Non-CTIMP Study Protocol

Rates, Risks and Routes to Reduce Vascular Dementia (R4VaD)

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CONTENTS

LIST OF ABBREVIATIONS

4AT	4 A's test
ACCORD	Academic and Clinical Central Office for Research & Development
AD	Alzheimer's disease
ADAS_Cog	Alzheimer's disease assessment scale cog
ADL	Activities of daily living
AE	Adverse Event
APPLE	Assessing post-stroke psychology a longitudinal evaluation
AVM	Arteriovenous malformation
BFI	Brief fatigue inventory
BI	Bathel index
BMET	Brief memory and executive test
BP	Blood Pressure
CI	Chief Investigator
CRF	Case Report Form
CROMIS-2	Clinical relevance of microbleeds in stroke 2
CT	Computed Tomography
DPUK	Dementia Platform UK
DTI	Diffusion tensor imaging
ECG	electrocardiogram
eCRF	Electronic Case Report Form
ESO	European Stroke Organisation
FLAIR	Fluid Attenuated Inversion Recovery
FOCUS	Fluoxetine or Control under Supervision
GAD	Generalised anxiety disorder
GCP	Good Clinical Practice
GWAS	Genome Wide Association Studies
ICA	Internal Carotid Artery
ICF	Informed Consent Form
ICH	Intracerebral haemorrhage
IL-β	Interleukin 1 beta
IPD	Individual patient data
IQCODE	Informant questionnaire on cognitive decline in the elderly
ISF	Investigator Site File
JPND	Joint programme neurodegenerative disease research
LACI-2	Lacunar intervention trial 2
MCI	Mild cognitive impairment
MI	Myocardial Infarction

MMSE	Mini mental state examination
MOCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
MSS2	Mild stroke study 2
NHS	National health service
NIHSS	National Institute for Health Stroke Scale
NPI-Q	Neuropsychiatric inventory questionnaire
O_2	Oxygen
OA-Cog	Optimising analysis of trials of cognition
PHQ	Patient health questionnaire
PI	Principal Investigator
PIS	Participant Information Sheet
PROHIBIT-ICH	Prevention of hypertensive injury to the brain – intracerebral haemorrhage
PSCI	Post-stroke cognitive impairment
PVS	Perivascular Spaces
QoL	Quality of life
RCTs	Randomised clinical trials
REC	Research Ethics Committee
SAE	Serious Adverse Event
SCANS	St George's cognition and neuroimaging in stroke
SIGNAL	A trial in patients with microbleeds and haemorrhage
SIS	Stroke impact scale
SPS3	Secondary Prevention of Subcortical Strokes Trial
SSCAS	Scottish Stroke Care Audit System
SSNAP	Sentinel Stroke National Audit Programme
STRATEGIC	A study about cognitive decline in vascular disease
SVD	Small Vessel Disease
TARDIS	Triple antiplatelets for reducing dependency after ischaemic stroke
TIA	Transient Ischaemic Attack
TICS	Telephone Interview for Cognitive Status
TNF-α	Tumor necrosis factor alpha
UK	United Kingdom
VAD	Vascular dementia
VCI	Vascular Cognitive Impairment
VCI-ICH	Vascular Cognitive Impairment-International Conference on Harmonisation
VISTA-COG	Virtual international stroke trials archive-cognition
WMH	White Matter Hyperintensities

SUMMARY

Stroke commonly affects cognition and, by definition, vascular dementia is driven by stroke disease in some way. However, fundamental knowledge about risk factors is widely acknowledged to be missing, restricting mechanistic understanding, prevention, treatment, and design of patient services.

We aim to recruit a wide range of patients with stroke, presenting to geographically diverse UK hospitals, into a longitudinal study to determine rates of, and risk factors for, cognitive and related impairments after stroke, to assess mechanisms and improve prediction models.

We will recruit about 2000 patients within six weeks of stroke, collect patient, stroke, socioeconomic, lifestyle, cognitive (plus fatigue, mood) and informant data using streamlined methods appropriate to the stroke stage. We will obtain more detailed assessments at 6+/- 2weeks post baseline assessment and follow-up by phone and post yearly to at least 2 years. We will assess diagnostic neuroimaging in all, and high-sensitivity inflammatory blood markers and genetic analysis in the majority; separate protocols will address neuroimaging and vascular function mechanism substudies.

Outputs will include reliable data on cognition long-term after stroke, stratified by prior cognition, stroke and patient-related variables, improved risk prediction and understanding the influence of neuroimaging, vascular, inflammatory and genetic markers. Participants will be in follow-up and consented for re-contact, facilitating future clinical trials.

Lay Summary

Background: 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.

Aims: Our 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?

Methods: We will invite many patients (about 2000) who attend hospital with a stroke of any type, or ministroke, to join the study. We will collect information about the person, their health, the stroke, assess their thinking and memory, and talk to their relatives. We will use short or longer assessments at different stages after the stroke to avoid tiring the patient. We will find out about recovery, changing symptoms and thinking skills at about 6+/- 2weeks after baseline assessment and by post/telephone annually to 2 years and beyond. We will assess routinely collected brain scans and other routine tests, and in where possible, do more blood tests or genetic analysis to work out what affects memory and thinking.

Outcomes: We 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. Patients in the study will be offered opportunities to join clinical trials as new treatments become ready for testing, to help avoid dementia in future.

1 INTRODUCTION

1.1 BACKGROUND

Stroke and dementia share many risk factors (1,2) and each is a risk factor for the other (3,4). Patients with stroke or TIA are at increased risk of post-stroke cognitive impairment (PSCI) and vascular dementia (VaD)(3), but risk-prediction for the individual is difficult. Improved understanding of clinical, demographic, laboratory, neuroimaging and social predictors would improve risk stratification, identification of mechanisms and intervention targets(5). VaD, including vascular cognitive impairment (VCI) that falls short of dementia, can arise from apparently 'silent' vascular brain damage on scanning (multiple infarcts, small vessel disease (SVD), amyloid angiopathy, haemodynamic ischaemia), rare genetic variants, as well as after ischaemic or haemorrhagic stroke (PSCI)(6). Patients with VCI or VaD can present to GPs, stroke, memory, or mobility services, as acute emergencies with an unrelated comorbidity, or go unrecognised until late stage in the community.

We focus on cognition in patients with stroke for several reasons. Patients with stroke are at high risk of cognitive decline(3) presenting an 'enriched' sample with substantial progression to cognitive outcomes, similar to mild cognitive impairment (MCI) and Alzheimer's disease (AD). PSCI is a common, under- researched problem for patients, carers and health services (7). It reaches medical attention at a time-point defined by the stroke, capturing cognitive decline that was unmasked by the stroke, or that followed the stroke. The distinction between PSCI and VaD without stroke seems increasingly arbitrary(8) many strokes are 'silent' so that patients may not notice or may ignore(9) subtle vascular neurological or cognitive symptoms(10,11); vascular lesion patterns on imaging often overlap;(6) and the triad of stroke, cognitive impairment and gait problems are often present.

The strength of a PSCI cohort study is our established access to stroke patients providing prompt and substantial recruitment of very well phenotyped patients (including both cortical and subcortical VaD/VCI), in follow-up and consented for re-contact for future trials. This is particularly important given the recent difficulties recruiting patients with VCI into trials (http://www.isrctn.com/ISRCTN31208535). Our proposal combines the UK's considerable stroke research strengths, which have helped transform stroke care into co-ordinated prevention, treatment and recovery in the last 25 years, with the dementia research expertise of the Dementia Platform UK (DPUK)(12).

Fundamental gaps in knowledge on stroke, cognition and dementia have been highlighted by recent expert groups(5,12). Dementia varies from 7% (population studies, 1st stroke, no pre-stroke dementia) to 41% (hospital studies with recurrent stroke and pre-stroke dementia) at one year(3,13), but with confidence intervals spanning 2-3 fold differences in dementia that are largely unexplained. Prevalence of MCI (29-68%) and dementia (8-22%) after transient ischaemic attack (TIA) are similarly variable and based on few patients(14). The aetiology, risk factors and prognosis of PSCI(5) are poorly understood. They lack information on stroke subtype, e.g. lacunar stroke(13) or intracerebral haemorrhage (ICH)(15), progression of VCI to dementia(5), or PSCI rates beyond the first year after stroke (3,13). Few studies consider pre-morbid intelligence(16) or failing cognition pre-stroke(13), yet lower IQ in youth(16) and failing cognition(4,17) increase stroke risk. There are few data on the complex interplay between individual risk factors and PSCI or dementia, how risk factors affect dementia pathophysiology, or brain health and resilience(12), making it difficult to advise individuals, plan randomised clinical trials (RCTs) or develop clinical services(18). Generalisability of data is restricted by selection bias(19,20), suboptimal testing(21) and attrition(6,22).

