise (30). Interestingly, just 20 minutes of moderate-intensity aerobic exercise has been shown to

increase hippocampal blood flow by 10-12% for at least 65 minutes post-exercise in healthy individuals (31). The hippocampus plays a key role in the growth of new neurons, memory formation and learning (32). These processes are moderated by the binding of mBDNF to its receptor, tropomyosin-related kinase B, which is abundantly expressed in the hippocampus (33,34). Increased availability of mBDNF within the hippocampus in response to aerobic exercise may therefore promote neurological recovery. In addition, increased blood flow to metabolically active tissues exerts shear stress on the vascular endothelium (29). Endothelial shear stress stimulates the bidirectional release of mBDNF from endothelial cells; mBDNF can be secreted into interstitial fluid via the basal membrane, where it may interact with astrocytes and neurons, or can be secreted from the luminal membrane into the blood (35). Platelets are the primary storage site of mBDNF in the blood, accounting for 99% of the blood-borne mBDNF pool (29,36). During aerobic exercise, sympathetic activation of the spleen leads to thrombocytosis which transiently augments the circulating pool of mBDNF (29,37).

In summary, during moderate-intensity aerobic exercise, interconnected central and peripheral stimuli lead to a heightened production, secretion and transport of mBDNF. Increased availability of mBDNF in the brain after stroke may enhance neurological recovery, particularly during the acute phase when reparative processes are upregulated.

4.2. Aerobic exercise training during acute stroke: pre-clinical evidence overview

The timing of aerobic exercise training initiation relative to stroke onset is an important variable. In the first 24 hours after stroke, most cell death and neurological deficit occurs. This critical period is known as the hyperacute phase (38). Pre-clinical evidence suggests that undertaking aerobic exercise training in the hyperacute phase of stroke amplifies cellular stress which exacerbates cerebral injury and neurological deficit (39–41). During the subsequent acute phase (1 to 7 days post-stroke), growth-promoting genes are spontaneously upregulated which elicit neurogenesis, axonal growth, dendritic branching and synaptogenesis (42,43). During this transient window of heightened neuroplasticity, the nervous system is highly amenable to environmental stimuli (e.g. rehabilitation). Delaying rehabilitation beyond this sensitive period (e.g. by 14 or 30 days) impairs functional recovery and blunts neural reorganisation (43).

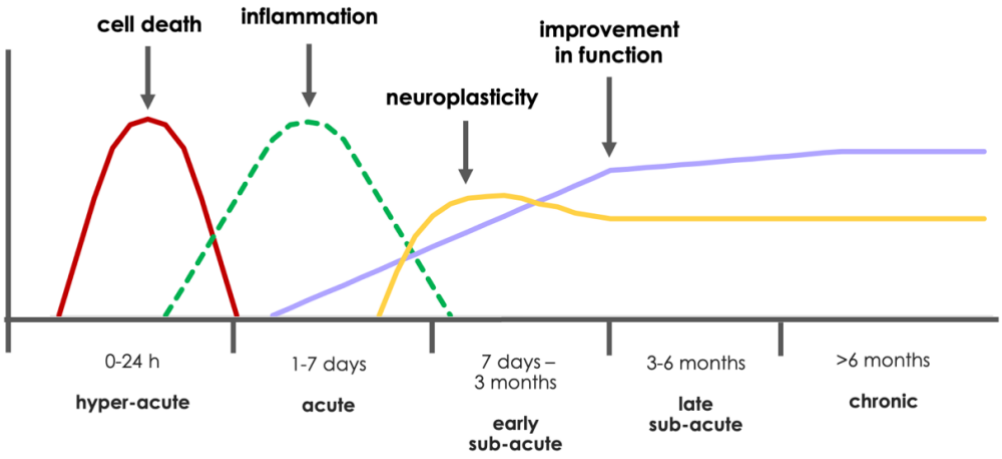

Figure 1. Framework depicting key post-stroke phases and temporally related biological processes. Adapted from Bernhardt et al. (2017).

Pre-clinical studies demonstrate that aerobic exercise training initiated in the acute phase of stroke augments neuroplasticity, evidenced by enhanced structural reorganisation of neuronal networks (e.g. dendritic branching and synaptogenesis) and elevations in biomarkers of neuroplasticity such as mBDNF (25). In rodent models of ischaemic stroke, the optimal exercise parameters which promote neuroplasticity are: 30 minutes of moderate-intensity aerobic exercise per day, initiated 3 to 7 days post-stroke (25). In addition, aerobic exercise training initiated in the acute phase of stroke may induce neuroprotective effects. Aerobic exercise training interventions that start 24 to 48 hours after stroke have been shown to reduce biomarkers of inflammation, oxidative stress and cell death, promote angiogenesis and reduce lesion volume (24). Neuroprotective effects were most commonly found with interventions that started in the early acute phase (24 hours vs. 3 to 7 days) and were carried out at low to moderate intensity for 20 to 30 minutes (24). In light of the pre-clinical evidence, it is plausible that a training intervention consisting of a daily 20 to 30 minute bout of low- to moderate-intensity aerobic exercise for 5 days, initiated 1 to 7 days after stroke, may have neuroprotective and neuroplasticity-promoting effects in the clinical stroke population.

4.3. Aerobic exercise training during acute stroke: clinical evidence overview

To our knowledge, there is only one clinical study (44) that has investigated the use of aerobic exercise training initiated within the acute phase of stroke. The purpose of this study was to assess the feasibility of a task-specific walking exercise training programme, and to determine if participants could attain a sufficient exercise intensity to improve cardiorespiratory fitness. Of note, this study did not investigate mechanisms related to

neuroprotection or neuroplasticity. Strømmen et al., (44) recruited 20 acute stroke patients (41.5± 14 h post-stroke; mild to no disability) and implemented a 5-day intervention consisting of twice-daily 30-minute bouts of treadmill walking at a moderate exercise intensity (50% of heart rate reserve [HRR]) (45). Standing and sitting rest breaks were permitted as required. More than half of participants experienced at least 1 adverse event (AE) during exercise. Dizziness was the most frequent AE, occurring in 8.5% (19/224) of all exercise sessions, and 4 sessions ended prematurely due to dizziness. In addition, although not reported as an adverse event, 8 sessions were cancelled due to tiredness (5 participants) and 28 sessions finished early due to exhaustion (number of participants not reported). Lastly, the target exercise intensity was only attained in 31% of sessions, and 8 participants (40%) did not achieve the target exercise intensity in any exercise session. The authors attributed the low exercise intensity to lower limb motor deficit which limited step frequency. This suggests that walking may be an unsuitable mode of aerobic exercise training during the acute phase of stroke recovery. No serious adverse events (SAEs) (e.g. neurological deterioration) occurred in the 30-day follow-up period therefore the authors concluded that a 14.7% AE rate was acceptable (33 AEs in 224 exercise sessions). As this was a feasibility trial, clinical outcomes were not explored. The occurrence of dizziness suggests that frequent and prolonged upright standing and walking may induce orthostatic stress which could be detrimental, especially during the acute phase of stroke when blood-brain barrier function is impaired (46). Indeed, standing upright has been shown to reduce CBF velocity by 13% relative to a supine position in chronic stroke (47). The landmark international AVERT trial found that very early (first mobilisation at a median of 18.5 hours post-stroke) and more frequent (3 additional bouts per day) mobilisation (out-of-bed sitting, standing or walking) was associated with a poorer functional outcome at 3 months post-stroke compared to usual care (first mobilisation at a median of 22.4 hours post-stroke). The physiological mechanisms were not explored in the AVERT trial, but it is plausible that orthostatic stress was a contributing factor to the negative outcome (47,48).

4.4. Aerobic exercise in clinical practice

UK stroke rehabilitation guidelines recommend that walking-orientated activities should have a cardiorespiratory focus (49). In clinical practice, walking is undertaken at low intensities for very short periods of time. For example, Prajapati et al., (50) reported that in subacute stroke patients (mean 32 days post-stroke), over 80% of walking bouts were less than 1 minute long and mean walking intensity was 20% of HRR. Polese et al., (51) reported similar findings in chronic stroke survivors (mean 26 months post-stroke), where basic and advanced walking activities elicited intensities of 26% and 32% of HRR, respectively. The only study which has reported inpatient walking activity during the acute phase of stroke

found that elderly patients spend less than 1 minute per day walking (52) and time spent inactive was positively correlated with stroke severity (HR not reported). During the first week of stroke ~70% of patients have a lower limb motor deficit (53) and ~60% are unable to walk or require walking assistance (54,55). A more accessible and tolerable mode of aerobic exercise may therefore be necessary to achieve a cardiorespiratory stimulus of sufficient intensity (moderate) and duration (20 to 30 minutes) to elicit elevations in CBF and mBDNF.

4.5. Accessibility of aerobic exercise

Findings from patient and practitioner surveys (56,57) and our PPI events highlight that physical disability, lack of appropriate exercise equipment and fear of falling are key barriers to engagement in aerobic exercise during acute stroke. These barriers may exclude patients who have the most to gain from participating in aerobic exercise training. We will utilise a bedside cycle ergometer with a power assistance function (Figure 2; Letto 2, Medimotion, Germany). This will enable participants to cycle even if they have hemiplegia or hemiparesis, without needing to be transferred out of their bed. Using a bedside cycle ergometer eliminates the risk of falling and enables people with lower limb motor deficits to participate in sustained aerobic exercise. Another benefit of using a bedside cycle ergometer is that participants exercise in a semi-recumbent position. In contrast to walking which may induce orthostatic stress (47), moderate-intensity semi-recumbent cycling is likely to preserve or increase cerebral perfusion (30). Our preliminary (ongoing) work supports this hypothesis; we have shown that in acute stroke patients (n=4), a single 30-minute bout of low- to moderate-intensity aerobic exercise is safe and tolerable, and increases CBF velocity by 9% above resting levels. We will build on this work by assessing the feasibility of an aerobic exercise training intervention versus standard care in the acute phase of stroke.

Figure 2. A bed-side power-assisted cycle ergometer (Medimotion, Letto 2).

5. Aims and objectives

Aim 1: **To assess the feasibility of conducting a RCT to assess the intervention.**

Objectives:

1a) Assess the recruitment/consent and dropout rates

1b) Assess the safety of the intervention via SAEs and AEs

1c) Assess the completeness of planned data collection

Aim 2: **To assess the acceptability and feasibility of the intervention.**

Objectives:

2a) Determine the retrospective acceptability of the intervention from the participant perspective using qualitative interviews and Likert scales.

