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Understanding cognitive decline after stroke and the impact of COVID-19

Submission date
21/06/2019

Recruitment status
No longer recruiting

Registration date
29/07/2019

Overall study status
Completed

Last Edited
27/09/2024

Condition category
Circulatory System

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
People affected by stroke report that memory and thinking problems are amongst their greatest concerns. Stroke and vascular dementia are closely related but traditionally have been studied as separate processes and this has delayed advances in knowledge and treatment. A more 'joined-up' study would help. Stroke patients are good at joining studies, and some blood vessel related treatments might help protect thinking and memory in future. A collaboration of experts in stroke and vascular dementia have worked with people affected by both diseases to create a program of work that answers fundamental questions: who will develop memory and thinking problems after stroke, why does this happen, how can we treat it?
Added 17/06/2020: People with stroke may also be more vulnerable to coronavirus and may have more severe symptoms such as phenomena if they become infected. This study will also look at who will develop coronavirus, why they develop it and what symptoms do they have?

Who can participate?
Patients aged 18 and over who attend hospital with a stroke of any type or ministroke

What does the study involve?
The researchers collect information about the person, their health, the stroke, assess their thinking and memory, and talk to their relatives. They use short or longer assessments at different stages after the stroke to avoid tiring the patient. Recovery, changing symptoms and thinking skills are assessed at about 6+/- 2 weeks after the first assessment and by post /telephone annually to 2 years and beyond. The researchers assess routinely collected brain scans and other routine tests, and where possible, do more blood tests or genetic analysis to work out what affects memory and thinking.
Added 17/06/2020: There is also an option to have an additional brain scan at 6 weeks.

What are the possible benefits and risks of participating?
The study will provide much better information on how many patients thinking and memory are affected, how to identify them, their outlook for recovery. This will help to understand vessel mechanisms better, advise patients, and plan health services. Participants will be offered opportunities to join clinical trials as new treatments become ready for testing, to help avoid dementia in the future. The participants will get more detailed assessments of memory, thinking

and mood than would happen in standard care. The results of these assessments and any other medically relevant results can also be shared with the hospital team or the participants' GP, which may be useful to their care. Possible disadvantages of taking part include that some people may find these extra questions tiring and they will take up the participants' time.

Where is the study run from?
1. Centre for Clinical Brain Sciences (UK)
2. NHS Greater Glasgow and Clyde (UK)
3. Nottingham University Hospitals NHS Trust (UK)
4. Salford Royal NHS Trust (UK)
5. University College London Hospitals NHS Trust (UK)
6. Cambridge University Hospitals NHS Trust (UK)
7. University Hospitals Leicester NHS Trust (UK)
8. Lancashire Teaching Hospital NHS Trust (UK)
9. Kings College Hospital NHS Trust (UK)
10. Oxford University Hospitals NHS Trust (UK)

When is the study starting and how long is it expected to run for?
July 2018 to September 2024

Who is funding the study?
Stroke Association (UK)

Who is the main contact?
Prof. Joanna Wardlaw
joanna.wardlaw@ed.ac.uk

Study website
https://stroke.nottingham.ac.uk/r4vad/live/r4vad_login.php

Contact information

Type(s)
Scientific

Contact name
Prof Joanna Wardlaw

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
244590; 239109

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
AC18001

Study information

Scientific Title
Rates, Risks and Routes to Reduce Vascular Dementia

Acronym
R4VaD

Study objectives
Current study hypothesis as of 17/06/2020:
Overall study:
To determine the rates of cognitive impairment and dementia to at least two years after stroke, across a wide range of patients, stroke severities and subtypes, stratified by patient-related (age, premorbid and prestroke cognition, socioeconomic status, vascular risk factors, lifestyle) and stroke-related (severity, ischaemic, haemorrhagic, lacunar vs non-lacunar, imaging findings) factors.

MRI DTI substudy:
To test the prognostic value of clinically accessible MRI brain imaging features in addition to conventional features on long term cognitive impairment after stroke.

COVID-19 substudy:
To determine the prevalence of COVID-19 infection in patients with acute stroke who are participating in R4VaD and compare the clinical and laboratory features, outcomes, stroke mechanisms and phenotypes of patients with and without COVID-19 infection and between mild and severe COVID-19 infection. This substudy will also examine the neuropsychological impact of the COVID-19 outbreak on patients with stroke.