Cognitive testing is recommended in UK stroke guidelines (23), but many tests are impractical for stroke or insensitive to VCI.(6,5). Lack of proven clinical utility may explain why many GPs do not do cognitive screens routinely. Use of different cognitive tests inflates variance in VCI/dementia rates, hampers between-study comparisons(24) and efforts to understand mechanisms, e.g: meta-analyses were uncertain if systemic/carotid arterial stiffness affected cognitive decline(25) as individual studies lacked vascular risk factor adjustment; similarly, systematic reviews(3) and routine health data(2) disagree on the importance of common risk factors. Cognitive testing alone does not capture the psychological sequelae of stroke: fatigue, apathy, mood (26) affect cognition; in turn, 3-month cognition scores correlate highly with dependency, mood, and quality of life (QoL)(27).

1.2 RATIONALE FOR STUDY

The proposed study is needed now, as other current work will not fill the gaps. The applicants are engaged in several relevant pooling initiatives of individual patient (IPD) or tabular data from RCTs or cohorts. These include:

Optimising Analysis of Trials of Cognition [OA-Cog, Bath; RCTs of vascular prevention, VaD, AD; 49 studies, n=115,312, but young mean age (67±9.5 yrs), 36% female, only MMSE/ADAS-Cog];

Virtual International Stroke Trials Archive-Cognition [VISTA-COG, Quinn; IPD of stroke RCTs and observational cohorts, >5,000 patients, with cognition/mood; but also young, male, memory focused];

DPUK [31 studies, median n=2700, range 80-1,300,000, of dementias, excludes stroke, VCI/VaD and lacks vascular risk factor data];

JPND METACOHORTS [Wardlaw(28) >90 studies, n=667,064, mean age 72 (15-106) yrs, on vascular disease, but gaps in prediction data];

Sentinel Stroke National Audit Programme [SSNAP, Rudd; logs cognitive testing activity not results(29); 31% of 79,720 eligible patients (2013-14) were not assessed];

studies collecting PSCI data: RCTs [TARDIS, Bath; PRESERVE, Markus; LACI-2, Wardlaw; PROHIBIT-ICH, Werring] and observational studies [APPLE, Quinn; OxVasc-Cognition; SCANS, Markus; MSS2, Wardlaw; CROMIS-2, SIGNAL, Werring; STRATEGIC, O'Sullivan], either focus on restricted stroke subtypes, have short follow-up, or research intense settings.

In summary, as noted at recent expert workshops(12), despite large amounts of data, prior studies, frustratingly, will not improve risk prediction modelling in the individual, inform service design, or clarify risk factor interactions on PSCI pathophysiology. They will not provide detailed patient-level stratification by risk of PSCI or mechanisms, tell us little about the optimal approach to, or clinical utility of, early cognitive screening, and thus are hampering advances in clinical practice.

2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

Determine rates of cognitive impairment and dementia up to at least two years after stroke;

2.1.2 Secondary Objectives

I. Identify key risk predictors and develop better risk prediction models for individual patients;

II. Perform studies to improve cognitive testing and mechanistic understanding of PSCI;

III. Establish a well phenotyped population, in follow-up, with consent for re-contact for future trials;

IV. Provide data to plan future RCTs and services for patients with PSCI.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

Cognitive decline or dementia up to at least two years post stroke assessed with an ordinal scale that includes death.

2.2.2 Secondary Endpoints

I. Death
II. Disability (mRS)
III. Function in activities of daily living (Barthel; SIS)
IV. Recurrent stroke or other vascular disease
V. Other neuropsychological consequences of stroke: Mood, Frailty, Apathy, Fatigue
VI. Quality of life assessment
VII. Vascular measures: Blood pressure from serial readings, carotid stenosis, vascular stiffness, cardiac dysfunction
VIII. Imaging findings (lesion location, size, background pre-stroke changes)
IX. Inflammation (blood markers)
X. Genetic markers

3 STUDY DESIGN

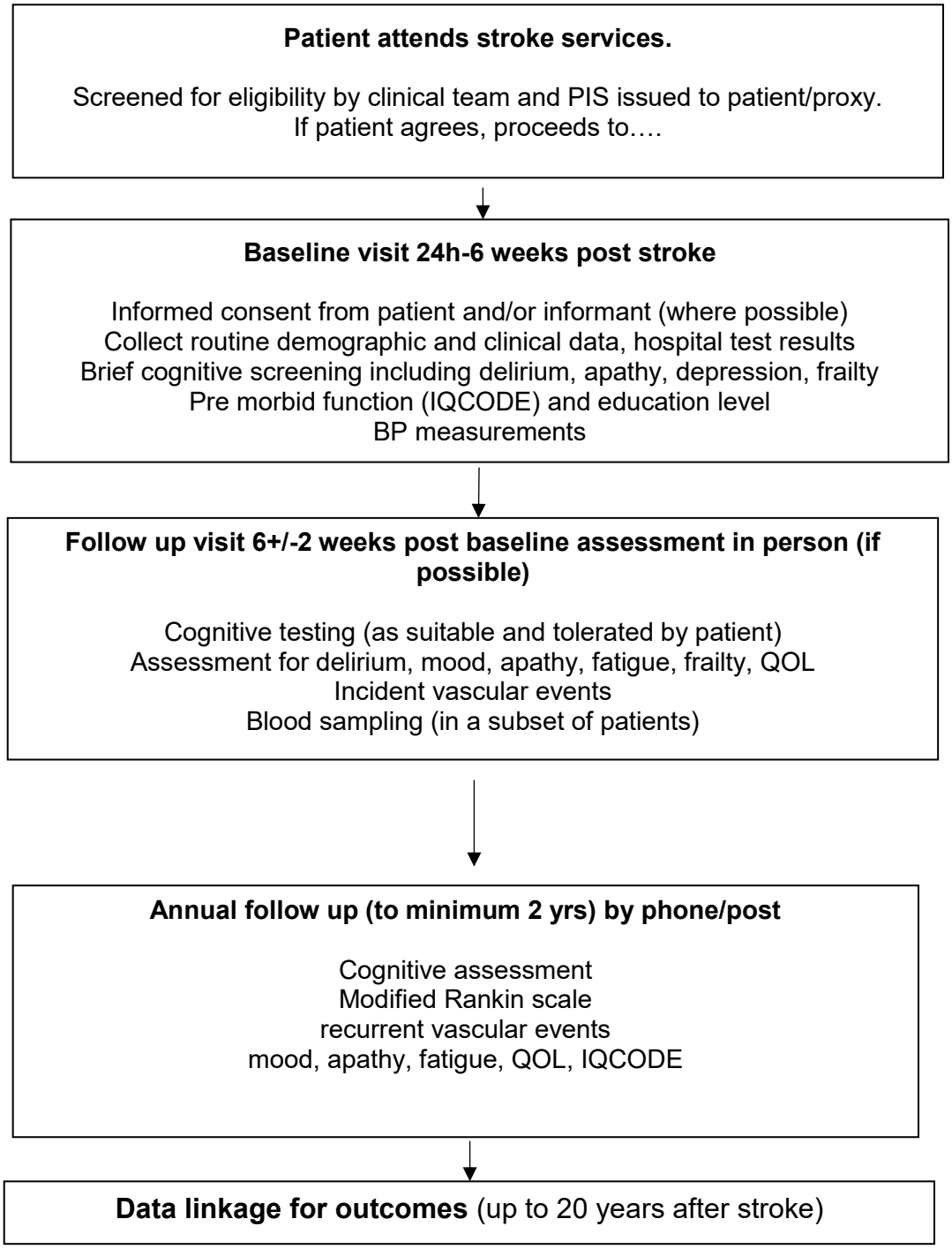
We propose a large, multicentre, longitudinal, inclusive study in patients presenting with stroke to UK Stroke Centres, using standardised proportionate ascertainment methods to assess cognition to at least two years after stroke. The strength of a post stroke cohort is our access to these patients through the CRN-Stroke infrastructure allowing prompt and substantial recruitment. We aim to capture the 'messy reality' of PSCI, determine its rates and progression by clinically-relevant strata(5,8): pre-morbid and pre-stroke cognition, medical, lifestyle and socioeconomic factors (Figure 1). A broad stroke cohort will capture all potential VaD phenotypes (SVD, multi-infarct, strategic infarct, mixed pathologies)(6), adding considerably and uniquely to knowledge on VaD. We propose to collect cognitive information across a continuum of stroke severities because data are limited and it is inappropriate to assume that cognition is not relevant after either severe or very mild stroke which have previously been under studied. Prospects for recovery, even after severe stroke, are changing radically with thrombolysis, thrombectomy, improved discharge support and community rehabilitation, but their impact on cognition is largely unknown: therapists say that potentially limiting cognitive deficits may be more apparent in patients who make a good physical recovery from initially severe stroke (Roffe, personal commun); equally, deficits in mild stroke may be missed(30). We acknowledge the mortality and attrition associated with including the spectrum of stroke severities(31), so propose multimodal patient focussed follow-up to minimise losses and analysis methods to account for competing risk biases associated with early mortality. The proposed study will embed important substudies at scale: imaging, vascular function, inflammation, genetics, and store blood samples for discovery work in 'omics. It will provide 'trial ready' patients, stratified, consented and in follow-up, aid trial design, create synergies and efficiencies between researchers from differing fields towards a common goal(12), and accelerate discovery of new interventions, like the 'trial-ready' cohorts and accessible data sources available for AD. The proposed study will inform service design (18) and assist those at risk of PSCI to plan their future(7).

