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RICFAST 2: A study on treating post-stroke fatigue

Submission date	Recruitment status	[ ] Prospectively registered
16/04/2025	Recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
28/05/2025	Ongoing	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
28/05/2025	Other	[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Approximately half of stroke survivors experience post-stroke fatigue (PSF), which is a feeling of exhaustion and lack of energy that doesn't improve with rest. PSF is one of the most troublesome symptoms affecting recovery, social engagement, and quality of life. This study aims to explore if Remote Ischaemic Conditioning (RIC), a simple treatment using a blood pressure cuff, can help reduce PSF by improving energy production in muscle cells and blood flow to different organs.

Who can participate?
The study will recruit 60 people aged 18 years or older who have PSF.

What does the study involve?
Participants will be randomly assigned to one of four groups:
Group 1: RIC 3 times a week for 6 weeks at "Pressure 1"
Group 2: RIC 3 times a week for 6 weeks at "Pressure 2"
Group 3: Intense RIC 5 times a week for 6 weeks at "Pressure 2"
Group 4: Long RIC 3 times a week for 12 weeks at "Pressure 2"
Participants will undergo tests to measure fatigue, physical function, and cellular energetics at baseline, 6 weeks, 3 months, and 6 months.

What are the possible benefits and risks of participating?
Participants will be contributing positively to our knowledge on stroke, in particular our knowledge about post-stroke fatigue and the effects of RIC. This will hopefully lead to future treatments that can improve health and recovery after stroke. Further, if RIC is found to improve fatigue after stroke, then participants will hopefully have benefited from its effects through this trial.

We have tried to minimise any burden on the patient, making as many of the visits remote as possible, and where they have to be face to face providing expenses to cover travel. Further, we acknowledge that the outcome measures may be too burdensome for some participants to complete all in one session. As such we will include the option of spreading sessions out over extra visits and the option of completing some of the questionnaires remotely or in the

participants’ homes. No major risks are expected for this treatment; previous studies completed involving the treatment didn't report any. The expected adverse events are below:

Treatment: pain/discomfort from the pressure of the cuffs, headache, skin petechiae, paraesthesia of the arms, discolouration of the arms, numbness in the arms.

Substudy clinical visit: Bruising or pain from phlebotomy, discomfort from the CPET if they have difficulty with moving or breathing. Also potential injury during the MRI relating to pacemakers, medical implants or other metal objects, however safety screening procedures will be maintained.

Where is the study run from?
Sheffield Teaching Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
July 2024 to October 2027

Who is funding the study?
The Stroke Association (UK).

Who is the main contact?
Alessia Dunn, alessia.dunn@nhs.net

Contact information

Type(s)
Public, Scientific, Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
349042

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 65828, PG2S21\100019

Study information

Scientific Title
Remote Ischaemic Conditioning for Fatigue After Stroke – RICFAST 2. A multi-arm, randomised controlled feasibility study

Acronym
RICFAST 2

Study objectives
Approximately half of stroke survivors experience post-stroke fatigue (PSF): a feeling of exhaustion and lack of energy that does not improve with rest. They report PSF as one of their most troublesome symptoms affecting recovery, social engagement and quality of life.

Remote Ischaemic Conditioning (RIC), a simple, self-delivered treatment whereby a blood pressure cuff is used to stop the flow of blood to the arm for 5-minute intervals, may reduce inflammation, increase energy activity of cells, and improve blood flow to different organs. This may counteract the effects of PSF.

We will measure fatigue and its sub-types (physical, mental and psychosocial symptoms), physical function (exercise testing) and cellular energetics (muscle MRI scanning) at baseline, 6 weeks, 3 months and 6 months, to understand:
1. If a more intense or longer duration of RIC are feasible and if they appear to result in greater improvements in fatigue than regular RIC and control
2. If the benefits last beyond stopping treatment (6 months)
3. If we can characterise the type of fatigue people with PSF experience and if this influences their response to RIC
4. How RIC works
5. How physical activity is related to fatigue using smart wearable technology

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 13/01/2025, Yorkshire & The Humber - Sheffield Research Ethics Committee (NHS Blood and Transplant Blood Donor Centre,Holland Drive, Newcastle upon Tyne, NE2 4NQ, United Kingdom; +44 207 1048135; sheffield.rec@hra.nhs.uk), ref: 25/YH/0006

Study design
Interventional randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Home, Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet.