2b) Determine the retrospective acceptability of the intervention from the perspective of healthcare practitioners using qualitative interviews.

2c) Determine the intervention fidelity by assessing the extent to which participants complete the prescribed exercise components (e.g. exercise intensity, duration and frequency).

Aim 3: **To develop mechanistic knowledge of the intervention.**

Objective:

3a) Measure the acute physiological response to the intervention including CBF velocity and mBDNF.

Aim 4: **To identify potential primary outcomes for a subsequent definitive RCT.**

Objective:

4a) Estimate the effect signal for potential primary outcome measures. The effect signal reflects the effectiveness of the intervention (difference between means of the groups) and the 'noise' (inter-individual variability) in the measurement (i.e. precision of the measure) and will inform the selection of primary outcome for a subsequent definitive RCT.

6. Study overview

6.1. Study design

A phase II, single-centre, single-blinded, two-arm, parallel group, randomised, controlled feasibility trial.

6.2. Study setting

The study will be conducted at The Royal Hallamshire Hospital (RHH), Beech Hill Rehabilitation Unit (BHRU) and the Advanced Wellbeing Research Centre (AWRC), Sheffield. Most study activity (screening and intervention) will take place on the hyper acute stroke unit (HASU), the acute stroke unit (ASU) or the neurology day care unit at RHH. Follow-up visits will be conducted at either the RHH, BHRU or the AWRC.

6.3. Success criteria

Progression to a definitive trial will be considered if the following a priori success criteria are met:

- Recruitment rate: ≥2 participants per month (30 participants recruited in 18 months)
- Safety - The following traffic light-style system is proposed:
    - Red: >10 adverse events related to the intervention – do not proceed.
    - Amber: 5-10 adverse events related to the intervention – review and revise protocol.
    - Green: <5 adverse events related to the intervention – proceed.
- Acceptability: average comfort score > 3/5 Likert scale (1= very uncomfortable to 5= very comfortable).
- Completeness of data: >80% of planned measurements recorded.
- Identification of an appropriate outcome measure.

6.4. Study flow chart

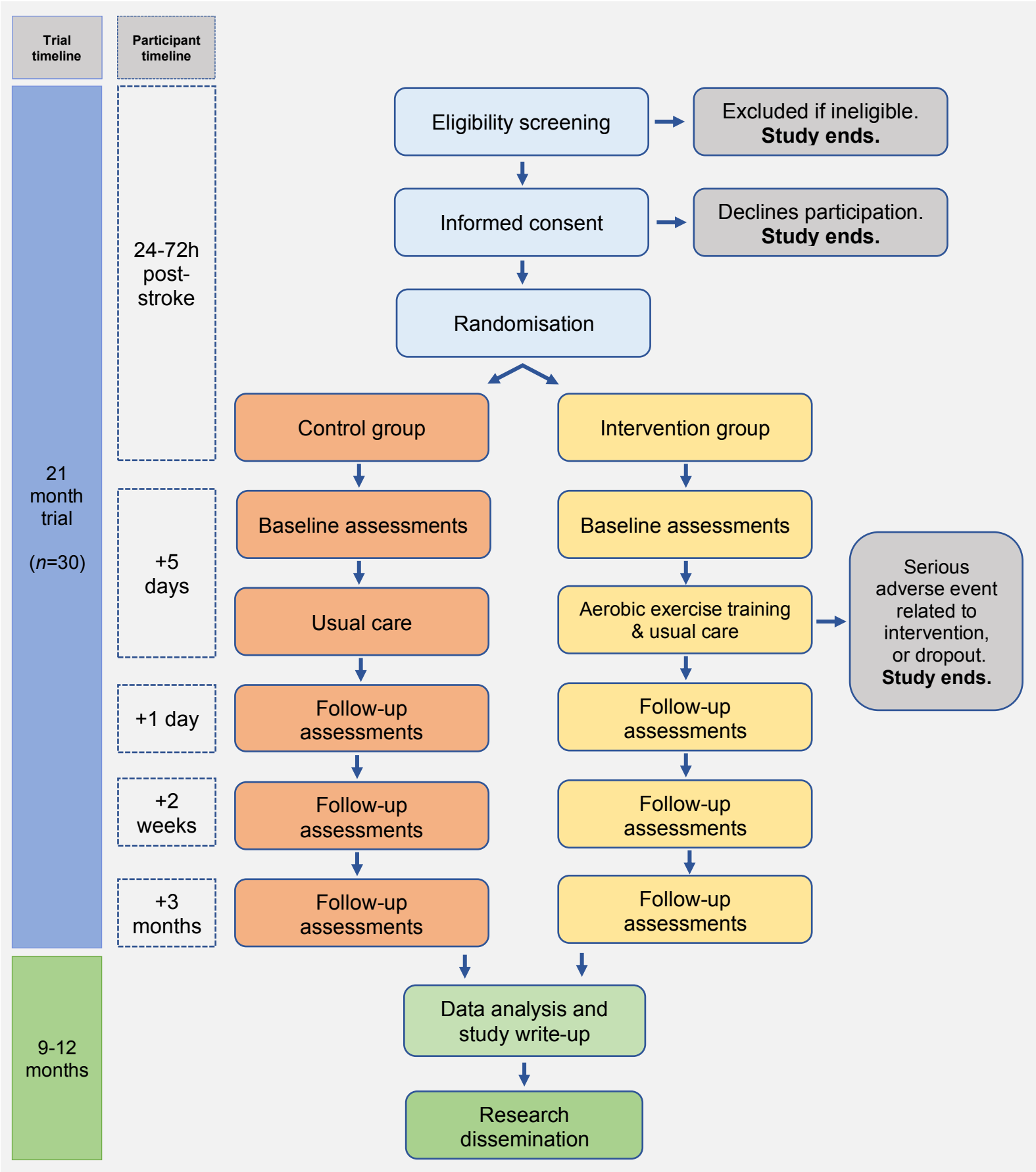

Figure 3. Study flow chart

7.1. Patient throughput and planned recruitment

According to NHS England figures, RHH HASU will receive approximately n=1335 stroke patient admissions in 2019/20 (58). 85% of these patients will have had an ischaemic stroke (6), thus, ~1135 ischaemic stroke survivors will potentially be eligible for our study per year (n=1700 in 18 months). A systematic review of recruitment rates in stroke rehabilitation trials suggests that 1.5 to 2 participants per month is a realistic target for a single site (59); hence, our recruitment target of 30 patients over 18 months.

7.2. Recruitment strategy

The Study Doctor will identify eligible patients located on the HASU, the ASU and the neurology day care unit. Eligibility will be determined in accordance with the inclusion and exclusion criteria. Daily ward rounds will be the primary means of identifying eligible patients. Once identified, the Study Doctor and an Investigator will greet eligible patients and inform them about the study. Patients will be informed about the potential risks, benefits and burden of participating, and will be made aware of the randomised group allocation procedure. Patients will be provided with a participant information sheet and will be politely asked to contemplate the information and make a decision within 48 hours of the initial discussion. This is due to the time-sensitive nature of the research. An aphasia-friendly version of the participant information sheet will be made available. A notepad and pen will be provided for patients with dysarthria (speech disorder). Where possible, family members and other supporting individuals will be informed about the study. At a later time point, an Investigator and the Study Doctor will revisit the patient at a mutually convenient time to answer any questions the patient, family member or supporting individual may have about the study. Patients will then be asked if they would like to participate. If they are willing to participate, informed consent will be taken. If the patient is undecided, the Investigator and the Study Doctor will return at a later time point (<48hrs of initial discussion) and repeat the process.

7.3. Sample size

A minimum of 24 participants (12 per arm) will be recruited. 12 has been recommended as a minimum number of participants per arm to be recruited for a clinical trial where there is no prior information to guide sample size (60). This figure is suggested to represent the lower threshold required to estimate the standard deviation of measures with adequate precision (60). Adjusting for a predicted 20% attrition rate, the target sample size is 30.

7.4. Inclusion criteria

- Adult (age >18 years) patients diagnosed with acute ischaemic stroke 1-7 days previously.
- Medically stable, assessed by a stroke physician.
- Sufficient English language comprehension and cognitive ability to understand the study protocol, follow instructions, complete questionnaires and give informed consent.
- Ability to mobilise lower body limbs in a cyclical manner (at least one leg).

7.5. Exclusion criteria

The following criteria are adapted from (45,61,62).

- Haemorrhagic stroke.
- <1 day or >7 days after onset of stroke symptoms.
- Clinically unstable, assessed by stroke physician.
- Disability preventing unipedal cycling.
- New York Heart Failure Classification stage III/IV.
- Terminal illness (life expectancy <6 months).
- Resting blood pressure >180/110 mmHg.
- Uncontrolled arrhythmia causing symptoms or haemodynamic compromise.
- Unstable angina.
- Uncontrolled diabetes mellitus.
- Acute deep vein thrombosis, pulmonary embolism or pulmonary infection.
- Already participating in a clinical research trial.
- Pain during mobilisation of lower limbs.
- Lower-limb spasticity or contracture which impairs ability to cycle.

7.6. Patient screening

The Study Doctor will review patients' clinical data to determine eligibility in accordance with the inclusion and exclusion criteria. Patients will be screened for absolute and relative contraindications to aerobic exercise prior to participation (Table 1, section 8.1). Absolute contraindications will preclude individuals from undertaking aerobic exercise. The Study Doctor will use clinical judgment to determine if individuals with relative contraindications to aerobic exercise can participate. Established exercise termination criteria (Table 2, section 8.2) will be used to minimise risk of harm during aerobic exercise.

The following routine medical examinations and clinical information will be used to determine eligibility and stratification:

- Time and date of stroke onset.
- Stroke treatments initiated.
- Stroke severity.
- Medication use.
- Electrocardiography results.
- Blood test results.
- Neuroimaging results.
- Carotid ultrasound imaging results.
- Comorbidities.