Design: Prospective observational, longitudinal inception cohort with central follow-up and nested substudies in major UK stroke centres representing geographic and socioeconomic diversity. An electronic case record form (eCRF), as for RCTs (Bath), will streamline baseline and follow-up data collection and verification. Central follow-up by validated telephone and post methods will reduce local research burden, data loss and facilitate analyses. Data collected for SSNAP (Rudd, Tyrrell) will reduce duplication, patient and researcher burden, and determine the study's representativeness of UK hospital-assessed stroke patients (29), We will use safe havens to link our data to other health datasets providing an anonymised, ethics- and governance-approved secure database.

Recruitment: Patients with stroke presenting to participating Stroke Centres will be recruited. NIHR CRN- Stroke (lead Robinson) and DeNDRoN (lead O'Brien) research practitioners will aid recruitment and data collection (Figure 1, Flow Diagram).

Participants: All patients with ischaemic or haemorrhagic stroke or TIA who are expected to survive to at least 12 weeks after stroke. Due to the varying and evolving concepts and definitions of VaD, rather than restrict the cohort, we will include all and collect necessary investigations, cognitive, functional data to allow varying diagnostic criteria and stratification to be explored.

Figure 1 – flow chart of recruitment and study protocol



4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

At least 2000 from UK Stroke Centres.

4.2 INCLUSION CRITERIA

To avoid the selection biases of previous studies, and recognising changes in recovery with new treatments, we propose inclusive recruitment:

- patients aged ≥18,
- no upper age
- no severity limit,
- ischaemic, or spontaneous haemorrhagic (non-traumatic, non-subarachnoid haemorrhage, non-AVM) stroke and transient ischaemic attack (TIA; where feasible),
- expected to survive at least to 12 weeks.

4.3 EXCLUSION CRITERIA

Inclusion criteria are not met, in particular, at onset, the patient is not expected to survive more than 12 weeks.

Aneurysmal, traumatic or AVM-associated haemorrhage or subarachnoid haemorrhage.

Stroke mimics such as brain tumours.

Prior diagnosis of cognitive impairment or dementia is NOT an exclusion criterion.

4.4 CO-ENROLMENT

R4VaD is intended to facilitate recruitment to other observational and interventional studies.

Thus, co-enrolment in other observational studies in stroke is encouraged. Where the data collected in R4VaD are consistent in type and time with the co-enrolled study, use of already collected data will be encouraged in R4VaD, and vice versa, to reduce the burden of data collection on patients.

Co-enrolment is also permissible in RCTs of interventions, including CTIMPs, as long as the other study and R4VaD would not confound each other's results or make attribution of adverse reactions difficult in the CTIMP.

Local researchers should avoid overburdening patients.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Participants will be recruited from the stroke clinical service in the participating centres. At the initial hospital visit, potentially eligible patients will be approached by the usual clinical team including CRN research practitioners who are members of the clinical team, and then given a PIS. If patient/informant is agreeable then they will have the baseline assessment (as inpatient or outpatient, whichever is easier for the patient). At the baseline visit, the member of the study team will inform the patient of all aspects pertaining to participation in the study and go through the PIS again with the patient. It will be explained to the potential participant that entry into the study is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time. In the event of their withdrawal, it will be explained that their data collected so far should not be erased and we will seek consent to use the data in the final analyses where appropriate. The discussion of the study and

preferred method of contact will be recorded in the patients' notes. Patients will be given/have had as much time as they require (but at least 24 hours) to consider the study information before deciding whether to join the study or not.

5.2 CONSENTING PARTICIPANTS

Consent: will be modular and sensitive to different stages after stroke. It will include collection of:

- baseline core clinical and imaging data,
- information from carers/informants,
- follow-up to at least two years,
- taking/storing/analysing blood,
- permission for data linkage to primary care, SSNAP and other central hospital and deaths registry datasets for longer term outcomes (e.g. death, admission to care-home) for up to 20 years after the index stroke.

Participants (and informants where available)) will give informed written consent upon entry to the trial (baseline assessment), prior to any trial related procedures taking place. The decision to participate in clinical research is voluntary and should only be based on a clear understanding of what is involved. The lack of availability of an informant will not preclude participation in the study.

Consent will be sought for permission to approach the patient about possible participation in other relevant studies.

Consent will be sought for sharing of data with collaborators to analyse the study data and for future data linkage.

Consent will also be sought for further analyses of data in future studies and sharing of anonymised data, including stored blood derived samples or imaging data, for analyses in other relevant secondary analyses.

Consent will be sought for linkage of study data to individual participant's SSNAP data, Scottish Stroke Audit data, NHS Digital central hospital records including the Information Statistics Division in Scotland, GP data, and General Registry Office deaths data.

Consent will be obtained by Good Clinical Practice (GCP) trained staff who are members of the clinical research team after full discussion of the study procedures and requirements with the patient. The Investigator is responsible for ensuring that the ICF is completed, signed and dated by all parties prior to any protocol specific procedures being carried out. Participants must receive adequate oral and written information – appropriate PIS and ICF will be provided. The oral explanation to the participant should be performed by the Investigator or designated person, and must cover all elements specified in the PIS/ICF. The participant must be given every opportunity to clarify any points that they do not understand and, if necessary, ask for more information. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which he/she would be entitled.

The participant should be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor. The date that the patient is given the PIS should be documented in the patient's medical records.

The Investigator or delegated member of the study team and the participant should sign and date the ICF(s) to confirm that consent has been obtained. The participant should receive a copy of this document, and the original filed in the investigator site file (ISF). The patient should retain their copy of the PIS, and a copy of the completed ICF.

Consent, assent or opinion will be obtained from the appropriate person for each jurisdiction (Scotland, Northern Ireland, England, Wales) where a potential participant is unable to consent for themselves at the start of the study. Assessing tests that a patient is unable to complete is valuable, so we will record non-testability and inability to consent. It will also allow us to track

patients' recovery when initially unable to provide consent within the first few weeks post-stroke. This person may also act as the informant.

If the capacity of the participant previously unable to consent improves sufficiently during the course of the study, they will receive information about the study via a participant information sheet and be approached to give consent. Should a participant indicate in any way that they do not wish to be involved in the study, they will be withdrawn from the study.

We will continue to collect data from patients who lose capacity during the course of the study, and will seek consent for this. Should this happen, we will consult the appropriate consultee, relative, friend, welfare attorney, as defined by local guidelines, to inform them of their continuation in the study.

5.2 SCREENING FOR ELIGIBILITY

The treating physician and study team combined will screen for eligibility before taking informed consent.

