ISRCTN41647111 https://doi.org/10.1186/ISRCTN41647111

Treatment including surgery versus treatment without surgery for people with symptoms due to a cavernoma in the brain

Submission date
02/06/2021

Recruitment status
No longer recruiting

Registration date
18/06/2021

Overall study status
Completed

Last Edited
30/05/2024

Condition category
Nervous System Diseases

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

Plain English summary of protocol

Background and study aims
A cavernoma is a cluster of blood vessels that form blood-filled ‘caverns’ that look like a raspberry. Brain cavernomas can cause strokes or epileptic seizures. In the UK, most people with cavernomas have medical management (which may involve scans, drugs, or rehabilitation) to manage these symptoms. About one fifth also have ‘surgical management’ with either brain surgery to remove a cavernoma or stereotactic radiosurgery to stabilise it with radiation.

The pros and cons of medical management versus medical and surgical management are finely balanced. Finding out which is best was identified through work involving the charity Cavernoma Alliance UK as a top priority for cavernoma research. We first need to find out whether enough patients can be found for a randomised trial comparing ‘medical management' with ‘medical and surgical management’ of symptomatic cavernomas. We need to know this because cavernomas are rare and we do not know whether patients and doctors will take part. This will be the first randomised trial of its kind for brain cavernoma.

Who can participate?
We will recruit patients of all ages with brain cavernoma who meet the eligibility criteria, where there is uncertainty about the best treatment option.

What does the study involve?
Participants will be allocated at random to either medical management or medical and surgical treatment (neurosurgery or stereotactic radiosurgery). If patients do not have a preference for surgical treatment, type, they may be allocated randomly to neurosurgery or stereotactic radiosurgery. We aim to recruit ~60 participants.
An integrated qualitative research component (QuinteT), including analysis of screening log data and qualitative research (including interviews with patients and research staff), is included to understand recruitment processes and barriers as well as actions to address barriers.

What are the possible benefits and risks of participating?
There are some benefits from taking part in this research study:

Your participation in the Information Study will allow us to improve how cavernoma treatment research is discussed with patients.
• You may find it a relief to have the decision about whether to have surgery taken out of your hands.
• Your health in this study will be under review with the possibility of an additional brain MRI scan. You may feel supported by this.
• The results of this study will help us to improve the healthcare of patients in the future.

There are some risks from taking part in this research study:
Treatment without surgery and treatment including surgery in the CARE study involve health technologies that are available in standard clinical practice in the UK and Republic of Ireland.
• Treatment without surgery leaves patients at risk of a bleed/stroke and epileptic seizures.
• Neurosurgical excision is the most frequently-used form of surgical treatment for brain cavernoma in the UK. It involves an operation that creates an opening in the skull, called a craniotomy, which can result in infection, and the operation can cause a stroke or damage to the brain around the cavernoma.
• Stereotactic radiosurgery (using Gamma Knife) is non-invasive and may be used because neurosurgery is too risky or a patient wants a non-invasive treatment. This procedure uses ionising radiation to provide treatment. This can cause a stroke or damage to the brain around the cavernoma. Ionising radiation can cause cell damage that may, after many years or decades, turn cancerous. Taking part in this study will not significantly alter the chances of this happening to you. We are all at risk of developing cancer during our lifetime. The normal risk is that this will happen to about 50% of people at some point in their life. Taking part in this study will increase the chances of this happening to you from 50% to between 50 and 50.5%.

Where is the study run from?
The University of Edinburgh (UK)

When is the study starting and how long is it expected to run for?
September 2020 to October 2023

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
Prof Rustam Al-Shahi Salman, Rustam.Al-Shahi@ed.ac.uk

Contact information

Type(s)
Scientific

Contact name
Prof Rustam Al-Shahi Salman

ORCID ID
https://orcid.org/0000-0002-2108-9222

Contact details
Centre for Clinical Brain Sciences
Chancellor’s Building

University of Edinburgh
49 Little France Crescent
Edinburgh
United Kingdom
EH16 4SB
+44 (0)131 242 7014
Rustam.Al-Shahi@ed.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
289197

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 49352, IRAS 289197

Study information

Scientific Title
Cavernomas A Randomised Effectiveness (CARE) pilot study, to address the effectiveness of active treatment (with neurosurgery or stereotactic radiosurgery) versus conservative management in people with symptomatic brain cavernoma

Acronym
CARE study

Study objectives
The shortage of high-quality evidence to inform the management of patients with brain cavernomas has prevented clinical guidelines in the UK and USA from making strong recommendations about whether to use treatment without surgery or treatment including surgery for brain cavernomas. We are working towards conducting a large-scale randomised controlled trial to find out which is best. This pilot phase randomised trial aims to assess the feasibility of conducting a definitive main phase randomised trial.