Previous study hypothesis:
To determine the rates of cognitive impairment and dementia to at least two years after stroke, across a wide range of patients, stroke severities and subtypes, stratified by patient-related (age, premorbid and prestroke cognition, socioeconomic status, vascular risk factors, lifestyle) and stroke-related (severity, ischaemic, haemorrhagic, lacunar vs non-lacunar, imaging findings) factors.

Ethics approval required

Old ethics approval format

Ethics approval(s)
1. Approved 09/07/2018, Scotland A Research Ethics Committee (2nd Floor, Waverley Gate, Edinburgh, EH1 3EG, United Kingdom; 01314655680; manx.neil@nhslothian.scot.nhs.uk), ref: 18/SS/0055
2. Approved 26/07/2018, North East - Newcastle and North Tyneside 1 Research Ethics Committee (HRA Newcastle, Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, United Kingdom; 02071048084; nrescommittee.northeast-newcastleandnorthtyneside1@nhs.net), ref: 18/NE/0150

Study design
Prospective multicentre observational longitudinal study

Primary study design
Observational

Secondary study design
Longitudinal study

Study setting(s)
Hospital

Study type(s)
Other

Participant information sheet
Not available in web format

Health condition(s) or problem(s) studied
Stroke

Interventions
Current interventions as of 17/06/2020:
Baseline assessment will record demographic, clinical, family history, education, socioeconomic, lifestyle and prestroke functioning (mRS), including non-testability in patients without capacity. Lab data (including BP, carotid Doppler, ECG, echocardiography where performed) will also be collected. Initial direct-to-patient cognitive assessment will use brief cognitive screening tools including delirium, fatigue, mood, apathy, and frailty. Informants will be asked about prestroke cognition. Routine bran imaging (CT or MRI) will be collected to classify the index stroke and pre stroke findings with standard tools. Bloods will be taken for analysis of genetics.

Early follow up will be at 4-8 weeks post baseline assessment. Here the researchers will also assess cognition, fatigue, mood, apathy and health-related quality of life. Bloods will be taken for analysis of inflammatory markers and stored for future analysis. The researchers will also record if the patient has died or changed their place of residence.

Annual follow-up will be conducted for a minimum of 2 years, maximum of four years by post or phone, using validated functional (mRS), recurrent vascular events, cognition, mood, apathy, fatigue, health-related quality of life assessments as above, from both participant and informant.

The MRI DTI substudy will be conducted in a subsample of R4VaD at selected centres. Multimodal MRI scanning including DTI and additional blood pressure readings will be conducted once at either baseline assessment or early follow up and again at 1 year. An estimate of peak adult cognitive ability will be recorded at the first assessment.

The COVID-19 substudy will evaluate the impact of the COVID-19 pandemic on patients presenting with stroke. Information on COVID-19 status, treatment, additional risk factors and relevant laboratory and or radiological investigations such as chest CT will be collected for all patients at baseline and 1 year follow up.

Previous interventions:
Baseline assessment will record demographic, clinical, family history, education, socioeconomic, lifestyle and prestroke functioning (mRS), including non-testability in patients without capacity. Lab data (including BP, carotid Doppler, ECG, echocardiography where performed) will also be collected. Initial direct-to-patient cognitive assessment will use brief cognitive screening tools including delirium, fatigue, mood, apathy, and frailty. Informants will be asked about prestroke cognition. Routine bran imaging (CT or MRI) will be collected to classify the index stroke and pre stroke findings with standard tools. Bloods will be taken for analysis of genetics.

Early follow up will be at 4-8 weeks post baseline assessment. Here the researchers will also assess cognition, fatigue, mood, apathy and health-related quality of life. Bloods will be taken for analysis of inflammatory markers and stored for future analysis. The researchers will also record if the patient has died or changed their place of residence.

Annual follow-up will be conducted for a minimum of 2 years, maximum of four years by post or phone, using validated functional (mRS), recurrent vascular events, cognition, mood, apathy, fatigue, health-related quality of life assessments as above, from both participant and informant.