5.3 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

Participants who have been approached for the study and subsequently found to be ineligible will be informed of the reasons why and receive routine medical care.

Screening logs will not be used as part of the data collection for this study. Case mix and assessment of representativeness of the recruited population will be assessed using data from the Sentinel Stroke National Audit Programme (SSNAP) which publishes anonymised site-specific data on all stroke admissions in England and Wales quarterly, and using data from the Scottish Stroke Central Audit System (SSCAS) which provides similar data on all stroke admissions in Scotland.

5.3.1 Withdrawal of Study Participants

Participants may withdraw consent at any point. We will retain the data collected up to the point of withdrawal for analysis. If the participant is willing, we will record the reason for withdrawal in the case record form.

6 STUDY ASSESSMENTS

6.1 STUDY ASSESSMENTS

Our approach to assessment recognises that different stages after stroke need specific approaches(5). We will assess:

i) pre-morbid cognitive ability,
ii) pre-stroke cognitive decline and
iii) post stroke cognitive status at specific points after stroke to map cognitive trajectories (Figure 1, flow chart).

Our choice of tests uses the following principles: a) avoid overburdening participants and carers, b) avoid duplication, c) each test is essential, d) consistent across stages, e) valid, with wide stroke usage (32,33,24) for external comparison (e.g. we already have data on TICS (cognition) & Zung (mood) for >7500 pts (27,34), and f) minimise known biases(22,20).

Our choice of tests is also guided by Cochrane Dementia and NIHR Complex Reviews Support Group, focus groups with study nurses and many service users. The latter commented particularly on timing and duration of cognitive assessments, care of patients with cognitive difficulties, importance of including all stroke severities, carer involvement and careful wording of study information to convey the work's importance but not exacerbate worry in those recently overwhelmed by acute stroke.

Our test paradigm, based on stakeholder feedback, majors on efficiency (minimising test time & duplication)(5), validity (systematic reviews of test properties(24,35); relevance to VCI (32) and feasibility (postal or telephone versions available (36), Table 1. Neuropsychological batteries may become overly burdensome(37), so we propose a stepped approach with core brief assessments for all participants, supplemented by more detailed tests as feasible(5). Where previous studies focussed on cognition, the neuropsychological effects of vascular disease include delirium, fatigue, apathy and mood disorder (26) which we will assess. Recognising substantial attrition in previous studies,(22) our follow-up will be flexible and include face-to-face (although this is ideal, it is unfeasible in all, or in a study of this size), telephone or postal follow-up. Combining phone and postal questionnaires allows a greater range of cognitive assessment than either alone (e.g. postal allows visuospatial tests) and improves rates of completion.

Activity / assessment	**Baseline assessment**	**Study visit 1**	**Annual follow up**	**End of study**
Eligibility Criteria	X			
Informed Consent	X			
Demographics	X			
Medical/Surgical History	X			
Vital Signs	X			
Premorbid function	X			
Collect routine tests*	X			
Vascular events		X	X	
Function	X	X	X	
Cognitive/mood testing	X	X	X	
Blood sampling		X		
Genetic sampling	X[A]			
Data linkage				X
End of study				X

*blood results, carotid or cardiac imaging results, routine diagnostic brain imaging results
[A] Genetic sampling may also be performed at study visit 1

Assessing tests that a patient is unable to complete is valuable, so we will record non-testability, employing “intention to diagnose” approaches to deal with partial or total test non-completion (20). Finally, informants know the patient well, can recognise change (35), and are invaluable if communication problems preclude even brief direct-to-patient assessments, so we have identified relevant validated informant versions. Engagement with relatives and partners will be sought to increase retention and data completeness, plus we will collect data on care-giver strain.

Baseline assessment will occur as soon as possible, but we allow between 24h to 6 weeks after stroke to enable patients to be included who were very ill in the first week but start to recover. We will record demographic, clinical, family history, education (for premorbid IQ16), socioeconomic, lifestyle, pre-stroke functioning (mRS) (including non-testability in patients without capacity (38) and lab data (including BP, carotid Doppler, ECG; echocardiography

where performed). Initial, direct-to- patient cognitive assessment (Table 1) will use brief cognitive screening tools(32,33), including for delirium(39), fatigue(40), mood(41), apathy (42) and frailty(43), prioritised and done as feasible, noting incomplete items (details Appendix 1)(20). Informants will be asked about pre-stroke cognition (IQCODE, (35)). BP will be assessed using standard protocols (44). Routine brain imaging (CT in many, MRI in some; see below) will be collected to classify the index stroke and pre-stroke findings with standard tools(45,46). Bloods will be taken for analysis of genetics.

Early follow-up will be at 6+/-2weeks post baseline assessment (i.e. 4-14 weeks after stroke depending on the timing of the baseline assessment) when participants are more likely to be able to complete multidomain cognitive tests(32), or shorter tests(30). We will also assess fatigue (BFI (40)), mood(33), apathy (21) and health-related quality of life (Table 1). BP will be assessed in all using standard protocols and validated, calibrated monitors to obtain three measures with at least one minute between them. Bloods will be taken for analysis of inflammatory markers (and genetics where not taken at the baseline assessment) and stored for future analysis. The assessment will coincide with local clinic review, those remaining in hospital being assessed in hospital. We will also record if the patient has died or their place of residence.

Contact by post or phone will also be offered.

Annual follow-up (to 2 years, minimum, maximum 4 years) will be by post and phone using validated functional (mRS)(38), recurrent vascular events, cognition(36), mood, apathy, fatigue and quality of life assessments as above, from both participant and informant (IQCODE), death or place of residence. We considered online/email follow-up but only 53% of 1-adult and 85% of 2-adult households aged>65 have internet (Office of National Statistics 2016). Most patients in FOCUS (fluoxetine for recovery after stroke) are not online and strongly preferred paper/post or phone (Dennis, personal commun); of Biobank's healthy subjects (C Sudlow, personal commun) only 40% use online follow-up and most preferred paper/post. Therefore online methods are for future consideration.

Consensus cognition diagnosis. Data from a subsample of those reaching 1 & 2 year follow-up will be assessed by an expert, multidisciplinary panel to assign a definitive cognition diagnosis (Quinn, O'Brien, Doubal).

Data linkage: We will use data linkage to ascertain recurrent stroke, dementia, death, place of residence and vital status and limit losses. We will use GP records (McManus) and registry data to ascertain long term outcomes (recurrent stroke, dementia, myocardial infarct, death, place of residence) to supplement follow-up information to two years and thereafter.

Workpackages benefit from the well-phenotyped inclusive sample stratified by patient, stroke, vascular risk and neuroimaging variables. Where a subset is required, a sample representative of known key predictive variables will be invited based, where possible, on random selection. The following are core to the study.

a) ***Cognition assessment validation***: Purpose: The study provides a major opportunity to validate the proposed staged approach to cognition and related assessments, both for research and clinical use.
Method: The achievement of recruitment targets and completeness of baseline and follow-up data, including of informant data, will give practical evidence of the acceptability, feasibility and practicality of the assessments. Active feedback from participants will identify areas for improvement. We will compare phone/post data with clinical diagnosis of dementia and, in a random sample, compare remote with in-person assessments and central adjudication of dementia diagnoses.

b) ***Neuroimaging***: Purpose: To stratify patients by acute and pre-stroke features(45,46) determine sensitivity/specificity of acute and pre-stroke lesion patterns for VaD subtypes,(6) test independent effects of pre-stroke 'brain frailty' markers (45) on VCI/dementia risk and test the predictive value of imaging markers for cognitive decline (47) and dementia.
Method: All diagnostic scans (MR and CT) from all patients will be collected centrally and analysed by validated methods (acute lesion(45), SVD features(46) including brain and lesion volumes). MRI standard sequences (T1, T2, T2*, FLAIR, DTI)(46) are used in many UK centres

particularly in milder strokes; in severe stroke, CT is more feasible and the acute lesion is usually visible(45). MRI would not be feasible in all. Both CT and MR were used concurrently, with standard assessments, in large stroke trials(45,34).