Ethics approval required
Ethics approval required

Ethics approval(s)
1. approved 31/03/2021, Yorkshire & the Humber - Leeds East Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, United Kingdom; +44 (0)207 104 8109; leedseast.rec@hra.nhs.uk), ref: 21/YH/0046

2. approved 25/11/2022, Ethics (Medical Research) Committee - Beaumont Hospital (Beaumont, Dublin, Dublin 9, Ireland; +353-1-809 2680; beaumontethics@rcsi.com), ref: 21/84

3. approved 23/08/2022, Clinical Research Ethics Committee of the Cork Teaching Hospitals (University College Cork Lancaster Hall 6 Little Hanover Street, Cork, T12 WV09, Ireland; +353-21-4901901; crec@ucc.ie), ref: ECM 4 (l) 10/8/2021 & ECM 5 (3) 26/10/2021 & ECM 3 (o) 20/09/2022

Study design
Interventional randomized controlled trial with integrated qualitative sub-study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Brain cavernoma

Interventions
Current interventions as of 28/10/2022:
This prospective randomised open blinded end-point (PROBE) randomised controlled trial (RCT) aims to estimate the feasibility of performing a definitive main phase RCT comparing medical management to medical and surgical management (with neurosurgery or Gamma Knife stereotactic radiosurgery, according to their availability in clinical practice) for improving outcome for people with symptomatic brain cavernoma.

Randomisation will allocate participants to groups in a 1:1 ratio, stratified by preferred type of surgical treatment, but if there is no clear preference for the type of surgical treatment, and both are available, the patient will be randomly allocated to either neurosurgery or stereotactic radiosurgery. The trial design includes an integrated QuinteT Recruitment Intervention (QRI) which aims to understand recruitment barriers (e.g. related to selection of patients during screening and recruitment processes, or equipoise), and optimise informed consent and recruitment processes in the trial.

In one arm of the trial, participants will receive brain cavernoma treatment without surgery that is available in standard clinical practice. This may include anti-epileptic drugs to prevent epileptic seizures, rehabilitation of neurological deficits (e.g. physiotherapy, speech and language therapy), medical treatment of other neurological symptoms (e.g. headache, body pain, spasticity, dysaesthesia), and psychological support. In standard clinical practice, these treatments are usually provided for as long as they are required or likely to benefit patients.

In the other arm of the trial, participants will receive brain cavernoma treatment including surgery that is available in standard clinical practice. This involves trying to remove the cavernoma using brain surgery (known as neurosurgery) or trying to stabilise the cavernoma using focussed radiation treatment (known as stereotactic radiosurgery) in addition to all of the treatments in the other arm of the trial. It is expected (but not mandated by the trial protocol) that surgical management will be delivered within 3 months of randomisation to the trial. Neurosurgery will be undertaken by a consultant neurosurgeon responsible for neurosurgical aspects of the clinical care of the cavernoma patient in CARE. The neurosurgical technique employed will be that used by the consultant neurosurgeon in clinical practice. Adjuncts such as image direction, microscopy, ultrasonic aspiration, awake/general anaesthesia surgery, cortical mapping/stimulation, and intra-operative MRI, will be used as considered appropriate by the consultant neurosurgeon. Stereotactic radiosurgery will be performed at the National Centre for

Stereotactic Radiosurgery in Sheffield or the Queen Square Radiosurgery Centre, which are the two referral centres in the UK that are commissioned to provide Gamma Knife stereotactic radiosurgery for cavernoma. Standard clinical treatment protocols will be used which involve targeting the brain cavernoma, but not the surrounding haemosiderin ring. Treatment dosages will range from 12-16 Gy depending on size, shape, definition and site of the cavernoma.

Around 6 months after the baseline visit that precedes randomisation, participants will be contacted by their local research team for a follow-up visit. This visit will involve a brain MRI scan and completion of questionnaires to check how the participant is doing. Every 6 months thereafter, participants will be contacted by a member of the central research team at the trial coordinating centre who will get in touch by phone or email to complete questionnaires and check how the participant is doing. Follow-up will end approximately 6 months after recruitment finishes.

Participants are asked to consent to long-term follow up (i.e. beyond the planned follow-up in the CARE pilot trial), including the use of routinely collected data (such as hospital admissions, procedures, and death certificates), in case the CARE pilot trial is successful and runs seamlessly into a definitive main phase trial.