Health condition(s) or problem(s) studied
Post-stroke fatigue

Interventions
Sixty participants (15 per group) will be randomised in a 1:1:1:1 manner into one of four treatment groups:
Group 1: Participants will be asked to inflate the BP cuff around the arm to "Pressure 1", three times per week for six weeks. This group will successfully blind participants.
Group 2: Participants will be asked to perform the active RIC treatment three times a week for six weeks, inflating the cuff to "Pressure 2" for each treatment.
Group 3: Participants will be asked to perform the active RIC treatment ("Pressure 2") five times a week for six weeks.
Group 4: Participants will be asked to complete the active RIC ("Pressure 2") treatment three times a week for twelve weeks.

In the South Yorkshire region, most patients admitted with acute stroke come to either Sheffield Teaching Hospitals or Doncaster Royal Infirmary, and are then repatriated to Rotherham and Barnsley if they are from these areas. A central database will be used to search for patients who have experienced a stroke within the last three years and have consented to be contacted about future research. After eliminating any deceased patients and those who are severely frail, living in nursing homes, or with severe dementia, the locations of the patients will be mapped geographically. This will allow preferential invitation of individuals from areas with higher indices of deprivation and ethnic minority populations. These searches and invitation strategies will be undertaken in waves, with real-time review of recruited population characteristics to amend invitation targets in subsequent waves.

For this trial, potential participants identified through database searches will be sent an invitation letter and Participant Information Sheet (PIS), either via email or post, along with contact details to enable them to contact the trial team.

The trial population will consist of participants suffering from debilitating post-stroke fatigue (PSF) who are not participating in any other stroke rehabilitation trial. Interested individuals will contact the central research team and be invited to an initial screening visit.

At this initial visit, a consent form will be signed and the FFS-7 completed. If the patient scores equal to or greater than 4 (overall score), they will be eligible to participate in the study. The researcher will then collect baseline sociodemographic and clinical data and complete baseline assessments.

If the participant consents to participate in the mechanistic sub-study, they will require two further visits before starting the intervention (CPET and MRI scan). If they are not participating in the mechanistic sub-study, the researcher will set up the use of the Inspire3 Fitbit and the participant will be randomised to one of the four treatment allocations. The researchers will then demonstrate how to deliver the RIC treatment and how to use the symptom diary and treatment log.

Participants will then go home and start the self-delivered treatment. Weekly follow-up visits will be organised, which can be via telephone, video call, or face-to-face if required. These visits will ensure participants are using the intervention correctly, completing the symptom diaries and treatment logs, and help identify and resolve any issues.

All treatment groups will have follow-ups at 6 weeks, 3 months (12 weeks), and 6 months (26 weeks). At the baseline visit and follow-ups, the following tests will be carried out: FFS-7, MFIS, BI, mRS, SIS, EQ-5D, GAD-7, PHQ-9, and the 6-minute walk test. At the 6-week follow-up visit, participants will also be invited to take part in a short 20-minute interview about their experience using the RIC treatment. The 26-week follow-up is remote, and the 6-minute walk test is not carried out at this time.

The mechanistic sub-study will explore mechanisms by which RIC may act. This includes whether RIC results in increased levels of muscle adenosine triphosphate (ATP), the energy currency of the cell, and whether this leads to improvements in exercise measures. It will also assess whether RIC alters levels of inflammatory markers. Thirty participants (10 from Groups A, B, and C) will be invited to undertake a mechanistic evaluation, including inflammatory marker analysis, CPET, and MRI 31-Phosphorous Spectroscopy. These tests will be carried out at baseline and again at the 6-week follow-up.

Following completion of the 6-month (26-week) follow-up, participants will be asked which group they thought they were in. After this, their involvement in the study will be complete.

Intervention Type
Behavioural

Primary outcome measure
1. Feasibility of the intervention will be measured via assessment of:
1.1. Safety, measured by evaluating whether there have been any SAEs related to RIC.
1.2b. Acceptability, measured using a Likert scale rating of RIC-related symptoms and qualitative semi-structured interviews at end of treatment.
1.3. Compliance, measured by evaluating whether >80% intended treatment sessions have been completed.
2. Feasibility of the trial will be measured using the assessment of recruitment rates (at least 1.5 participants/month).

Secondary outcome measures
1. Fatigue is measured using the fatigue severity scale 7 (FSS-7) questionnaire at baseline, end of treatment, and 6 months post-treatment.
2. Fatigue is also measured and fatigue symptom profiles are characterised using the modified fatigue impact scale (MFIS) questionnaire at baseline, end of treatment, and 6 months post-treatment.
3. Degree of disability and dependence are measured by the modified Rankin scale (mRS) questionnaire at baseline, end of treatment, and 6 months post-treatment.