c) ***Vascular***: Purpose: to determine if carotid stenosis and pulsatility (stiffness) predict current and future cognition since existing data, mostly from non-stroke studies, disagree(25); to assess if blood pressure at admission predicts cognitive decline(44); and to assess the role of routinely measured cardiac dysfunction on predicting PSCI(3).
Method: Internal carotid artery (ICA) stenosis will be obtained from routine carotid imaging and carotid artery velocities from carotid Doppler ultrasound (routine in many patients) to estimate carotid stiffness (pulsatility index for input; resistivity index for downstream resistance(25)). Systolic, mean, diastolic BP will be recorded on admission to calculate pulse pressure and BP variability (48)). Cardiac function (rhythm, echo parameters) collected routinely will be analysed against cognitive outcomes.

d) ***Inflammation***: Purpose: Identification of blood-derived risk predictors for future cognitive decline is a fast-moving field, therefore blood-derived samples will be stored for current analysis and future discovery analyses. In R4VaD, we will assess the role of inflammation in PSCI. Inflammatory cytokines (e.g. IL-1β and TNF-α) are involved in learning, memory and cognitive decline (50) including PSCI(51). Increased serum TNF-α is associated with rapid cognitive decline in AD and sustained inflammatory response post-stroke may lead to vascular dementia(52). We will assess these markers vs. pre- and post-stroke cognitive status and trajectories.
Methods: Blood will be taken in as many patients as possible at 6+/-2 weeks after baseline assessment, for high sensitivity IL-1β and TNF-α analysis using single molecule counting technology (Singulex) to detect extremely low cytokine levels (details Appendix 2). Samples will be transferred to Manchester University for analysis.
Blood will be also stored for discovery 'omics, the use of such valuable samples being funded separately.

e) ***Genetics***: Purpose: To determine genetic factors in PSCI. Genetic susceptibility is recognised as important in AD and stroke but under-studied in VaD: in worldwide collaborations, we identified ~20 new gene variants for stroke using Genome Wide Association Studies (GWAS)(53). Genetic factors are likely to be important in VaD and may also identify novel pathways.
Method: blood will be taken for DNA (from all possible participants) for GWAS, with standard QC, imputation and statistical analysis methods to compare genetic profiles with and without PSCI (sample collection details Appendix 3). To estimate heritability of genetic risk for PSCI, we will use statistical techniques such as Genome-wide Complex Trait Analysis to identify the proportion of phenotypic variance explained by genome-wide Single Nucleotide Polymorphisms (SNPs) from zero (none) to one (complete). Studies with this technique gave estimates of heritability in ischaemic stroke of between 20-40%, similar to AD. A sample size of 1000 will have sufficient power to obtain useful information. We will also use GWAS to identify SNPs significantly associated with dementia at the genome wide significance level of 5 x 10-8. By combining with the International Stroke Genetics and other Consortia, we will have ~5,000 patients, the 1,000 patients from this proposal making a crucial contribution to the global cohort.

7 DATA COLLECTION

Please see section 6.1 above for measurements and timepoints.

The medical history, vital signs, NIHSS, mRS, physical examination and cognitive and other assessments, will be obtained from the patient in person and one or more informants and from medical notes to minimise burden on patient, by the study team and supporting research team. These researchers will also obtain blood samples. Samples will only be identified by their study ID number.

All baseline medical, cognitive and laboratory data will be entered into a secure password protected electronic case record form (eCRF) hosted at the University of Nottingham by the

recruiting researcher, which will also record the collection of study samples. The eCRF will include range and other validity checks, track missing/incomplete data and flag follow-up timepoints to aid the flow of data collection, study recruitment tracking and study management. All data derived from analysis of primary study data will also be retained in data files as created from these analyses linked to the main study database, with each subject identified only by their study ID, and matched with the eCRF data for statistical analysis.

The electronic study record will replace the usual role of the paper CRF as the source documents for efficiency and to streamline monitoring. Each electronic form will be signed electronically by the researcher with any changes or updates also signed by the individual making these changes.

Paper versions of the CRF will be available to assist with data collection when interviewing patients at baseline and during follow-up visits. Paper CRFs will be filed in the patient's paper-based folder and held in a secure locked filing cabinet at site.

Patients who fail to attend for planned follow-ups will be telephoned to see if they require assistance, e.g. with transport or if there is some other reason. All paper forms will be filed in the patient's paper-based folder in a secure locked facility after data have been entered onto the eCRF.

8 STATISTICS AND DATA ANALYSIS

8.1 SAMPLE SIZE CALCULATION

Sample size: We used meta-analyses and trial data to determine sample size and provide scenarios to address uncertainty (Table 2).

Table 2: Sample size estimations

Stroke	Mild	Severe	Total
Dementia %)	10	20	572
Dementia	10	15	1914
Dementia	20	40	236
Dementia	20	30	825
Dementia	20	25	3008
Dementia	20	27	1596

A key purpose of this work is to provide robust data on incidence and natural history of PSCI. SSNAP provides data on numbers of patients admitted to hospital in England & Wales:~7000 stroke patients are admitted to the applicants' hospitals/yr with ~5700 alive at discharge(29); about ~1000 (minor stroke) are seen as outpatients; numbers of TIAs are not available for all sites. Thus, recruitment of 1000+ patients (20%; 125/centre) is feasible in 1yr, ~2000 in 2yrs (250/centre), i.e. 1600-1700 ischaemic and ~400 ICH strokes, with streamlined, light touch approaches. This sample would, e.g. almost double ICH data(15), but represents ~20% of patients admitted per applicant centre, a conservative recruitment estimate for an observational study with very broad entry criteria. We also have considerable interest in the study from CRN-Stroke (Robinson), so expect to include up to 15 other NIHR LCRNs able to recruit ~1000 patients/yr, thus potentially recruiting more than 2000, or completing recruitment of 2000 participants faster.

Statistical Power: At power 0.90, alpha=0.05, we could detect the following differences in dementia in mild vs. severe stroke respectively (Table 2): 20 vs. 27%, n=1596; 10 vs. 15%, n=1914; 10 vs. 20%, n=572. Thus 2000 patients, with a wide range of stroke severities, will allow us to detect small (5% absolute), clinically meaningful differences in dementia between mild vs. severe stroke, although the difference in dementia between mild and severe is likely to be larger (10+% difference)(27). A sample of ~2000 will be able to detect differences in degrees of VCI and dementia and by subgroups such as age, pre-morbid cognitive ability, stroke subtype, or vascular risk factors, in multivariable models.

8.2 PROPOSED ANALYSES

We will assess prevalence of VCI and dementia and incidence by time after stroke using an ordinal outcome scale which assesses presence and severity of cognitive impairment (and dementia) and will include death. We will operationalise this scale using data obtained as above to classify outcome by pre- specified strata (age, sex, educational attainment, SES, vascular risk factors and disease burden, neuroimaging findings, and stroke severity) accounting for major acute treatments. We will tabulate cognitive scores by strata and use repeated measures to predict PSCI by baseline variables, adjusted for patient-, stroke- and life-course-related risk factors. We will use competing risks analyses to model losses due to severe stroke or death and global (rather than dichotomous) cognitive analysis to increase power. We will compare our sample to SSNAP, England/Wales, to determine the representativeness of the study patients in a) the participating hospitals and b) the UK(29).

9 ADVERSE EVENTS

AEs and SAEs will not be reported in this observational study in which there is no intervention or change to usual care. There are no pharmacovigilance issues specific to this work. Key events such as recurrent stroke or TIA, cardiac disorders, cognitive problems and other serious medical conditions will be recorded as outcome events at each follow-up visit as part of the study assessments. Pre-existing medical conditions (i.e. existed prior to informed consent) will be recorded as part of the medical history.

10 PREGNANCY

Pregnancy is not an exclusion criterion.

11 OVERSIGHT ARRANGEMENTS

11.1 STUDY MANAGEMENT

The study team will form a *Steering Committee* with an independent chair, funders, an external expert, and user representatives who will be consulted throughout. The work will be organised in Work-packages (Study Management including eCRF, Cognition, Imaging, Vascular function, Inflammation, Genetics, Statistical analysis) to share responsibilities, with Service User input

11.2 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit study related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

11.3 STUDY MONITORING AND AUDIT

The ACCORD Sponsor Representative will assess the study to determine if an independent risk assessment is required. If required, the independent risk assessment will be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and, if so, at what frequency.

Risk assessment, if required, will determine if audit by the ACCORD QA group is required. Should audit be required, details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

12 GOOD CLINICAL PRACTICE

12.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

A favorable ethical opinion will be obtained from the appropriate REC and local R&D approval will be obtained prior to commencement of the study.