7.7. Consent and withdrawal

Participants will only be enrolled in the study if they have capacity to understand the participant information sheet and give informed consent. An aphasia-friendly participant information sheet will be made available. All written material given to patients will have prior approval from a local NHS Research Ethics Committee (REC) and will comply with GCP, local regulatory requirements and legal requirements. Where participants have the capacity to understand the study and are willing to participate but cannot write due to motor impairment, a family member will be asked to sign on the patient's behalf. All research team members involved in recruitment have received training in communication with people that have communication difficulties (e.g. aphasia). Participants will be informed that their participation is voluntary and that they may withdraw from the study at any time without giving a reason and without it affecting their clinical care or legal rights. Any data provided to that point will be used unless the patient requests otherwise. If the patient requests to have their data withdrawn, all data relating to that participant up until anonymisation of the final dataset will be destroyed.

7.8. Randomisation

A web-based permuted block randomisation procedure (sealedenvelope.com) will be used to allocate participants into one of the study arms: 1) usual care alone; 2) aerobic exercise training plus usual care. Participants will be stratified using the National Institutes of Health Stroke Scale (NIHSS): mild to moderate (0-15) and moderate to severe (>15) measured after reperfusion therapy or at a similar timepoint if not eligible for reperfusion therapy. Block

sizes of either 4 or 6 will be randomly chosen and block size will be masked from research team members involved in patient-facing research activities. An independent research team member will be responsible for the block randomisation procedure. They will be notified via email with participant ID numbers and a corresponding NIHSS score using a remote web-based system. The independent research team member will publish the group allocation which will be remotely accessible only to authorised research team members.

7.9. Blinding

It is not possible to blind participants or on-site research team members to group allocation. Statistical analyses will be conducted by an independent research team member who is blinded to group allocation.

7.10. Payment

Reasonable travel expenses will be provided for follow-up appointments located at the AWRC or BHRU. This will cost approximately £600 (30 x £20) and will be funded by a PhD research budget.

7.11. Physical accessibility

Participants will be invited to attend routine follow-up clinics with Dr Ali at 2 weeks and 3 months post-stroke. These will take place at the RHH, AWRC or BHRU. The location will depend upon where Dr Ali's clinics are scheduled. The RHH, AWRC and BHRU are accessible for people with physical impairments; each building has ramps and elevators. The AWRC and BHRU have car parking facilities which are free of charge. Parking spaces will be reserved for participants and research team members attending the AWRC and BHRU. The RHH has a large pay-and-display car park. Each building has emergency evacuation strategies for people with physical disabilities.

8. Safety

8.1. Contraindications to aerobic exercise

Patients' medical notes will be reviewed by the Study Doctor to identify absolute and relative contraindications to aerobic exercise. Absolute contraindications are conditions or situations in which an intervention/procedure should not be performed due to a disproportionately high

risk of harm. Patients with absolute contraindications will be excluded from the study. Relative contraindications are conditions or situations in which an intervention/procedure should be used with caution if the benefits outweigh the risks (determined by the Study Doctor).

Table 1. Contraindications to aerobic exercise.

Absolute contraindications	Relative contraindications
Acute myocardial infarction (within 3–5 days)	Left main coronary stenosis or its equivalent
Resting ST segment displacement (>2 mm)	Moderate stenotic valvular heart disease
Significant aortic stenosis (aortic valve area <1.0 cm^2)	Tachyarrhythmia or bradyarrhythmia
Uncontrolled sinus tachycardia (HR >120 bpm)	High-degree atrioventricular block
Third degree (complete) atrioventricular block without pacemaker	Hypertrophic cardiomyopathy
Active endocarditis	Significant pulmonary hypertension
Unstable angina	Electrolyte abnormalities
Uncontrolled hypertension: resting systolic blood pressure (SBP) >180mmHg, or resting diastolic blood pressure (DBP) >110mmHg	Use of insulin or insulin secretagogues
Orthostatic blood pressure drop of >20 mmHg with symptoms	Orthopaedic impairment
Syncope	Advanced or complicated pregnancy
Uncontrolled arrhythmias causing symptoms or haemodynamic compromise	
Acute myocarditis or pericarditis	
Uncontrolled heart failure	
Severe grade 3 rejection (cardiac transplantation recipients)	
Acute pulmonary embolus or pulmonary infarction	
Thrombosis of lower extremities	
Suspected dissecting aneurysm	
Uncontrolled asthma	
Pulmonary oedema	
Room air desaturation at rest <85%	
Respiratory failure	
Acute noncardiopulmonary disorder that may affect exercise performance or be aggravated by exercise (i.e. infection, renal failure, thyrotoxicosis)	
Uncontrolled diabetes mellitus	
Other metabolic conditions, e.g. acute thyroiditis, hypokalaemia, hyperkalaemia or hypovolaemia (until adequately treated)	
Acute systemic illness or fever	
Medically unstable	
Cognitive impairment leading to inability to cooperate	

Note. Table adapted from (43,59,60).

8.2. Aerobic exercise termination criteria

Table 2. Aerobic exercise termination criteria.

Termination criteria
†CBF velocity 30% below baseline
Chest pain suggestive of ischaemia
Fall in systolic blood pressure >20 mmHg from the highest value during exercise
>225 mmHg systolic blood pressure
>130 mmHg diastolic blood pressure
Hypotension (<100 mmHg systolic)
Severe desaturation: $SpO_2 \leqslant 80\%$ when accompanied by symptoms and signs of severe hypoxaemia
Sudden pallor
Loss of coordination
Mental confusion
Dizziness or faintness
Signs of respiratory failure

Note. Table adapted from (45,61,62); † = Study Doctor's clinical judgement.

8.3. Safety of aerobic exercise

Low- to moderate-intensity aerobic exercise is considered to be safe for medically stable acute ischaemic stroke patients without contraindications (44,63). The only study which has conducted a moderate-intensity aerobic exercise training intervention (five days of twice-daily, 30-min bouts of moderate-intensity walking exercise) reported no SAEs but occasional dizziness (8.5%; 19/224 sessions) and exhaustion (44). Exhaustion is not classed as an AE but is an important outcome when considering exercise tolerability; 24 out of 224 (10.7%) exercise sessions ended early as a result of exhaustion (9/20 participants). In addition, Kramer et al., (64) investigated the energy cost of two different 6-minute fitness assessments in acute stroke patients (median 4 days post-stroke; mild to moderate stroke; n=21). Ambulatory participants (n=14) performed a 6-minute walk test, whereas non-ambulatory participants (n=7) completed a 6-minute sit-to-stand test. The median rating of perceived exertion (RPE) reported at the end of each test was 12/20 and 13/20 for the walk and sit-to-stand tests, respectively (both moderate intensity). No SAEs or AEs were reported, and only one participant was unable to complete the walk test due to fatigue. Furthermore, Johnson et al., (65) demonstrated the safety of a graded exercise test in acute

and subacute stroke patients (n=28, days post-stroke: median = 9; range = 5-11), although the authors did not specify the proportion of participants that were in the acute (1-7 days post-stroke) or early subacute phase of stroke (7-30 days post-stroke). One of the exercise test termination criteria was reaching 85% of age-predicted maximum heart rate (HRmax), which is classed as vigorous exercise intensity (45). Over half of the participants exceeded this upper heart rate threshold and no SAEs or AEs were observed. Lastly, in our preliminary work (ESCAPE trial; STH20750), 4 acute stroke patients successfully completed a single 30-minute moderate-intensity exercise session (13/20 RPE) and there were no AEs or SAEs. Importantly, none of the aforementioned studies reported follow-up safety outcomes. **We can confirm that there have been no SAEs or AEs related to aerobic exercise in the 3 months following our investigation.** In summary, there have been approximately 276 reported bouts of aerobic exercise conducted in the acute phase of stroke, ranging from 6 to 30 minutes in duration and from moderate to vigorous intensity. No SAEs have been reported, whereas the AE rate ranged from 0-14.7% (mean 12%). The higher frequency of AEs appears to be related to high exercise volume and the mode of exercise training (e.g. treadmill exercise twice per day for 5 days).

In our proposed aerobic exercise training intervention, participants will exercise at a moderate intensity (40-59% HRR; 12-13/20 RPE). Moderate-intensity aerobic exercise elicits a transient increase in cerebral perfusion and neurotrophin concentration (39,59) which may contribute to improved recovery after stroke (24–26). Exercise duration will gradually increase from 10 minutes in the first session (day 1) to 30 minutes in the fifth session (day 5) (5-minute increment per day). Heart rate (HR) will be monitored continuously during exercise to ensure that moderate intensity is not exceeded. Heart rate reserve – the difference between resting HR and HRmax – represents the capacity for the HR to increase under stress. Measurement of HRmax is not appropriate due to the required vigorous exercise intensity. Instead, age-predicted HRmax will be calculated using the Inbar equation which estimates HRmax with greater accuracy than the commonly used formula of 220-age (66).

Inbar equation: 205.8 - (0.685 x age).

To adjust for use of beta-blocker medication, age-predicted HRmax will be reduced by 30 beats (62). The following Karvonen method will be applied to determine the target exercise HR (67). Importantly, this will enable the identification of the upper limit of the moderate exercise intensity domain (60% HRR).

Karvonen method example: target HR = [(HRmax – resting HR) x 60%] + resting heart rate.

Peripheral oxygen saturation and brachial blood pressure will also be measured throughout exercise and during the recovery period. The recovery phase will be of sufficient duration (~10 minutes; minimum 5 minutes) to allow physiological measures to return to near baseline levels. If any physiological measures fall outside of pre-determined ranges (see Table 2, section 8.2), or symptoms of clinical worsening arise, exercise will be terminated and a medical professional will be notified immediately.

8.4. Risk management

Cardiovascular risk

Participation in aerobic exercise may increase the risk of cardiovascular complications such as cardiac ischaemia, arrythmia or hypotension. The use of an appropriate warm-up and cool-down will minimise these risks (62). Participants' physiological response to exercise will be closely monitored during and after exercise. Exercise will be stopped if any adverse signs or symptoms occur (see table 2, section 8.2). The research team are experienced in the supervision of exercise and are trained in cardiopulmonary resuscitation.

Musculoskeletal risk

Participation in aerobic exercise may increase the risk of musculoskeletal injury such as a muscle strain. This risk will be minimised by conducting a graduated warm-up (45) and by following the cycle ergometer manufacturer guidelines regarding correct positioning of participants.