4. General function and capacity are measured by the Barthel Index (BI) questionnaire at baseline, end of treatment, and 6 months post-treatment.
5. Anxiety severity is measured by the generalised anxiety disorder 7 (GAD-7) questionnaire at baseline, end of treatment, and 6 months post-treatment.
6. General quality of mental health is measured by the patient health questionnaire 9 (PHQ-9) at baseline, end of treatment, and 6 months post-treatment.
7. General quality of life is measured by the EuroQol 5-dimensional (EQ-5D) questionnaire at baseline, end of treatment, and 6 months post-treatment.
8. Stroke-related quality of life is measured by the stroke impact scale (SIS) questionnaire at baseline, end of treatment, and 6 months post-treatment.
9. Fatigue and physical stamina are measured by the 6 minute walk test (6MWT) at baseline and end of treatment.
10. General physical activity measures such as daily step count, sedentary time, distance moved, exercise time, estimated sleep per night are measured by the Google Inspire3 Fitbit provided to the participant throughout the duration of their involvement in the study (baseline to 6 months post-treatment).

Mechanistic sub-study secondary outcome measures:
11. Serum inflammatory markers (IL-1beta, IL-6, IL-10, TNFa, heat shock protein, GLP-1) are measured and analysed via exploratory mediation analysis performed on blood taken from participants at baseline and end of treatment.
12. VO2 peak, VAT and VE/VCO2 are measured via cardiopulmonary exercise testing (CPET) at baseline and end of treatment.
13. Tissue metabolism and mitochondrial function of the bilateral tibialis anterior muscles are indirectly measured by Phosphorus-31 magnetic resonance imaging, occurring at baseline and end of treatment.

Overall study start date
01/07/2024

Completion date
31/10/2027

Eligibility

Key inclusion criteria
1. Adults (>=18 years) with ischaemic or haemorrhagic stroke, at least 12 weeks prior
2. Symptoms of debilitating fatigue for at least 6 weeks (mean FSS > = 4)
3. Capacity to give consent
4. Able to complete study procedures

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex

Both

Target number of participants
Planned Sample Size: 60; UK Sample Size: 60

Key exclusion criteria
1. Participation in another intervention trial
2. Significant peripheral vascular disease, neuropathy, ulceration or lymphadenopathy in the upper limbs
3. Hospitalisation for cardiovascular or cerebrovascular disease within the last 4 weeks (this may act as an ischaemic conditioning stimulus)
4. Known causes of fatigue e.g. obstructive sleep apnoea, depression, active thyroid disease, active cancer, MS, MND and PD
5. Severe aphasia or cognitive impairment that would preclude their understanding of learning to self-deliver the RIC intervention or complete the required outcome measures (e.g. MRI, exercise tests, questionnaires). We will use the Consent Support Tool (CST) to aid this judgement.
6. Pregnant or trying to get pregnant
7. Prior use of RIC

For all participants entering the mechanistic sub-study only:
1. Contraindications to Magnetic Resonance Imaging (MRI) (e.g., metal implant)
2. Has previously experienced or is likely to suffer severe anxiety or claustrophobia in relation to MR imaging examination

Date of first enrolment
15/04/2025

Date of final enrolment
23/05/2027

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Sheffield Teaching Hospitals NHS Foundation Trust
Northern General Hospital
Herries Road
Sheffield
United Kingdom
S5 7AU

Study participating centre

Doncaster and Bassetlaw Teaching Hospitals NHS Foundation Trust
Doncaster Royal Infirmary
Armthorpe Road
Doncaster
United Kingdom
DN2 5LT

Study participating centre
The Rotherham NHS Foundation Trust
Moorgate Road
Rotherham
United Kingdom
S60 2UD

Study participating centre
Barnsley Hospital NHS Foundation Trust
Gawber Road
Barnsley
United Kingdom
S75 2EP

Sponsor information

Organisation
Sheffield Teaching Hospitals NHS Foundation Trust

Sponsor details
Northern General Hospital, Herries Road
Sheffield
England
United Kingdom
S5 7AU
+44 1142265941
dipak.patel12@nhs.net

Sponsor type
Hospital/treatment centre

Website
http://www.sth.nhs.uk/

ROR
https://ror.org/018hjpz25

Funder(s)

Funder type
Charity

Funder Name
Stroke Association

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Associations and societies (private and public)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a peer-reviewed journal

Intention to publish date

Individual participant data (IPD) sharing plan
Unable as of yet to provide link to repository or details of the data available, but can confirm that electronic data will be stored for 5 years within the STH archiving facility on a secure computer network, accessible to the study team and the trust-approved research and governance auditors initially and then solely the study team after archiving. Consent from participants has been obtained and data is pseudo-anonymised with study IDs for each participant, with an enrolment log linking IDs to participants stored separately on an encrypted device only accessible by select members of the research team.

IPD sharing plan summary
Stored in non-publicly available repository