12.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff and recorded in a delegation log.

12.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate PIS and ICFs will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the PIS and ICF.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s) but understand that their name will not be disclosed outside the hospital.

The Investigator or delegated member of the trial team and the participant will sign and date the ICF to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the ISF and participant's medical notes.

Consent or assent will be obtained from the appropriate person for each jurisdiction (Scotland, Northern Ireland, England, Wales) will be sought where a potential participant is unable to consent for themselves. An information leaflet and appropriate consent form have been developed for this purpose. The research team will always approach the patient first about participating in the study. Verbal information will be tailored to each individual's ability. Should a participant indicate in any way that they do not wish to be involved in the study, they will be withdrawn from the study even if prior consent from a relative or guardian has been obtained.

If the capacity of the participant previously unable to consent improves sufficiently during the course of the study, they will receive information about the study via a participant information sheet and be approached to give consent. Should a participant indicate in any way that they do not wish to be involved in the study, they will be withdrawn from the study.

12.2.2 Study Site Staff

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

12.2.3 Data Recording

The Principle Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site. The source data plan identifies which source data correspond to CRF data and states which data are recorded directly into the CRF.

12.2.4 GCP Training

All study staff must hold evidence of appropriate GCP training.

12.2.5 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

12.2.6 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 1998 and General Data Protection Regulation 2018 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to those clinicians treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

13 STUDY CONDUCT RESPONSIBILITIES

13.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the CI.

Amendments to the protocol must be submitted in writing to the appropriate REC and local R&D for approval prior to participants being enrolled into an amended protocol.

13.2 PROTOCOL VIOLATIONS AND DEVIATIONS

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation.

13.3 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

13.4 END OF STUDY

The end of study is defined as the completion of study visits and data analysis.

The Investigators and/or the study steering committee and/or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved.

A summary report of the study will be provided to the REC within 1 year of the end of the study.

13.5 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the CI and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the CI and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's Nation Health Service will have the benefit of NHS Indemnity.

14 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

14.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the whole study team. On completion of the study, the study data will be analysed and tabulated. A clinical study report will be prepared in accordance with the funder’s requirements.

14.2 PUBLICATION

Publication will be planned in advance and a publication strategy to deal with primary and key secondary outputs will be put in place via the Study Steering Committee. Publications will be in the name of the investigator group; all investigators will have to approve publications. Individual investigators will wish to publish the results of substudies or other outputs from the study; such proposals should be made to the SSC to avoid duplication and help maintain information on outputs for reporting to the funder and in ResearchFISH as appropriate.

A committee will be established to assess proposals for analyses from external groups.

The anonymized study data will be made available for use by external investigators in appropriate analyses upon request via a publicly accessible portal (eg University of Edinburgh datashare). The mechanisms and processes for managing external access will be determined during the course of the study.

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Appendix 1: Neuropsychological Testing

Appendix 2: Blood sampling instruction for inflammation analysis and long term storage

Appendix 3: Genetic samples

R4VAD MRI DTI Substudy Protocol Addendum

Background:

R4VAD is recruiting a large cohort of patients with stroke to identify predictors of future cognitive decline and dementia. In the overall cohort, phenotyping is performed using clinical and cognitive measures, as well as review of routine brain imaging which is a combination of clinically acquired CT and/or MRI brain imaging performed at stroke onset.

Previous prospective longitudinal studies have suggested that advanced MRI can provide additional predictive information on which patients with stroke will progress to dementia. For example, in patients with small vessel disease stroke, it has been shown that independent imaging predictors of dementia include the extent of white matter ultrastructural damage assessed using diffusion tensor imaging (DTI),[1] the number of new lacunes,[2] and in some studies the rate of loss of brain tissue (atrophy).[3] However, it is unclear if these features predict dementia in other stroke subtypes. Features which predict cognitive impairment and dementia after stroke in general include the severity of white matter hyperintensities (WMH) on MRI or leukoaraiosis on CT,[4] plus the severity of brain tissue loss and presence of old infarcts, including when these features are combined into 'SVD scores' or 'brain frailty scores'.[5] These features have the advantage of being easy to detect on brain scanning at admission to hospital. Other markers, such as perivascular spaces (PVS)[6,7] and cerebral microbleeds (CMB)[8] visible only on MRI, are associated with dementia risk in some studies. The former are thought to indicate impaired small vessel function, interstitial fluid and amyloid clearance.[9] Several of these markers predict dementia in patients without prior stroke[7,8,10] but it is not clear if their risk prediction is different after stroke. Furthermore their value as possible risk stratifiers for use in early phase clinical trials, or for future risk prediction for individual patients (precision medicine), is unclear.[11] Finally, large prospective studies including a range of stroke subtypes, severities and co-morbidities, to test the independent predictive value of brain imaging features in the 'real world', are lacking.

A predefined substudy in R4VAD is to evaluate advanced neuroimaging, in which MRI, including DTI, would be performed at the early follow up which takes place 4-8 weeks after the baseline assessment (i.e. 4-14 weeks after stroke depending on the timing of the baseline assessment), in selected centres with relevant equipment and capacity, to test the prognostic value of clinically accessible (though not currently routine) MRI brain imaging features in addition to conventional features on long term cognitive impairment after stroke.

To maximise the value of the brain MRI data and R4VaD as a whole, we will also collect an estimate of peak adult cognitive ability using the National Adult Reading Test (NART), and additional blood pressure (BP) readings including 24 Hour ambulatory monitoring where feasible. Currently, since it was impractical to collect the NART across 35+sites in all 2000+ participants planned to be enrolled, R4VaD collects educational attainment/duration as a proxy measure of peak adult cognitive ability and covariate adjustor for analysis of cognition after

stroke. However, it is more feasible to train a small number of sites to perform the NART, and the data will be extremely valuable to validate a) the use of educational attainment as a proxy measure of peak adult cognitive ability and b) to test independent associations with the DTI: peak cognitive ability is a strong predictor of risk of stroke,[12] of vascular lesions on brain imaging,[13] of DTI measures,[14] of age at stroke and of post-stroke cognitive impairment.[15,16] NART has been validated in ageing,[17] and early dementia[18] but to a limited extent after stroke,[19] therefore requires further validation in post stroke cohorts, as well as being an important covariate adjustor in the DTI analysis. A small study in patients with minor stroke suggested that education and cognitive ability had similar predictive power,[15] but larger studies are needed to improve confidence in use of education in clinical practice. Additional BP measurements, including ambulatory BP monitoring (ABPM) where possible, will be collected and the BP data will be most useful where there is detailed brain MRI data in addition to the usual R4VaD data.

Inclusion criteria:

- Consented to participate in R4VaD
- .
- .
- All ischaemic stroke subtypes.
- Patients with capacity to consent (at baseline), i.e. no dementia prior to stroke.
- Estimated life expectancy >/= 1 year.
- No contraindications to MRI scanning.
- Willing to have additional MRI scan as close to 8 weeks after stroke as possible, preferably timed to coincide with the existing R4VaD early follow-up assessment.
- All ages included in R4VaD.

Additional study interventions:

- Multimodal MRI scanning including DTI performed as close to 8 weeks after stroke as possible, preferably timed to coincide with the existing R4VaD 4-14 week post stroke early follow-up clinical and cognitive assessment.
- Two blocks of three sitting blood pressures will be measured during the visit for MRI, the first block prior to and the second block after the MRI. Where the MRI visit is combined with the 4-14 week post stroke R4VaD follow up, only one block of three BP readings will be obtained, after the MRI scan, since the 4-14 week R4VaD early follow-up visit already includes three BP measures.
- Estimate of peak cognitive ability in early adulthood using the National Adult Reading Test (NART).[12-19]
- In centres where this is feasible, participants will be supplied with an ambulatory BP monitoring device to record 24 hr BP to test associations with DTI parameters and

cognitive status after stroke. Alternatively, additional BP readings will be taken at the study visit.

- Where feasible, participants will be invited for repeat MRI at two years after stroke, which can coincide with the two year R4VaD follow-up after stroke where feasible.
- All other follow up will be according to established R4VaD methods.

Setting:

- Selected centres with definite capacity to perform, and experience in carrying out, MRI studies including DTI.
- 3T scanners.
- Ideally, all patients in each centre to be scanned on the same scanner.