Blood glucose regulation risk

Aerobic exercise has insulin sensitising effects, therefore it is important to consider the use of blood glucose-regulating medication. The prevalence of diabetes mellitus in the acute ischaemic stroke population is 28% (95% CI 26-31%) (68). It is unclear what proportion of this population require insulin or insulin secretagogues. Where patients are receiving insulin or insulin secretagogues (relative contraindications), the Study Doctor will decide if the patient may participate in aerobic exercise at that particular time. To minimise the risk of exercise-induced hypoglycaemia, patients receiving insulin or insulin secretagogues will have their capillary blood glucose levels assessed before and after exercise (69). If blood glucose level is below 4mmol/L prior to exercise, the planned exercise session will be

delayed until euglycemia is achieved. Only clinical staff will be responsible for the provision of medication and carbohydrate.

8.4.1. Risk categorisation

Taking into account the absence of reported SAEs and our risk management procedures, we believe that this intervention is low risk. However, there is a lack of reported long-term follow-up outcomes. Due to this uncertainty, we propose that this intervention should be categorised as type B, that is, somewhat higher than the risk of standard medical care.

8.5. Risks and benefits to be communicated to patients (lay summary):

8.5.1. Potential benefits of aerobic exercise training

- Aerobic exercise training may help the brain recover from injury (neuroprotection). However, this has only been shown in animal studies.
- Aerobic exercise training may help the nervous system adapt after injury and improve learning (neuroplasticity). However, this has only been shown in animal studies.
- Aerobic exercise may help to slow down the loss of fitness, muscle size and muscle strength whilst in hospital.
- Aerobic exercise training may improve mood.

8.5.2. Risks of aerobic exercise training

Previous studies have shown that aerobic exercise is safe for people to do in the first week after stroke. So far, 276 aerobic exercise bouts have been completed in the first week after stroke. 237 sessions (86%) involved walking, 32 sessions (12%) involved seated cycling or stepping, and 7 sessions (3%) involved sit-to-stand exercise. From these studies, we estimate that the risk of:

- Cardiovascular, neurological, or musculoskeletal complications is less than 1% (no adverse events have happened so far).
- Lower-limb pain is less than 2% (adverse events only happened in treadmill exercise).

- Getting a blister or superficial wound on the foot is 1.1% (adverse events only happened in treadmill exercise. Cycling places less pressure on the feet than walking).
- Dizziness is less than 7% (adverse events only happened in treadmill exercise which is possibly related to an upright head position. Cycling will be completed in bed with a reclined backrest).

Figure 4. Pie charts displaying the risk of adverse events related to aerobic exercise.

9. Investigations

Table 3. Schedule of investigations and outcome measures. Note: orange ticks indicate standard care.

	Study period																			
	Enrolment	**Allocation**		**Post-allocation**																
Post-stroke timeline	24-72 h **(study starts)**			≥48 h; 5-day intervention										+1 day		Follow-up				
																+2 weeks		+3 months **(study ends)**	
Study timeline	t_{-1}	t_0		t_1		t_2		t_3		t_4		t_5		t_6		t_7		t_8	
	Group →	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**
Eligibility screen	✓																		
Informed consent		✓	✓																
Age, sex, ethnicity		✓	✓																
Time since stroke (hours)	✓																		
Stroke severity (NIHSS)		✓	✓											✓	✓			✓	✓
Cardiovascular risk profile		✓	✓																
Group allocation		✓	✓																
Thigh muscle morphology (ultrasound)		✓	✓											✓	✓			✓	✓
Thigh accelerometer fitted		✓	✓																
Inpatient physical activity levels (thigh accelerometer)				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓						

	Study period																			
	Enrolment	**Allocation**		**Post-allocation**																
Post-stroke timeline	24-72 h **(study starts)**			≥48 h; 5-day intervention										+1 day		Follow-up				
																+2 weeks		+3 months **(study ends)**		
Study timeline	t_{-1}	t_0		t_1		t_2		t_3		t_4		t_5		t_6		t_7		t_8		
	Group →	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**
Thigh accelerometer removed														✓	✓				
Physical function (SPPB, 10-m walk, handgrip strength)		✓	✓											✓	✓			✓	✓
Activities of daily living (Barthel Index)		✓	✓											✓	✓	✓	✓	✓	✓
Disability (mRS)		✓	✓											✓	✓			✓	✓
Acute fatigue (RoFS)		✓	✓		✓		✓		✓		✓		✓	✓	✓			✓	✓
Cognitive function (MoCA)		✓	✓															✓	✓
Chronic fatigue (FSS)		✓	✓															✓	✓
Pre-morbid physical activity levels (GPAQ)														✓	✓				
Anxiety and depression (GAD-7, PHQ-9)		✓	✓															✓	✓
Optimism (rLOT)		✓	✓															✓	✓
Health-related quality of life (EQ-5D)		✓	✓															✓	✓
Exercise self-efficacy		✓	✓											✓	✓			✓	✓
Wrist accelerometer fitted														✓	✓				
Post-discharge physical activity (wrist accelerometer returned)																✓	✓		

	Study period																			
	Enrolment	**Allocation**		**Post-allocation**																
Post-stroke timeline	24-72 h **(study starts)**			≥48 h; 5-day intervention										+1 day		Follow-up				
																+2 weeks		+3 months **(study ends)**		
Study timeline	t_{-1}	t_0		t_1		t_2		t_3		t_4		t_5		t_6		t_7		t_8		
	Group →	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**
Post-discharge physical activity (GPAQ)																		✓	✓
Resting cerebral blood flow velocity (transcranial Doppler ultrasound)				✓	✓							✓	✓						
Resting mature brain-derived neurotrophic factor												✓	✓						
Serious/adverse events		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Length of stay														✓	✓	✓	✓		
Qualitative interviews														✓	✓			✓	✓
Aerobic exercise-specific investigations:																			
Δ heart rate (telemetry or ECG)					✓		✓		✓		✓		✓						
Δ blood pressure (oscillometry)					✓		✓		✓		✓		✓						
Δ perceived exertion (RPE scale)					✓		✓		✓		✓		✓						
Δ oxygen saturation (pulse oximeter)					✓		✓		✓		✓		✓						
Δ cerebral blood flow velocity (transcranial Doppler ultrasound)					✓								✓						
Δ mature brain-derived neurotrophic factor													✓						
Δ end-tidal CO_2 and $\dot{V}O_2$													✓						

9.1. Qualitative data

One Co-Investigator (NK) will conduct semi-structured interviews with patients and healthcare professionals to assess the retrospective acceptability of the inpatient phase of the trial. If signs of emotional or cognitive issues or distress arise, the Study Doctor will be informed so that participants can be signposted to the appropriate services for longer term support if necessary. At the beginning of each interview participants will be assured that they can stop the interviews at any point should they become distressed. Further, participants will be able to withdraw their involvement in the study (including their transcribed interview data) at any point until anonymisation of the final data has occurred.

All interviews will be audio-recorded and transcribed verbatim. A computer-assisted qualitative data analysis software package will be used to store, manage and code the interview transcripts. All transcripts will be checked for accuracy, with a sample being independently reviewed and coded by a Co-Investigator (HS). Interviews will be analysed inductively using thematic (framework) analysis, from a realist perspective (70). Briefly, framework analysis involves systematic management and mapping of textual data into a matrix consisting of rows (participants) and columns (labels/codes which describe relevant information/events such as behaviours, values, emotions etc.). The reduced textual data enables a comparison between data sets and facilitates the identification of themes across the data (70). A semantic approach will be used to identify themes, where the surface meaning of the data will interpreted, as opposed to a latent approach which finds deeper meanings from 'between-the-lines' (71). NK is trained in conducting semi-structured interviews and qualitative data analysis. HS has extensive experience in the field of qualitative research.

The following definition of acceptability is used:

"A multi-faceted construct that reflects the extent to which people delivering or receiving a healthcare intervention consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention" (72).

9.1.1. Participant interviews

At the point of group allocation, a sub-sample of participants from the intervention group (n=8) and the control group (n=8) will be randomly selected for interviews. Interviews will be held 1-3 days after completion of the intervention in a private clinical room (30-45 minutes).

Using an intention-to-treat approach, individuals who drop out of the intervention will be asked to participate in an interview. Based on the positive feedback from our ongoing preliminary trial and our PPI events, we anticipate a low dropout rate. For this reason, all participants whom drop out will be asked to partake in an interview (non-randomly) to ensure that key information is not missed.

Participant interviews will focus on:

- Exercise equipment: comfort and ease of use.
- Exercise components: mode, duration, intensity and frequency.
- Perceived effectiveness of the intervention.
- Intervention-related burden on participant.
- Exercise self-efficacy, motivation and optimism.
- Acceptability of the study procedures.

At the 3-month follow-up appointment, a brief semi-structured interview (15-20 minutes) will be conducted with the same participants that were interviewed during their hospital stay (n=16) to gather information regarding the impact of hospital-based stroke rehabilitation on lasting exercise-related self-efficacy, motivation, optimism and emotional wellbeing.

9.1.2. Healthcare professional interviews

After the final participant has completed the trial, we aim to interview healthcare professionals to understand the retrospective acceptability of the study procedures and what impact the research had on clinical practice. We will recruit a convenience sample of 3-5 healthcare professionals. We aim to select a range of practitioners from different disciplines with different levels of seniority. Each interview is estimated to last for up to 30 minutes. Healthcare professional interviews will focus on:

- Attitude towards the intervention.
- Intervention-related burden on staff and participants.
- Perceived effectiveness of the intervention.

9.1.3. Minimising bias

The same Co-Investigator (NK) will supervise the intervention and undertake subsequent interviews. To reduce bias in favour of the intervention, NK will emphasise the importance of interviewees giving well-rounded feedback including positive and negative aspects. NK will

frame the interview as a critical exercise that will help future participants to have a positive experience. The interviewer will ask broad, exploratory questions which do not restrict participants' potential responses. For example, instead of asking the participant: "Did the exercise improve your mood?", an unbiased question would be "How did the exercise intervention make you feel? This could be positive or negative".

9.2. Justification of investigations and outcome measures

The proposed study activities, investigations and outcome measures aim to achieve a balance between scientific rigour, practicality and patient burden. Where possible, routine measures will be utilised to prevent duplication of work and to reduce patient burden. We acknowledge that the timing of routine assessments may vary depending on staff workload and patients' health. If relevant assessments are missed or significantly delayed, where appropriate, the research team will conduct them. Follow-up assessments will be conducted at a 3-month follow-up appointment with the Study Doctor.