Previous interventions:
This prospective randomised open blinded end-point (PROBE) randomised controlled trial (RCT) aims to estimate the feasibility of performing a definitive main phase RCT comparing medical management to medical and surgical management (with neurosurgery or Gamma Knife stereotactic radiosurgery, according to their availability in clinical practice) for improving outcome for people with symptomatic brain cavernoma.

Randomisation will allocate participants to groups in a 1:1 ratio, stratified by preferred type of surgical treatment, but if there is no clear preference for the type of surgical treatment, and both are available, the patient will be randomly allocated to either neurosurgery or stereotactic radiosurgery. The trial design includes an integrated QuinteT Recruitment Intervention (QRI) which aims to understand recruitment barriers (e.g. related to selection of patients during screening and recruitment processes, or equipoise etc), and optimise informed consent and recruitment processes in the trial.

In one arm of the trial, participants will receive brain cavernoma treatment without surgery that is available in standard clinical practice. This may include anti-epileptic drugs to prevent epileptic seizures, rehabilitation of neurological deficits (e.g. physiotherapy, speech and language therapy), medical treatment of other neurological symptoms (e.g. headache, body pain, spasticity, dysaesthesia), and psychological support. In standard clinical practice, these treatments are usually provided for as long as they are required or likely to benefit patients.

In the other arm of the trial, participants will receive brain cavernoma treatment including surgery that is available in standard clinical practice. This involves all of the treatments in the other arm of the trial that are available without surgery, as well as trying to remove the cavernoma using brain surgery (known as neurosurgery) or trying to stabilise the cavernoma using focussed radiation treatment (known as stereotactic radiosurgery). It is expected (but not mandated by the trial protocol) that surgical management will be delivered within 3 months of randomisation to the trial. Neurosurgery will be undertaken by a consultant neurosurgeon responsible for neurosurgical aspects of the clinical care of the cavernoma patient in CARE. The neurosurgical technique employed will be that used by the consultant neurosurgeon in clinical practice. Adjuncts such as image direction, microscopy, ultrasonic aspiration, awake/general anaesthesia surgery, cortical mapping/stimulation, and intra-operative MRI, will be used as

considered appropriate by the consultant neurosurgeon. Stereotactic radiosurgery will be performed at the National Centre for Stereotactic Radiosurgery in Sheffield or the Queen Square Radiosurgery Centre, which are the two referral centres in the UK that are commissioned to provide Gamma Knife stereotactic radiosurgery for cavernoma. Standard clinical treatment protocols will be used which involve targeting the brain cavernoma, but not the surrounding haemosiderin ring. Treatment dosages will range from 12-16Gy depending on size, shape, definition and site of the cavernoma.

Around 6 months after the baseline visit that precedes randomisation, participants will be contacted by their local research team to do a follow-up visit. This will involve completing some questionnaires to see how the participant is doing and having a brain MRI scan. Every 6 months thereafter, participants will be contacted by a member of the central research team at the trial coordinating centre who will get in touch by phone or email to complete some questionnaires and check how the patient is doing. Follow-up is scheduled to continue until February 2023.

We will ask study participants to consent to long-term follow up (i.e. beyond the planned follow-up in the CARE pilot trial), including the use of routinely collected data (such as hospital admissions, procedures, and death certificates), in case the CARE pilot trial is successful and runs seamlessly into a definitive main phase trial.

Intervention Type
Procedure/Surgery

Primary outcome(s)
Feasibility measured using the following questions answered from the assessments performed and data collected at the baseline, 6-month local in-person follow-up and 6-monthly central follow-up:
1. What proportion of the collaborating centres take part and recruit participants to the CARE pilot trial?
2. Can the investigators implement trial procedures correctly?
3. What proportion of screened patients is eligible?
4. What proportions of eligible patients are approached and randomised (and why are eligible patients not approached or not randomised)?
5. What is the distribution of participants between neurosurgery and stereotactic radiosurgery?
6. Do participants adhere to the allocated intervention and follow-up?
7. How complete are baseline, imaging and outcome data?
8. What are the outcome event rates?
9. How do the baseline characteristics, outcome event rates and differences between treatment groups compare to observational data about outcomes during medical management or after medical and surgical management?
10. What estimates of effect size/variability should be used in the design of the CARE definitive main phase trial?
11. What is the sample size required for a definitive trial to address the overall question over a 10-year follow-up?
12. Can the CARE pilot trial data describe care pathways, linked to health states and outcomes, to develop a robust economic model to evaluate cost-effectiveness in a CARE definitive main phase trial?
13. Which international research partners in other countries could contribute to the CARE definitive main phase trial?