Intervention Type
Other

Primary outcome measure
Rates of cognitive impairment and dementia up to at least two years after stroke, measured using a seven-level ordered categorical scale compromising cognition (normal, impairment in one domain, impairment in two or more domains), dementia (mild, moderate, severe) and death. The outcome scale is driven by information from the Montreal Cognitive Assessment (MoCA), the Modified Telephone Interview for Cognitive Status (TICS-m), Modified Rankin Scale (MRS), Barthel Index, IQCODE, disposition (need for nursing care), and evidence of dementia (formal diagnosis, taking a cholinesterase inhibitor or memantine) or death. These outcomes are measured at baseline, 4-8 weeks, and annually for a minimum of 4 years.

Secondary outcome measures
Current secondary outcome measures as of 17/06/2020:
Measured in all patients at baseline, 4-8 weeks and annually for a minimum of 2 years, maximum of 4 years:
1. Cognition is measured using; presence of memory of thinking problems: single question yes /no, Verbal Fluency phonemic (letter F, A, S, Montreal Cognition Assessment (MoCA), Trail Making A & B, Telephone Interview of Cognition Scale- modified (TICS-m), Letter digit coding, Consortium to Establish a Registry for Alzheimer's Disease (CERAD), Boston naming test (BNT) and a clinical diagnosis of dementia (e.g. from a memory clinic)
2. Mood is measured using; Patient health questionnaire (PHQ-9 and PHQ-SADS); Generalised

Anxiety Disorder (GAD), Zung depression scale (ZDS), Office National Statistics-4 (ONS-4) and a clinical diagnosis of depression

Measured as part of DTI substudy at baseline, 4-8 weeks and 1 year:
3. Features of small vessel disease on MRI are measured using; mean diffusivity (MD) peak height; peak width of skeletonized mean diffusivity (PSMD), MD in normal appearing white matter, index stroke size, location, subtype; WMH volume, score; SVD score; brain volume loss and other metrics including composite measures of brain damage (e.g. brain age metric, brain health index)
and others that emerge during the study
4. Peak adult cognitive ability is measured using the National Adult Reading Test (NART)
5. Additional blood pressure measures

Measured as part of the COVID-19 substudy at baseline and 1 year:
1. Details of COVID-19 infection are measured using; clinical features of suspected COVID-19 infection; date of onset of symptoms; date and result of nasopharyngeal swap; antiviral treatment; NEWS score; level of respiratory support; relevant blood and imaging findings (e.g. chest CT)

Previous secondary outcome measures:
Measured at baseline, 4-8 weeks and annually for a minimum of 2 years, maximum of 4 years:
1. Cognition is measured using; presence of memory of thinking problems: single question yes /no, Verbal Fluency phonemic (letter F, A, S, Montreal Cognition Assessment (MoCA), Trail Making A & B, Telephone Interview of Cognition Scale- modified (TICS-m), Letter digit coding, Consortium to Establish a Registry for Alzheimer's Disease (CERAD), Boston naming test (BNT) and a clinical diagnosis of dementia (e.g. from a memory clinic)
2. Mood is measured using; Patient health questionnaire (PHQ-9 and PHQ-SADS); Generalised Anxiety Disorder (GAD), Zung depression scale (ZDS), Office National Statistics-4 (ONS-4) and a clinical diagnosis of depression

Overall study start date
01/07/2018

Completion date
01/09/2024

Eligibility

Key inclusion criteria
Current inclusion criteria as of 17/06/2020:
1. Patients aged 18 years and over
2. No upper age limit
3. No severity limit
4. Ischaemic or spontaneous haemorrhagic (non-traumatic, non-subarachnoid haemorrhage, non-AVM) stroke and transient ischaemic attack (TIA)
5. Expected to survive at least 12 weeks

DTI substudy only
1. Estimated life expectancy >= 1 year
2. No contraindications to MRI
3. Patients with capacity to consent at baseline

COVID-19 substudy: expected to survive 12 weeks is not an inclusion criterion.