Table 4. Justification of investigations and outcome measures

Domain	Outcome measure	Justification
Demographic	Age, sex and ethnicity	Description of **demographic data** will improve the generalisability of this work and may help us to identify demographic trends which otherwise may be masked by inclusion within a larger, more diverse group.
Diagnostic	Time since stroke	Careful attention must be paid to the **timing of the intervention relative to stroke onset**. Distinct biological events occur within the first week of stroke. Intervening too early may exacerbate health, whereas intervening too late may miss a 'window of neuroplasticity' (see section 4, Rationale).
	Stroke aetiology	This research builds on promising findings from pre-clinical studies utilising rodent models of ***ischaemic* stroke**. The effects of aerobic exercise early after *haemorrhagic* stroke are less clear. Patients with haemorrhagic stroke will be therefore excluded from the study.
Pharmacological	Use of medications which modify haemodynamics and psychoemotional state	It is important to know if **medications** are likely to affect other outcome measures. For example, beta-blockers lower heart rate and blood pressure. The recommended method of prescribing exercise intensity relies on the estimation of peak

		heart rate (62). Without knowledge of beta-blocker use, there would be uncertainty around what exercise intensity an individual is exercising at. Further, beta-blockers reduce resting heart rate which may cause side effects including fatigue and dizziness (73). This may adversely affect exercise performance, fatigue, mood, cognition and HRQoL.
Disability	The National Institutes of Health Stroke Scale (NIHSS) (74) Modified Rankin Scale (mRS) (75)	The **NIHSS** is a clinical measure of **neurological disability** which is routinely used in stroke medicine. We will use baseline NIHSS score to stratify participants into two subgroups: 1) minor to moderate stroke (NIHSS: ≤15), and 2) moderate to severe stroke (NIHSS: >15). Stratification by NIHSS score will ensure that each study arm contains an even balance of participants from across the stroke severity spectrum. The mRS is a questionnaire-based measure of stroke-induced **disability** which is commonly used in stroke research. We will use the mRS to assess the trajectory of stroke recovery. Using the mRS will enable follow-on research to be included in meta-analyses. *The mRS is routinely used in the STH NHS acute stroke service.
Cardiovascular risk	Body mass index, cholesterol/HDL ratio, systolic blood pressure, smoking status, demographics, comorbidities	It is of interest to understand how baseline **cardiovascular risk factors** relate to the incidence of cardiovascular events (e.g. stroke recurrence) throughout the study (76). *Cardiovascular risk factors are routinely measured in clinical practice, therefore no additional assessments will be undertaken by the research team.
Length of hospital stay	Number of days spent in hospital	**Length of stay** (LoS) is a key NHS quality indicator. Longer LoS is associated with poorer medical outcomes and greater financial costs (77). Aerobic exercise may influence stroke recovery trajectory and thereby LoS.
Psychoemotional state Health-related quality of life Depression Anxiety	EuroQol Quality of Life Index (EQ-5D) (78) Patient Health Questionnaire (PHQ-9) (79) Generalised Anxiety Disorder (GAD-7) (80)	**Health-related quality of life** (HRQoL) and **mood** can be adversely affected after stroke (4,81,82). Exercise interventions improve mood and HRQoL (81,83). Measuring EQ-5D, PHQ-9 and GAD-7 will enable the assessment of the effects of the intervention on HRQoL and mood. *PHQ-9 and GAD-7 are the only routine psychoemotional assessments used in the STH NHS acute stroke service.

Optimism	Revised Life Orientation Test (rLOT) (84)	A higher level of **optimism** is associated with lower levels of inflammation and better health outcomes across a number of health conditions (85). An optimistic outlook may mitigate inflammation and in turn contribute to a better recovery after stroke. It is of interest to understand how the level of optimism at baseline may contribute to health outcomes. In addition, it is of interest to assess how the intervention may alter optimism. *Optimism is not routinely measured in the STH NHS acute stroke service.
Exercise self-efficacy	Short Self-Efficacy for Exercise scale (86)	**Self-efficacy** plays an influential role in the adoption and maintenance of exercise behaviour in older adults (87). Those with higher levels of exercise self-efficacy are better equipped to overcome barriers to exercise compared to those with low self-efficacy. Initiating an aerobic exercise intervention during the early stage of stroke rehabilitation may enhance self-efficacy and result in higher levels of participation in exercise. *Self-efficacy is not routinely measured in the STH NHS acute stroke service.
Fatigue & perceived exertion	Fatigue Severity Scale (FSS) (88)	Post-stroke fatigue is a common, debilitating complication of stroke (91). The management and prevention of **post-stroke fatigue** was ranked 6th in the top 10 research priorities relating to life after stroke (agreed by stroke survivors, caregivers, and health professionals)(92). There is limited evidence regarding the effects of exercise interventions on post-stroke fatigue (93). Measuring this outcome using the FSS will help develop the evidence base.
	Rating of Fatigue Scale (RoFS) (89)	The RoFS will enable us to understand **transient (acute) fatigue** as opposed to generalised chronic fatigue. This is relevant because a patient may partake in various therapies and assessments throughout each day (differing in intensity and duration) which may adversely affect a their performance during a subsequent therapy or assessment.
	Rating of perceived exertion (RPE) (90)	RPE is a **subjective measure of exercise difficulty**, from the participant's perspective. We will utilise the RPE scale to guide exercise workload during each exercise session. RoFS and RPE are not routinely used in the STH NHS acute stroke service. FSS, is routinely used.
Cognitive function	Montreal Cognitive Assessment (MoCA) (94)	Improvement of post-stroke cognition was ranked 1st amongst the top 10 research priorities relating to life after stroke (92). Aerobic exercise has positive effects on **cognitive function** after stroke (95). The MoCA is a simple assessment which will

		help elucidate the impact of the intervention on cognitive function. *The MoCA is routinely used in the STH NHS acute stroke service.
Quadricep muscle morphology	Muscle ultrasound (96,97): Rectus femoris cross sectional area and muscle thickness. Vastus lateralis muscle thickness and angle of pennation.	Acute stroke patients spend 98% of their time physically inactive (52). Sedentary behaviour during hospitalisation causes accelerated muscle atrophy. This increases the risk of sarcopenia, disability and stroke recurrence (98,99). This issue is particularly important in stroke where recovery of motor function is dependent on intensity of rehabilitation, and fitness level represents a 'neurorehabilitation ceiling' (26). In non-ambulatory acute stroke patients, a single week of immobility leads to 12.8% and 9.3% reductions in quadricep muscle thickness in the paretic and non-paretic limbs, respectively (100). Aerobic exercise may mitigate muscle atrophy therefore measurement of **muscle morphology** is of interest. Hypoallergenic ultrasound gel and nitrile gloves will be used. If a patient has a known allergy to ultrasound gel, this test will be excluded. *Muscle ultrasound is not routinely used in the STH NHS acute stroke service.
Physical activity	Accelerometers Global Physical Activity Questionnaire (GPAQ) (101)	Total physical activity (i.e. rehabilitation) dose moderates change in motor function and level of disability (102). We will use therapist medical notes to quantify usual care therapy dose. However, patients only spend a minor proportion of their time with therapists. We will quantify physical activity levels for the remaining portion of each day using a **light-weight accelerometer.** This will be secured to the anterior thigh of the non-affected limb using a hypoallergenic adhesive dressing (103). The ActivPAL thigh-based accelerometer differentiates sitting, standing and walking postures, which wrist-based accelerometers cannot do. The device will be fitted immediately after the baseline thigh muscle ultrasound measurement, and retrieved immediately before the post-intervention thigh muscle ultrasound measurement. Participants will then be given a wrist-based accelerometer to wear until their post-discharge 2-week follow-up appointment. This will record daily step count. The reason for switching to a wrist-based device is that the thigh-mounted device would need to have the adhesive dressing changed which would be impractical. The wrist-based accelerometer will be retrieved at the 2-week follow-up appointment. Due to limited availability of the wrist-based accelerometers, only the **GPAQ will be conducted at the 3-month follow-up appointment.**

		In addition, the **GPAQ will be used to estimate pre-stroke physical activity levels**. This will be assessed the day after the intervention period. A higher level of physical activity pre-stroke is associated with more favourable recovery after stroke (104,105), therefore it is important to account for this confounding variable. *Accelerometery and the GPAQ are not routinely used in the STH NHS acute stroke service.
Activities of daily living & physical function		Over half of stroke survivors live with a physical disability (2). Finding optimal strategies to improve post-stroke physical function is a research priority (92). Measurement of physical function is necessary to understand the effects of the aerobic exercise intervention compared to usual care alone.
	Barthel Index (106)	**The Barthel Index** is a simple measure of a person's ability to undertake **activities of daily living** and to what degree assistance is needed. This assessment is routinely used by the STH NHS acute stroke service.
	Short physical performance battery (SPPB) (107)	The SPPB is short series of physical assessments that measure **lower-extremity function**. The test battery is designed for use in elderly and clinical populations and includes: a **3-metre walk, 5 sit-to-stand repetitions, and a set of standing balance tests.**
	10-metre walk test (108)	The **10-metre walk** test will also be used in accordance with expert recommendations for core outcome measures in stroke recovery trials (110). Instead of testing 10-metre walk speed separately to the SPPB walk speed, we will extend the SPPB 3-metre walkway by 7 metres and record the average walking speed at both distances.
	Handgrip strength (109)	**Handgrip strength** is a simple measure of upper-limb function. *The Barthel Index is the only physical function assessment that the STH NHS acute stroke service use.