Resources available:

- £300-£400 is available at present for the initial scan; no funding is currently available for any follow up scans, but other local or R4VaD resources may become available in the course of the study.
- No additional travel expenses apart from those already available for the 4-14 week post stroke R4VaD follow-up, hence combine with clinical/cognitive follow-up.
- Training in administration of the NART will be provided to practitioners.
- BP monitoring devices will be provided where these are not already available at site. Several devices are available. All devices are approved for this purpose by the British Hypertension Society, are simple to use, and have up to date service and maintenance checks. Data will be uploaded to the central study database. Where participants agree to undergo 24 hour ambulatory monitoring, additional travel expenses will be provided to return the devices.

Study MRI and sequences:

Details of the scanner manufacturer and model will be obtained from each site. A rigorous quality control will be implemented prior to any patient assessment to ensure standardisation of sequence parameters as much as possible, as in e.g. PRESERVE,[1] preferably by performing a test scan. Centers should be able to demonstrate that they undertake a regular quality assurance monitoring of their scanner's performance. Centers participating in this R4VaD substudy are likely to have participated in prior multicenter studies using MRI including DTI. The overall process will take less than 30 minutes.

The following sequences will be used:

- 3D T1 - 1-mm3 isotropic voxel resolution and TR and TE, optimized to ensure comparable T1 weighting and tissue contrast across sites.

- FLAIR – preferably 3D with 1-mm3 isotropic voxel resolution-.
- T2 – preferably 3D with 0.9-mm3 isotropic voxel resolution,
- SWI - TE matched and kept a similar TR to ensure comparable susceptibility weighting across sites;
- DTI - (2-mm3 isotropic voxel resolution) single shell sequence, optimized for each scanner to avoid T1 relaxation effects. In addition to the b=0s mm−2 acquisitions, all DTI acquisition will include around 60 equally spaced, non-collinear diffusion gradient directions (b=1000 s mm−2) to ensure identical angular resolution and noise characteristics.

Resolution for T2*W and FLAIR sequences may vary between sites. Isotropic 3D acquisitions for structural images are essential.
Where performed, the scan at two years will be identical and preferably on the same scanner as the 4-14 week scan.

Data transfer:

As per usual R4VaD procedures, anonymised data will be sent initially to Edinburgh (an established pathway that will simplify procedures for sites) using the established R4VaD transfer processes and then routed to Cambridge for DTI and related analyses. On arrival at Edinburgh, all data will be checked for date and identification, via an established scan housekeeping system for efficient data tracking.
The NART and additional BP readings will be entered into a short extension of the R4VaD CRF. BP readings will be downloaded and stored in the equipment database; summary data output and/or raw data will be transferred to Edinburgh for subsequent analysis.

Parameters to be measured:

Image processing: Volumes of intracranial compartment, whole brain, white matter hyperintensity (WMH), normal appearing white matter (NAWM), grey matter (GM) and the index stroke lesion will be measured using established validated methods.[1,11,20,21] All segmentations will be visually checked and manually corrected as necessary. Stroke lesions will be manually outlined. SVD lesions will be defined and assessed according to STRIVE criteria.[22] All analyses will be by trained observers.
DTI: Fractional Anisotropy (FA), mean diffusivity (MD), in normal appearing white matter (NAWM), deep grey matter (GM), and in white matter hyperintensities (WMH).[23,24] MD peak height[1] and peak width of skeletonised mean diffusivity (PSMD)[10] will be calculated.
WMH: Fazekas score, volume, including of less and more intense WMH.[20,21]
PVS: visual score,[25] computational (total volume, count, individual median width, length, size, shape, dispersion)[26]
Cerebral Microbleeds (CMB): visual score of number, location[27]
Siderosis: visual score[28]
Basal Ganglia mineral: visual score[20,29]

Brain atrophy: validated visual score of deep and superficial tissue loss.[5,20]
The data will also enable further analyses of generalised brain damage features (eg[30,31]), their ability to predict poor outcomes and their practicality for translation to clinical practice.

Objective and Outcomes

The objective of this study is to test the prognostic value of clinically accessible MRI brain imaging features in addition to conventional features on long term cognitive impairment after stroke.
Primary: Seven point cognitive score at 1 year, as for R4VaD
Secondary: at 1 year, dementia; mild cognitive impairment; individual cognitive subdomains, recurrent stroke; fatigue; apathy; depression; all as assessed on established R4VaD instruments.
Primary predictor: MD peak height;
Secondary predictors: 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 (eg brain age metric,[31] brain health index[30]) and others emerging during the study will be tested.
Covariate adjustments: age, baseline MOCA, baseline trail making test B, initial stroke severity (NIHSS), time after stroke to DTI, education level/amount, hypertension Y/N, mean BP at DTI, change in BP from baseline to DTI, smoking status (current, ex for >1yr, never), diabetes Y/N, dietary salt, and other variables.

Sample size and power

R4VaD planned for 20% of the planned target sample of 2000 in R4VaD (i.e. up to 400 total) to be invited for DTI and structural MRI at 4-14 weeks after stroke using established multicentre protocols (e.g. PRESERVE)[1] to obtain white and grey matter integrity as predictors of cognitive decline. The R4VaD substudy is exploratory, therefore no formal sample size estimation is performed. The following indicate likely power to detect relevant associations and derive predictions in a sample of 300-400 patients.
The MD peak height method was tested in 109 participants with symptomatic lacunar infarction and confluent WMH across five sites in the PRESERVE DTI substudy[1] using five Siemens or Philips scanners and found that DTI metrics from all white matter were significantly associated with global cognition (standardized β =0.268), verbal fluency (β =0.376), and Montreal Cognitive Assessment (MoCA) (β =0.273), with magnitudes that were comparable to previously reported single-centre values.
The PSMD method showed associations with processing speed when applied retrospectively in several single centre studies including patients with genetic SVDs (n = 113), inherited SVD (n = 57), sporadic SVD (n = 444), and memory clinic patients with SVD (n = 105), at p-values between 2.8 x 10(-3) and 1.8 x 10(-10) in all samples, explaining most of the variance in processing speed (R(2) ranging from 8.8% to 46%).[10]

R4VaD will provide further prospective validation of these DTI (and related brain imaging) metrics in a novel population, i.e. patients with acute ischaemic stroke, across several stroke sites in the UK. This is important for planning future intervention trials, determining practicality and effect sizes, and comparing several imaging-derived metrics. The planned sample of up to 400 patients will be substantially larger than any of the above studies in which the DTI-based methods have been derived, suggesting that there will be power to determine the practicality and prognostic value of MRI DTI and related brain imaging variables in predicting global cognitive outcome at 1 year after stroke. We also note that while processing speed and other tests of executive function may be sensitive to white matter damage, stroke is a complex disease where all cognitive domains may be affected and hence are being assessed in R4VaD. Therefore the neuroimaging substudy will test a range of DTI metrics and other neuroimaging variables on cognitive and functional outcomes to achieve a comprehensive view of brain predictors and their practicality for translation to future routine clinical practice.

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R4VaD COVID-19 Substudy Addendum.

Background

In December 2019, an outbreak of pneumonia caused by a novel coronavirus occurred in Wuhan, China and spread rapidly to other parts of the country, then Europe, North America and Asia. The World Health Organisation (WHO) declared the outbreak to be a public health emergency of international concern on 30th January 2020 and recognised it as a pandemic on 11th March 2020. The disease, which typically causes respiratory symptoms, fever, myalgia and fatigue, with characteristic laboratory findings and lung CT abnormalities, has been named coronavirus disease 2019 (COVID-19).

Recent reports from China of patients with laboratory confirmed COVID-19 suggest that patients with pre-existing comorbidities such as cardiovascular disease, diabetes, hypertension and cerebrovascular disease may be among those at highest risk of acquiring the infection, and may have worse outcomes[1-4]. One study of 1099 patients reported that compared with milder cases, those with more severe COVID-19 (n= 173) were more likely to have comorbidities such as hypertension (23% vs 13.4%), diabetes (16.2% vs 5.7%), coronary heart disease (5.8% vs 1.8%) and cerebrovascular disease (2.3% vs 1.2%)[2]. Another study by Yang and colleagues (2020)[3] found that the most distinctive comorbidities of 32 non-survivors from a group of 52 intensive care unit patients with COVID-19 were cerebrovascular diseases (22% vs 0%) and diabetes (22% vs 10%).