Previous inclusion criteria:
1. Patients aged 18 years and over
2. No upper age limit
3. No severity limit
4. Ischaemic or spontaneous haemorrhagic (non-traumatic, non-subarachnoid haemorrhage, non-AVM) stroke and transient ischaemic attack (TIA)
5. Expected to survive at least 12 weeks

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
2,000

Total final enrolment
2441

Key exclusion criteria
1. Inclusion criteria not met
2. Aneurysmal, traumatic or AVM-associated haemorrhage or subarachnoid haemorrhage
3. Stroke mimics such as brain tumours
4. Prior diagnosis of cognitive impairment or dementia is NOT an exclusion criteria

Date of first enrolment
25/09/2018

Date of final enrolment
01/10/2022

Locations

Countries of recruitment
England

Scotland

United Kingdom

Study participating centre
Centre for Clinical Brain Sciences
Chancellor's Building
Little France Crescent
Edinburgh
United Kingdom
EH16 4SB

Study participating centre
NHS Greater Glasgow and Clyde
Glasgow Royal Infirmary
84 Castle Street
Glasgow
United Kingdom
G4 0SF

Study participating centre
Nottingham University Hospitals NHS Trust
Nottingham City Hospital
Hucknall Road
Nottingham
United Kingdom
NG5 1PB

Study participating centre
Salford Royal NHS Trust
Salford Royal Hospital
Stott Lane
Salford
United Kingdom
M6 8HD

Study participating centre
University College London Hospitals NHS Trust
University College Hospital
235 Euston Road
Fitzrovia
London
United Kingdom
NW1 2BU

Study participating centre
Cambridge University Hospitals NHS Trust
Cambridge Biomedical Campus
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
University Hospitals Leicester NHS Trust
Leicester Royal Infirmary
Infirmary Square
Leicester
United Kingdom
LE1 5WW

Study participating centre
Lancashire Teaching Hospital NHS Trust
Royal Preston Hospital
Sharoe Green Lane
Fulwood
Preston
United Kingdom
PR2 9HT

Study participating centre
Kings College Hospital NHS Trust
Kings College Hospital
Denmark Hill
Brixton
London
United Kingdom
SE5 9RS

Study participating centre
Oxford University Hospitals NHS Trust
Horton General Hospital
Oxford Road
Oxford
United Kingdom
OX16 9AL

Sponsor information

Organisation
Academic and Clinical Central Office for Research and Development (ACCORD)

Sponsor details
University of Edinburgh & NHS Lothian
ACCORD
The Queen's Medical Research Institute
47 Little France Crescent
Edinburgh
Scotland
United Kingdom
EH16 4TJ
+44 (0)131 242 3326
resgov@accord.scot

Sponsor type
Hospital/treatment centre

Website
www.accord.ed.ac.uk

ROR
https://ror.org/01x6s1m65

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

Funder Name
Alzheimer's Society

Alternative Name(s)
alzheimerssoc

Funding Body Type
Private sector organisation

Funding Body Subtype
Associations and societies (private and public)

Location
United Kingdom

Funder Name
British Heart Foundation

Alternative Name(s)
the_bhf, The British Heart Foundation, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Prior to the presentation of the primary results, the statistical analysis plan will be published. Protocol paper is in preparation. Study materials can be accessed via the website or on contacting Dr Rosalind Brown (Rosalind.Brown@ed.ac.uk). Planned publication of the results in peer-reviewed journals and presentations at national and international conferences.

Intention to publish date
31/05/2025

Individual participant data (IPD) sharing plan
The anonymised study data will be made available for use by external investigators in appropriate analyses upon request via a publicly accessible portal (e.g. University of Edinburgh datashare https://datashare.is.ed.ac.uk/). Data from R4VaD will also be shared with individual

patient data pooling projects involving stroke and dementia (e.g. Virtual International Stroke Trials archive-Cognition, VISTA-COG; Virtual International Cardiovascular and Cognitive Trials Archive, VICCTA, http://www.virtualtrialsarchives.org; and STROKOG https://cheba.unsw.edu.au/consortia/strokog; Dementia Platform UK Portal https://portal.dementiaplatform.uk). Similarly, anonymised baseline and on-treatment neuroimaging data will be published. The mechanisms and processes for managing external access will be determined during the course of the study.

IPD sharing plan summary

Stored in publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
HRA research summary			28/06/2023	No	No
Preprint results		01/05/2024	21/06/2024	No	No