Acute physiological response to aerobic exercise	• Heart rate • Blood pressure • Oxygen saturation	Only one study has investigated the use of aerobic exercise in the acute phase of stroke (44). The only physiological variable reported was mean exercise heart rate. Collecting more in-depth physiological data will improve the mechanistic knowledge of how aerobic exercise influences cerebral perfusion and recovery from injury. Furthermore, monitoring **heart rate**, **blood pressure** and **oxygen saturation** in real-time will improve the safety of exercise prescription. Heart rate will be measured telemetrically via a chest strap or using wireless ECG; brachial blood pressure will be measured with an oscillatory monitor; and peripheral oxygen saturation will be measured with a fingertip pulse oximeter.
	• Cerebral blood flow (CBF) velocity	**CBF velocity** is a non-invasive proxy measure of cerebral perfusion (111). Moderate-intensity aerobic exercise increases CBF velocity by 10-30% (30). Increasing blood flow to the peri-infarct area may enhance reparative processes and promote neuroplasticity (24–26,30,31,36,37,95,112). We will use a transcranial Doppler (TCD) ultrasound device to determine changes in CBF velocity measured bilaterally at the middle cerebral arteries. A specially designed, comfortable headset will be used to fix the ultrasound probes in place during exercise sessions. To minimise time burden, CBF velocity will be measured a maximum of two times per participant. Both the control group and the intervention group will have resting CBF velocity measured on the second study day (t_1) and the sixth study day (t_5). For the intervention group only, we will record changes in CBF velocity throughout the exercise sessions immediately after resting measures. Measuring resting CBF velocity will enable us to understand how this variable changes in the first week of stroke under conditions of usual care and aerobic exercise training. Furthermore, as the aerobic exercise duration progresses throughout the 5-day intervention from 10 to 30 minutes, a repeated measure (first vs. fifth exercise session) will help to identify if there is a dose-response relationship between exercise duration and change in CBF velocity (intervention group only). Hypoallergenic ultrasound gel and nitrile gloves will be used. If a patient has a known allergy to ultrasound gel, this test will be excluded.
	• Oxygen consumption ($\dot{V}O_2$)	During moderate-intensity aerobic exercise, increased energy turnover within working muscle leads to increased **$\dot{V}O_2$** and **CO_2** production (30). CO_2 is a potent vasodilator and is a key regulator of CBF (30). $\dot{V}O_2$ can be used to estimate the energy expenditure of physical exercise. Combined measurement of $\dot{V}O_2$ and end-tidal CO_2 enables the estimation of the metabolic

	• End-tidal carbon dioxide (CO_2)	stress and thereby intensity of exercise (61). Both $\dot{V}O_2$ and end-tidal CO_2 can be measured concurrently using an expired gas analysis system. Expired gas will be collected via a non-invasive face mask. $\dot{V}O_2$ and end-tidal CO_2 will be measured in the intervention group only during the fifth exercise session.
	• Mature brain-derived neurotrophic factor (mBDNF) • Platelet count • Plasma volume	**mBDNF** is a key mediator of neuroprotection, neuroplasticity, memory formation and learning (28). Aerobic exercise transiently increases the systemic production and secretion of mBDNF (29). Platelets are a primary storage site of mBDNF in the blood (29). Aerobic exercise stimulates the release of platelets from the spleen which increases the circulating level of mBDNF (29,37). To accurately determine exercise-induced changes in serum mBDNF independent of **platelet count,** mBDNF concentration will be calculated per platelet. In addition, blood plasma contains a freely circulating pool of mBDNF that is not bound to platelets. Possible sources of plasma BDNF include the brain, skeletal muscle, peripheral blood mononuclear cells and vascular endothelial cells (29). Measurement of plasma mBDNF is neccessary to determine if cellular sources of BDNF are secreted into circulation during exercise. However, during moderate-intensity exercise, water shifts from plasma into both the interstitial and intracellular fluid compartments of contracting skeletal muscle. Thus it is important to correct for changes in **plasma volume** to prevent erroneous interpretations of changes in mBDNF concentration (113). In sum, by assessing changes in the total mBDNF system (serum, volume-corrected plasma, platelets, and mBDNF per platelet), it is possible to quantify cellular sources of denovo mBDNF, and to differentiate this from changes in mBDNF that result from altered blood plasma volume and movement of mBDNF between plasma and platelet pools (29). Due to the invasive nature of venous blood sampling and the expense of analysing mBDNF, we have chosen to limit blood sample collection to a maximum of two timepoints per participant at t_5: 1) baseline (both groups), and 2) post-exercise (intervention group only). We have chosen to measure mBDNF at the fifth aerobic exercise session which is 30 minutes in duration. This exercise duration has consistently been shown to increase circulating mBDNF (29). Hypoallergenic nitrile gloves, dressings and plasters will be used.

9.3. Scheduling research activity

Research team members will liaise with clinical staff to decide upon the most suitable times to conduct research activity. Key factors to consider will include patient clinical status, patient wellbeing and fatigue, and scheduled routine care.

9.4. Participant food and drink consumption

Participants will not be asked to alter their food intake. Participants will be politely asked to refrain from consuming caffeinated beverages prior to any research activity on the second and sixth study days, where CBF will be measured. Caffeine is a cardiovascular stimulant (114). In patients recovering from an acute ischaemic stroke, ingestion of 250 mg caffeine (approximately 2.5 cups of coffee) reduces CBF velocity and global blood flow by 13-30% (115). Restriction of caffeine intake will therefore improve the validity of CBF measurements. The research team will liaise with clinical and catering staff to ensure that this request is communicated. Alternative decaffeinated beverages will be offered instead. However, if participants refuse to restrict caffeine intake, they will not be excluded from the study. Data obtained from these participants will be interpreted with caution and this will be noted as a limitation of the study.

9.5. Preparation, storage and analysis of blood samples

Venous blood samples will be taken at t_5 (6-8 days post-stroke). Baseline blood samples will be collected from control and intervention group participants in a resting state. Post-exercise blood samples will be taken from the intervention group participants during the recovery (passive cycling) phase following aerobic exercise.

Blood samples will then be centrifuged and aliquoted at RHH. Processed samples will then either be stored in a designated -80°C freezer at RHH or put on ice (for up to 5 hours) and transferred to the AWRC and stored at stored at -80°C. mBDNF will be measured using an enzyme-linked immunosorbent assay (116). Platelet count will be measured using an automated haematology analyser. Blood plasma volume will be measured using the Dill and Costill method (117). Blood samples will be stored for 10 years to allow time to source additional funding and obtain ethical approval for further exploratory analyses that may improve mechanistic knowledge. 10 years after the trial end date samples will be destroyed in accordance with local laboratory procedures. Researchers are trained in venepuncture.

10. COVID-19 contingency plan

Currently, non-essential face-to-face research is suspended due to the COVID-19 pandemic. A restart date has not yet been announced, however it is unlikely that the proposed study will be able to take place before the end of 2020 due to the combination of winter pressures and a second wave of COVID-19-related hospital cases. If the proposed study is approved and is able to commence in the early months of 2021, we anticipate that patient follow-up appointments will be conducted virtually (via video call or telephone) for a transitional period of an unknown duration. Thus, the research activities that are planned to be conducted at follow-up appointments may be adapted or omitted. Table 5 outlines our contingency planning for research-related activities. In line with STH procedures, participants will be given an information leaflet providing technical support with regards to video call and telephone consultations. All face-to-face research activities will be conducted in accordance with STH risk management policy.

Table 5. COVID-19 contingency plan

Activity/measure	Plan A (no face-to-face research restrictions)	Plan B (COVID-19 restrictions)
National Institutes of Health Stroke Scale (NIHSS)	**Face-to-face assessment** conducted at the 3-month follow-up appointment by Dr Ali Ali.	Only possible to conduct via **high-quality video call**. This will be dependent on if the participant has access to a device with high-quality video calling function. This assessment will be conducted by Dr Ali Ali. If the video quality is deemed to be poor, this assessment will be omitted.
Barthel Index	Conducted at the 2-week and 3-month follow-up appointments via **face-to-face interview** by Dr Ali Ali.	Conducted at the 2-week and 3-month follow-up appointments via **telephone or video call interview** by Dr Ali Ali.
Thigh muscle ultrasound	Conducted at the 3-month follow-up appointment. **Requires physical contact.**	**Omitted**.
Physical function assessments (SPPB,	Conducted at the 3-month follow-up appointment. **Requires direct**	**Omitted**.

10-m walk, handgrip strength)	**supervision and in some cases, physical assistance.**	
Acute fatigue (RoFS)	Simple visual analogue scale conducted **before and after physical function assessments** at the 3-month follow-up appointment.	**Omitted.**
Modified Rankin Scale	Conducted at the 2-week and 3-month follow-up appointments via **face-to-face interview** by Dr Ali Ali.	Conducted at the 2-week and 3-month follow-up appointments via **telephone or video call interview** by Dr Ali Ali.
Cognitive function (MoCA)	Conducted at the 3-month follow-up appointment. **Requires direct supervision.**	**Omitted**.
Chronic fatigue (FSS) Anxiety and depression (GAD-7, PHQ-9)	Conducted at the 3-month follow-up appointment via **face-to-face interview** by Dr Ali Ali.	Conducted at the 3-month follow-up appointment via **telephone or video call interview** by Dr Ali Ali.
Optimism (rLOT) Health-related quality of life (EQ-5D) Exercise self-efficacy Post-discharge physical activity (GPAQ)	Conducted at the 3-month follow-up appointment via **face-to-face interview** by Mr Nik Kudiersky.	Conducted at the 3-month follow-up appointment via **telephone or video call interview** by Mr Nik Kudiersky.
Wrist-based accelerometer	Participant to bring activity monitor to 2-week appointment and **hand over** to Dr Ali Ali.	Participant will be provided with a **pre-paid envelope** to **post** the activity monitor back to the research team.
Qualitative interview	**Face-to-face interview** to be conducted by Mr Nik Kudiersky at the 3-month follow-up appointment.	Conducted at the 3-month follow-up appointment via **telephone or video call interview** by Mr Nik Kudiersky.

11. Feasibility outcome measures

Table 6. Feasibility outcome measures

Outcome	Description
Recruitment rate	Number of participants recruited per month of the recruitment period.
Exclusion rate	Number of ineligible patients divided by the total number of patients admitted to the RHH stroke service during the recruitment period.
Consent rate	Percentage of eligible patients who consent to participate.
Dropout rate	Percentage of individuals that discontinue participation after the study has commenced. Voluntary reasons for dropout will be recorded. Early discharge from hospital will not count as a dropout.
Participant fidelity	Completion of key exercise components in accordance with the exercise protocol including: percentage of planned exercise session duration completed, percentage of target exercise intensity per session attained, and percentage of total planned exercise sessions completed.
Completeness of data	Percentage of planned measurements completed and recorded.
Safety	Number of SAE and AEs related to the intervention.
Acceptability of intervention (participant interview)	Comfort and ease of using cycling apparatus.
Acceptability of study procedures (healthcare professional interview)	• Attitudes towards the intervention • Burden on staff and participants • Perceived effectiveness of the intervention

12. Intervention

12.1. Usual care

Participants randomised to the control group will receive usual care according to guidance from the National Institute for Health and Care Excellence (19) and the Royal College of Physicians (49). Briefly, it is recommended that patients complete at least 45 minutes of each appropriate therapy per day (physiotherapy, occupational therapy and or speech and language therapy) for five days per week. Patients should be mobilised (out-of-bed sitting, standing or walking) within the first 48 hours of stroke onset, or if physically capable, as soon as possible post-stroke.