A common treatment for these comorbidities are angiotensin-coverting enzyme (ACE) inhibitors and angiotensin II type-I receptor blockers (ARBs) which increase the expression of ACE2[5]. ACE2 has been identified as a functional receptor for coronaviruses, and is highly expressed in the heart, lungs and blood vessels[6]. As a result, these medications may facilitate infection with COVID-19 and increase the risk of developing severe and fatal infection.

Although the clinical manifestations of COVID-19 are dominated by respiratory symptoms, recent data from China suggests that the disease may also have neurological manifestations. A recent study of 214 patients with laboratory confirmed COVID-19 reported that seventy-eight (36.4%) patients had neurological manifestations. Of the 214 patients, 88 were severe and 126 were non-severe. Severe patients were more likely to have neurologic symptoms (40 [45.5%] vs 38 [30.2%]), including cerebrovascular disease (5 [5.7%] vs 1 [0.8%])[1], suggesting that COVID-19 may play a causal role in acute stroke. The mechanisms behind these associations are unclear, but patients with severe COVID-19 were found to have higher D-dimer levels than non-severe patients[1].

COVID-19 may be a risk factor for ischaemic stroke and may influence the severity and prognosis of those who present with stroke. However, large-scale data on the prevalence and severity of COVID-19 in the stroke population are lacking. It is especially concerning from a public health perspective if patients with cerebrovascular disease are at higher risk of developing severe and fatal COVID-19. Stroke is amongst the most prevalent diseases worldwide and the impact of the current pandemic of COVID-19 could be devastating for these patients. Furthermore, the neuropsychological impact of the epidemic on patients who have experienced a recent stroke, and who are amongst those most at risk of infection, is also unclear. However, the ongoing follow-up of R4VaD participants who were recruited up to a year prior to the outbreak, and who were in follow-up during introduction of the UK social distancing measures, has already indicated high levels of anxiety on Neuropsychiatric tests.

The objective of this proposed substudy in R4VaD is to evaluate the impact of the current COVID-19 pandemic on patients presenting with stroke to UK stroke centres. R4VAD has already been recruiting for 18 months, has recruited over 1250 participants from 53 Centres across the UK, and will follow up patients to a minimum of 2 years, maximum of 10 years, post stroke. Therefore, this substudy will allow comparison of data collected before, during and after the pandemic, using existing funded infrastructure. It will be one of the few opportunities to obtain objective data on COVID-19 and stroke, a common and high risk vascular disorder.

Using existing procedures, additional information on COVID-19 status (not infected, possibly infected, definitely infected) and treatment will be collected for all patients at baseline, which takes place 24 hours to 6 weeks post stroke, and at the follow-up assessments, which are conducted 4-8 weeks after the baseline assessment and then annually. We will also collect information on additional risk factors for COVID-19, and additional relevant laboratory or radiological investigations, such as chest CT. The methods of recruitment and assessment, which are already very flexible, will remain the same to those of the main study, facilitating data collection by researcher practitioners who are already familiar with the procedures. The baseline assessment during the conduct of the substudy will be streamlined to reduce the overall length of assessment.

Aims

1. To determine the prevalence of COVID-19 infection in patients admitted with acute stroke to UK stroke centres currently participating in R4VaD.

2. In patients with both acute stroke and COVID-19 infection, to explore the relationship between the onset times of the symptoms related to these two illnesses.

3. To compare the clinical and laboratory features, stroke mechanism and phenotypes of patients with acute stroke and acute COVID-19 infection to those of patients with acute stroke without COVID-19 infection, and between mild and severe COVID-19 disease.

4. To characterize clinical outcomes (recurrent stroke, functional outcome) in patients with acute stroke and COVID-19 infection compared to those without COVID-19 infection.

5. Examine the neuropsychological impact of the COVID-19 outbreak on patients with stroke.

Inclusion criteria

- Patients aged ≥18
- No upper age limit or stroke severity limit
- Ischaemic or spontaneous haemorrhagic (non-traumatic, non-subarachnoid haemorrhagic, non-AVM) stroke and transient ischaemic attack (TIA).
- No stroke mimics.
- Patients both with and without the capacity to consent.

The current inclusion criterion of ‘expected to survive for 12 weeks after the stroke’ will **not** be an inclusion criteria for this substudy so that the full range of severities of stroke can be included.

Patients with incapacity
R4VaD currently recruits patients without capacity with the consent of a consultee, relative, friend or welfare attorney. In light of current restrictions on acute hospital wards, it may not be possible to obtain consent or opinion from a consultee, relative, friend or welfare attorney in cases where a person lacks capacity to consent for themselves. In these cases, in England and Wales we propose using a waiver of consent. The clinical team will make the decision as to whether a patient is enrolled into the study. In Scotland we will obtain consent from a relative or friend by phone. In both cases we will then seek written consent from the patient or relative subsequently during the admission or at the follow up assessment. Should a participant indicate in any way that they do not wish to be involved in the study, they will be withdrawn.

For patients with capacity we will include an option for witnessed consent if a patient is not able to read and/or sign the consent form themselves. This option can also be used when recruiting patients from COVID-19 wards where a consent form cannot be signed and removed from the ward.

Setting

- Centres with capacity to continue to recruit to R4VaD.
- All patients will be recruited from inpatient wards.
- Co-enrolment in other relevant COVID-19 studies will be sought.

Additional variables to be measured

At baseline

Recruitment details

- Place of recruitment (tick boxes): stroke ward, COVID-19 ward, ITU, other

Stroke details

- If mechanical thrombectomy not performed was COVID-19 infection given as the reason? (Y/N).

COVID-19 infection

- COVID-19 infection (tick boxes): not infected, possibly infected, definitely infected
- Recent contact with person with COVID-19 (tick boxes): yes, no, not known

For suspected or confirmed COVID-19 infection

- Clinical features of suspected COVID-19 infection (tick boxes): fever, dry cough, productive cough, rhinorrhea, dyspnea / high resp rate, headache, impaired consciousness, presyncope / syncope, loss of smell / taste, headache, dizziness, ataxia, myalgias, seizures
- Date and time of onset of symptoms suspicious of COVID-19 (as listed above)
- Date of nasopharyngeal swab test (if performed).
- Result (dropdown: positive, negative, not performed, performed no result)

- Antiviral treatment for COVID-19 infection: (dropdown: remdesivir, favipiravir, chloroquine, hydroxychloroquine, tocilizumab, other, none)
- NEWS score version (dropdown: 1, 2). Lowest NEWS score recorded.
- Level of respiratory support (dropdown: none, O_2 via nasal prongs, O_2 via mask, non-invasive ventilation, intubation and ventilation)
- Arterial blood gas recorded (Y/N). If yes: pH; PaO2; PaCO2; HCO_3, O_2 Sat.
- Chest CT performed (Y/N). If yes: findings will be recorded as: no evidence COVID-19, unilateral, bilateral features confirm COVID-19[7].
- Co-enrolment in other COVID-19 studies

Risk factors

- **In PMH:** (Tick boxes). Malignancy (state primary if known).

Medications at the time of the event

- (Tick boxes) Aspirin. Clopidogrel. Dipyridamole. Dabigatran. Warfarin. Other oral anticoagulant (please state). Low molecular weight heparin (dropdown: blank field by default, dalteparin, enoxaparin, tinzaparin, other).
- DOAC (dropdown: blank field by default, rivaroxaban, apixaban, edoxaban, dabigatran). Angiotensin II receptor blocker (blank field by default, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan)

(Followed by free text field)

Blood results on admission

- FBC: Neutrophils. Lymphocytes.
- INR. APTT. D-dimer
- Lactate dehydrogenase
- Ferritin

At follow up

- COVID-19 infection (not known to be infected/ possibly infected/ definitely infected/ recovered)
- Results of nasopharyngeal swab test (if performed) (Y/ N/ Don't know)
- If history of COVID-19 infection were they hospitalised (Y/ N) If yes: were they in intensive care? (Y/ N)
- Level of respiratory support (none/ 02 via nasal prongs/ O2 via mask/ non-invasive ventilation/ intubation and ventilation).
- Discharged from hospital (Y/N)
- Deceased (Y/N) If yes: Due to COVID-19 (Y/N)

Data transfer

All data will be entered into a shortened modified baseline version of the online R4VaD CRF.

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