12.2. Usual care therapy dose

Adequate reporting of therapy dose and timing of initiation is essential to understand the effectiveness of therapeutic interventions, and enables replication (118). This is particularly important in complex interventions such as stroke rehabilitation which involves a variety of active ingredients. The Stroke Recovery and Rehabilitation Roundtable recently highlighted the lack of consideration of dose complexity as a potential reason for neutral findings in stroke recovery and rehabilitation trials (119). Clinical trials tend to quantify therapy dose using duration (minutes/hours) only, which masks important variables such as the relative intensity of activities and number of repetitions – both of which moderate neuroplasticity and neurological recovery (120). In addition to a lack of clarity regarding therapy components, UK audit data from the 2018/19 Sentinel Stroke National Audit Programme (121) demonstrates that a large proportion of UK stroke units do not meet the minimum recommendation for therapy duration. Observations of UK stroke units have highlighted various organisational (e.g. staffing levels and time spent in information exchange) and patient (e.g. fatigue and therapy tolerance) factors that reduce therapy duration (122).

In recognition of the widespread underreporting of therapy composition and the reported variability in therapy duration and content across NHS sites, we aim to capture detailed information pertaining to therapy dose using therapy records and overall physical activity levels using accelerometer-based motion sensors. Timing of therapy initiation (hours/days post-stroke) will also be recorded.

12.3. Aerobic exercise training protocol

Detailed reporting of the intervention will align with the Consensus on Exercise Reporting Template (123).

12.3.1. Exercise equipment

A bedside cycle ergometer (MOTOmed Letto 2, Medimotion, Reck, Germany) will be positioned at the foot of the participant's bed. Both the bed and the cycle ergometer will be positioned at their lowest height which orientates the lower limbs at approximately chest height. The MOTOmed Letto2 detects asymmetrical force distribution and provides motor assistance to compensate for hemiparesis or hemiplegia. The bed backrest angle will be elevated to 45° and the participant will be positioned so that the lumbar spine is supported by the backrest. The participant's feet will be inserted onto the foot pedals which contain heel cups to prevent the feet from slipping downwards. To prevent knee hyperextension, support frames, which extend from each crank arm, will be positioned underneath the superior region of each shank. Flexible rubber straps will be fastened around the feet and shanks for stability. The foot pedals and support frames will fixate the lower limbs in a comfortable position, enabling a smooth cycling motion in the sagittal plane. The knee angle at the end of the pedal stroke will be 25°, which is considered to be optimal for both movement economy and injury prevention (124). Knee angle will be measured using a goniometer centred on the lateral epicondyle with each measuring arm aligned to the centre point of the corresponding greater trochanter and lateral malleolus (125). All equipment used in the study will have a CE mark for European use and will meet European safety regulations.

12.3.2. Exercise supervision

All exercise sessions will be supervised by the Principal Investigator (SN) or a Co-Investigator (NK) on a one-to-one basis. Dr Simon Nichols (SN) is a senior research fellow in clinical exercise physiology with expertise in conducting exercise-based cardiovascular rehabilitation trials in clinical populations. The assigned Co-Investigator (NK) is undertaking a PhD in Clinical Exercise Physiology, holds an MSc in Clinical Exercise Physiology, has extensive experience supervising exercise in healthy (>400 hours) and clinical (>50 hours) populations, and is trained in basic life support. A medical doctor will be readily available to intervene in the case of an adverse event.

12.3.3. Aerobic exercise

The exercise protocol will begin with a 5-minute passive cycling period (20 revolutions per minute [rpm]), where the participant will be relaxed (no exertion) and the bike will rotate the participant's legs to mobilise the lower limb joints and increase venous return. Subsequently, the participant will complete a low- to moderate-intensity warm-up phase. Starting in the lowest gear, the participant will be instructed to cycle a self-selected cadence aiming for an intensity equivalent to 'light' (11/20) on the RPE scale (90). At 60s and at each subsequent minute, the operator will increase the cycle gear by one level until a target RPE of 13 ('somewhat hard') is achieved. The warm-up duration will be individualised for each participant based on time taken to reach RPE 13. When RPE 13 is reached, the conditioning phase will commence and the participant will be instructed to maintain a consistent cadence (±10%) for 5-min. After which, passive mode (20 rpm) will be activated and the participant will be asked to rest for 1-min. The number of 5-min conditioning bouts will increase by one bout per session. The first session will contain 2 bouts (total = 10 mins), and the fifth session will contain 6 bouts (total = 30 mins). The rationale for this progressive design was developed with input from researchers, healthcare practitioners and people affected by stroke (see PPI section, 13.2.). Briefly, it was considered that starting with 30-min of aerobic exercise in session 1 may be too difficult for some patients due to fatigue, whereas a gradual progression in exercise duration would be more tolerable. Throughout the warm-up and conditioning phases, RPE will be measured in the last 15s of each minute, and the cycle gear will be adjusted accordingly if RPE deviates away from target. The target exercise intensity (moderate) will remain constant during the work intervals of the conditioning phase. To ensure that the intervention is tolerable (i.e. the conditioning phase can be completed), the cycling gear (resistance) will be adjusted according to the participant's level of function and RPE at that particular time. All performance metrics displayed on the MOTOmed interface (Watts, gear, left-to-right symmetry and distance) will be concealed from the participant with the exception of cadence (rpm). After the conditioning phase, the participant will undertake a graduated cool-down for 5 minutes and then will be instructed to relax whilst a final 2-min passive cycling recovery phase is completed.

The day after completing the first exercise bout, participants will undertake a single aerobic exercise session per day for 4 days (5 exercise sessions in total). If patients are discharged earlier, study participation will terminate on the day of discharge. The workload that elicited an RPE of 13 at the start of the conditioning phase in the first aerobic exercise session will be used to guide the initial workload for the conditioning phase in subsequent sessions. Number of repetitions (rpm multiplied by minutes) completed during the warm-up,

conditioning phase and cool-down will be included within therapy dose calculations. Verbal communication provided by the operator will be standardised (detailed in Table 6, Appendix).

Through consultations with stroke survivors and healthcare practitioners we acknowledge the need for a flexible exercise protocol. It was expressed to us that patients' level of fatigue and physical function may fluctuate throughout the duration of hospital stay depending on various intrinsic and extrinsic factors. Thus, the workload used for each exercise session will be a collaborative choice made between the researcher and the participant.

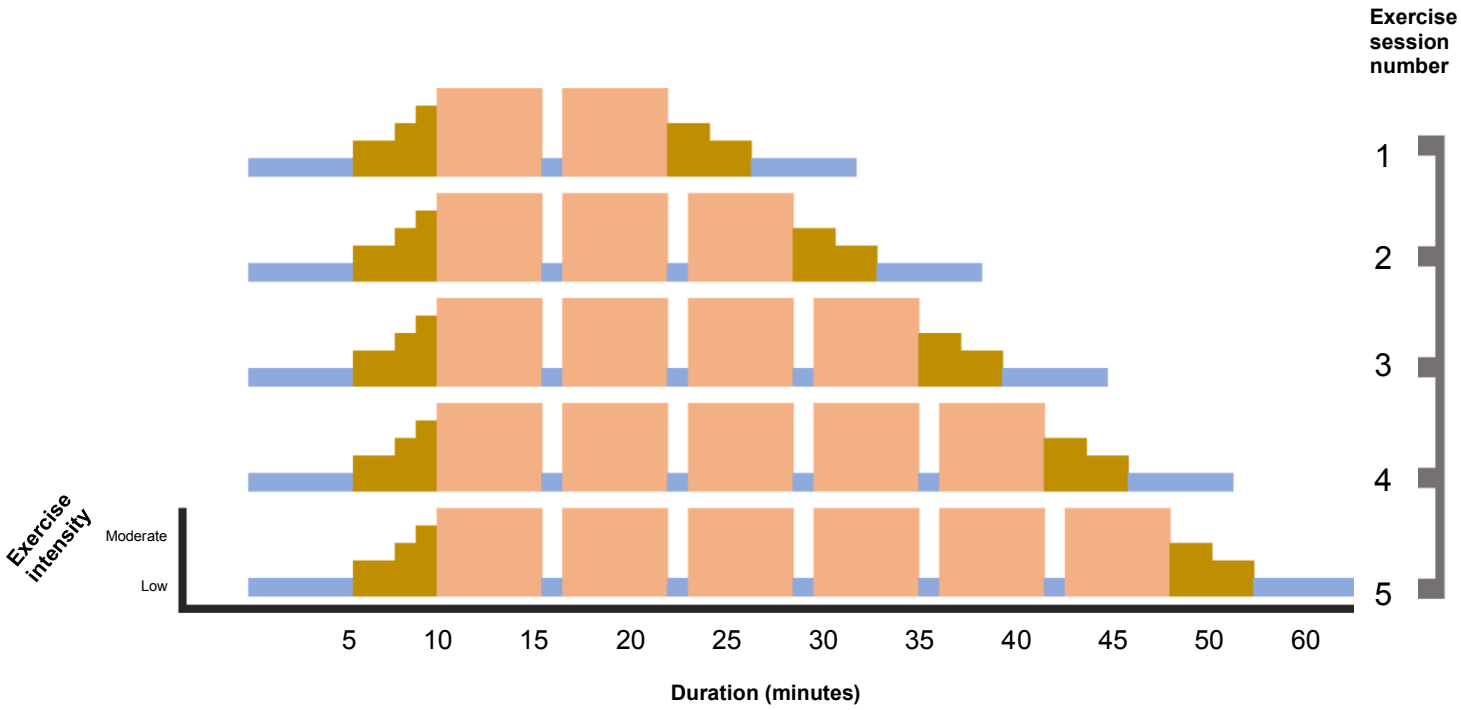

Figure 5. Schematic diagram of 5-day exercise protocol.

Note: Blue = passive cycling (no exertion) = 5 minutes; brown = warm up/cool down; pink = active cycling (moderate intensity). Active cycling duration = 5 minutes per bout. Passive recovery intervals = 1 minute (blue).

12.4. Operational definitions for (S)AEs

Adverse events

Any untoward medical or psychological occurrence in a patient or trial subject involved in a trial intervention and which does not necessarily have a causal relationship with this intervention. An adverse event can therefore be any unfavourable and unintended sign, symptom, or disease (including abnormal lab results or a traffic accident) in any subject in a trial (including those in an untreated control group), whether or not considered related to the investigational intervention.

Serious adverse events

Unless exempted by the approved protocol, any untoward medical or psychological occurrence that:

- results in death
- is life-threatening*
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- requires intervention to prevent one of the above occurrences

*Life-threatening in the definition of a SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

12.5. Recording and reporting of serious adverse events

All SAEs occurring from the time of start of the intervention until 3 months post cessation of trial intervention will be recorded on a STH-approved form and faxed/emailed to the Sponsor within 24 hours of the research staff becoming aware of the event. Once all resulting queries have been resolved, the Sponsor will request that the original form should also be posted to the Sponsor and a copy to be retained on site.

For each SAEs the following information will be collected:

- Full details in medical terms and case description.
- Event duration (start and end dates, if applicable).

- Action taken.
- Outcome.
- Seriousness criteria.
- Causality (i.e. relatedness to intervention), in the opinion of the Investigator.
- Whether the event would be considered anticipated.

Any change of condition or other follow-up information should be emailed/faxed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

12.6. Responsibilities

Principal Investigator:

1. Ensuring that all AEs related to the intervention are recorded and reported to the sponsor in line with the requirements of the protocol.
2. Ensuring that all SAEs related to the intervention are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.
3. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
4. Central data collection and verification of AEs and SAEs according to the trial protocol onto a database.
5. Reporting safety information to the Sponsor for the ongoing assessment of the risk/benefit.
6. Adhering to all aspects of the study protocol in accordance with GCP guidance.

Study Doctor:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk/benefit.
2. Using medical judgement in assigning the SAEs seriousness, causality and whether the event was anticipated (in line with data from previous studies) where it has not been possible to obtain local medical assessment.
3. Review of specific SAEs in accordance with the trial risk assessment and protocol.

4. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs.
5. Adhering to all aspects of the study protocol in accordance with GCP guidance.

Co-Investigators:

1. Adhering to all aspects of the study protocol in accordance with GCP guidance.

13. Data management

Where possible, all participant data will be coded using unique reference numbers (pseudo-anonymised). All hard copy data will be stored securely in the site file located in a locked office. The location of the site file will be specified to the Sponsor and regulatory bodies. The site file will be accessible to authorised individuals upon request. Scanned copies of hard copy data will be saved as encrypted PDFs and stored in the university SHU Research Store. Qualitative data will be recorded on encrypted Dictaphones and downloaded in either MP3. or WAV format as soon as possible after data collection. Audio recordings of interviews will be destroyed after they have been transcribed. Digital data will be transferred between devices using https://zendto.shu.ac.uk, which is an encrypted platform that enables users to upload and download data. If the internet is inaccessible, an encrypted external hard drive will be used to transfer data instead. Data will be transferred as soon as possible form the external hard drive to the relevant device and will be deleted from the hard drive after being transferred. Relevant data will be input into encrypted Microsoft Excel spreadsheets and saved in XLS format. Data will be analysed in SPSS version 24.0 according to established statistical principles. All data will be saved on the SHU Research Store with a file name corresponding to the study title e.g. 'Q:\RESEARCH\ATAS'. With the exception of participant personal data, data relating to the trial will be archived for 10 years in line with the Sponsor's requirements. Participant personal data (e.g. phone number, email address and home address) will be archived for 2 years after the end of the study so that participants can be contacted regarding research dissemination. An anonymised description the available data (metadata), including a list of key variables will be placed on University open-access repository (SHURDA).

The data collected from this project will be suitable for sharing on request because of the broad academic interest in stroke rehabilitation. Other researchers should have the

opportunity to explore this dataset to develop the field of research without having to repeat the same investigations, and expose patients to unnecessary risk. Original data will be provided on application rather than be offered open access. This is because it may not be possible to ensure that data is completely anonymised. We can only guarantee that data will be pseudo-anonymised. All external users of our data will be bound by a data sharing agreement between the research team and SHU, and the user themselves. Data will be supplied on the condition that their research is non-profit, and that their findings will be published in an open access domain. Data users will not be permitted to share the data with anyone outside of their immediate research team.

SHU storage arrangements conform to GDPR and NHS standards. The Principal Investigator (Dr Simon Nichols) will be the custodian of the data and the data processor.

14. Ethical and regulatory considerations

14.1. Research Ethics Committee review and reports

Before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent forms and other relevant documents. Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial. All correspondence with the REC will be retained in the site file. An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. It is the Principal Investigator's responsibility to produce the annual reports as required. The Principal Investigator will notify the REC of the end of the trial if the trial is ended prematurely, including the reasons for the premature termination within one year after the end of the trial. The Principal Investigator will submit a final report with the results, including any publications/abstracts to the REC.

14.2. Patient and public involvement

In January 2020, two PPI events were held at Graves Health and Sports Centre in Sheffield to gather ideas from key stakeholders regarding the use of aerobic exercise training early after stroke. The events were advertised on Twitter and at local organisations including health, leisure and rehabilitation centres. Attendees included five people affected by stroke, two physiotherapists, one stroke physician, one speech and language therapist, one fitness

instructor, two senior research fellows and two PhD students. People affected by stroke and practitioners participated in separate events that contained identical content. Researchers played a passive role by facilitating discussions and scribing. Discussions were transcribed and common themes were identified. Protocol amendments were made based on these PPI events. In October 2020, we hosted an online PPI event which was attended by people affected by stroke. The purpose of this PPI event was to obtain feedback regarding the design of participant information resources. At the end of the study, participants will be invited to a workshop where the research findings will be presented in a lay format. Using consensus-based methods, we will collaborate with participants to design an infographic which depicts the key findings in a meaningful way.

14.2.1. Protocol amendments based on patient and public involvement

We initially proposed a fixed 30-minute bout of aerobic exercise per session. However, the PPI consensus was that this duration may be too long for some individuals due to severe fatigue and disability after stroke. We responded to this issue with two solutions: 1) by adopting an interval training design consisting of shorter moderate-intensity aerobic exercise bouts interspersed with rest intervals; and 2) by gradually increasing the total exercise duration per session over 5 days. It was also noted that NHS staff capacity is reduced at weekends, therefore the intervention should be delivered over 5 working days. A key point raised at the PPI events was that aphasia may be a barrier to participation due to issues with reading and speech comprehension. We will therefore use aphasia-friendly design and communication techniques wherever possible to increase the accessibility of our study information and intervention protocol. In addition, discussions from the PPI events inspired the idea of assessing exercise self-efficacy and optimism. A summary of the PPI events is attached to the IRAS form.

14.3. Financial and other competing interests

None disclosed.

14.4. Notification of serious breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to affect to a significant degree:

a) The safety or physical or mental integrity of the participants of the trial; or
b) The scientific value of the trial.

The Sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of:

a) The conditions and principles of GCP in connection with that trial; or
b) The protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

The Sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The Sponsor's standard operating procedure on 'serious breaches' will be followed.

14.5. Data protection and patient confidentiality

All data will be collected, stored, analysed and reported in accordance with General Data Protection Regulation guidelines. Where possible, identifiable information will be replaced with unique identification codes.

14.6. Access to the final dataset

A summary of the final dataset will be anonymised and made publicly available via an open access publication. The full dataset will be made available upon request and under the conditions of a shared data sharing agreement between the research team and SHU, and the individual requesting the data.

15. Dissemination

We will seek the support of stroke survivors to determine the most appropriate ways to translate and disseminate our findings to the general public.

Publication definition: "Any activity that discloses, outside of the circle of trial investigators, any final or interim data or results of the Trial, or any details of the Trial methodology that have not been made public by the Sponsor including, for example, presentations at symposia, national or regional professional meetings, publications in journals, theses or dissertations."

All scientific contributors to the Trial have a responsibility to ensure that results of scientific

interest arising from Trial are appropriately published and disseminated. The Sponsor has a firm commitment to publish the results of the Trial in a transparent and unbiased manner without consideration for commercial objectives. To maximise the impact and scientific validity of the Trial, data shall be consolidated over the duration of the trial, reviewed internally among all Investigators and not be submitted for publication prematurely.

15.1. Lay summaries

Plain English research summaries will be produced in collaboration with PPI attendees. These will be written clearly and simply, without jargon and with an explanation of any technical terms that have been used. The summaries will answer the following questions: Why did we do this study?; How did we do it?; What did we find?; What does this mean? Research summaries will be sent to all participants and PPI attendees that provided consent to do so. In addition, copies will be sent to charities (e.g. Stroke Association, SameYou, British Heart Foundation) with the intention of publicising research summaries on their websites and social media platforms. Infographics will also be produced to aid research dissemination on social media platforms.

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17. Appendix

Table 7. Standardised verbal communication during aerobic exercise

Scenario	Verbal communication
Cadence drops below 10% of initial self-selected cadence.	Can you go a little bit faster? Aim for around 'x' rpm. Let me know if it feels too hard and I will change the resistance.
Cadence exceeds 10% of initial self-selected cadence.	Can you slow it down a little bit? Aim for around 'x' rpm. Let me know if it feels too easy and I will change the resistance.
Inconsistent cadence.	Try and stick to around 'x' rpm.
RPE drops below 13 but at target cadence.	Maintain your speed at 'x' rpm, I'm going to increase the resistance a little bit.
RPE exceeds 13 but at target cadence.	Maintain your speed at 'x' rpm, I'm going to reduce the resistance a little bit.
Beginning of each 5-min work phase.	You have five minutes of work at this intensity.
Fourth minute of each 5-min work phase.	One minute left, you're doing really well.
End of 5-min work phase.	Well done, you now have one minute of rest. Relax, the bike will move your legs for you.
End of conditioning phase.	Great effort, you have done really well today.