Primary clinical outcome:
Intracranial haemorrhage or new persistent/progressive focal neurological deficit due to brain cavernoma or surgical management (neurosurgery or stereotactic radiosurgery), whether fatal (leading to death within 30 days of the outcome event) or non-fatal measured using patient records at 6-monthly follow-up until the end of the trial

Key secondary outcome(s))
Measured at 6-monthly follow-up until the end of the trial:
1. Death not due to a primary clinical outcome measured using patient records
2. Seizure severity and frequency measured using the Liverpool Seizure Severity Scale plus epileptic seizure frequency (number of seizures in the preceding four weeks, and attainment of one-year seizure freedom)
3. Degree of disability or dependence in the daily activities measured using the Modified Rankin Scale (mRS) score
4. Impairment caused by stroke measured using the National Institute of Health Stroke Scale Score (adult or paediatric)
5. Quality of life measured using the EQ-5D-5L in adults and EQ-5D-Y in children
6. Functional status measured using the Karnofsky Performance Status (KPS) scale in adults and Lanksy Play-Performance Scale (LPPS) in children
7. Health service use and healthcare and socioeconomic costs measured from patient records

Completion date
31/10/2023

Eligibility

Key inclusion criteria
1. People of any age
2. At least one brain cavernoma diagnosed by brain MRI that included a gradient echo or susceptibility-weighted sequence, according to standard diagnostic criteria
3. Clinical history attributable to a brain cavernoma of:
3.1. Symptomatic stroke due to intracranial haemorrhage, or
3.2. Symptomatic stroke due to a persistent or progressive non-haemorrhagic, or not otherwise specified, focal neurological deficit, or
3.3. Epileptic seizure(s) meeting the definition of definite or probable cavernoma-related epilepsy
4. Patient and doctor are uncertain about medical management or medical and surgical management of the symptomatic brain cavernoma, following consultation with a neurosurgeon
5. Patient has mental capacity to consent for themselves (adult participants or paediatric participants with capacity) or parent/legal guardian provides consent (paediatric participants)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
All

Sex
All

Total final enrolment
72

Key exclusion criteria
Current exclusion criteria as of 28/10/2022:
1. Surgical management of a solitary symptomatic brain cavernoma with MRI evidence of cavernoma removal/obliteration
2. Spinal cavernoma alone, without symptomatic brain cavernoma
3. Asymptomatic brain cavernoma. Patients with radiographic cavernoma enlargement (with or without intralesional haemorrhage) but without new symptoms are still regarded as asymptomatic
4. Previously randomised in the CARE pilot trial

Previous exclusion criteria:
1. Surgical management of a solitary symptomatic brain cavernoma with MRI evidence of cavernoma removal/obliteration
2. Spinal cavernoma
3. Asymptomatic brain cavernoma. Patients with radiographic cavernoma enlargement (with or without intralesional haemorrhage) but without new symptoms are still regarded as asymptomatic
4. Previously randomised in the CARE pilot trial

Date of first enrolment
30/06/2021

Date of final enrolment
30/04/2023

Locations

Countries of recruitment
United Kingdom

England

Northern Ireland

Scotland

Wales

Ireland

Study participating centre
Royal Infirmary of Edinburgh at Little France
51 Little France Crescent

Old Dalkeith Road
Edinburgh
Lothian
United Kingdom
EH16 4SA

Study participating centre
Aberdeen Royal Infirmary
Foresterhill Road
Aberdeen
United Kingdom
AB25 2ZN

Study participating centre
Birmingham Childrens Hospital
Steelhouse Lane
Birmingham
United Kingdom
B4 6NH

Study participating centre
Southmead Hospital
Southmead Road
Westbury-on-trym
Bristol
United Kingdom
BS10 5NB

Study participating centre
Addenbrookes
Addenbrookes Hospital
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
Hull Royal Infirmary
Anlaby Road

Hull
United Kingdom
HU3 2JZ

Study participating centre
The Walton Centre for Neurology and Neurosurgery
Lower Lane
Liverpool
United Kingdom
L9 7LJ

Study participating centre
Alder Hey Childrens Hospital
Alder Hey Children's NHS Foundation Trust
Eaton Road
Liverpool
United Kingdom
L12 2AP

Study participating centre
Charing Cross Hospital
Fulham Palace Road
London
United Kingdom
W6 8RF

Study participating centre
King's College Hospital NHS Foundation Trust
Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
Great Ormond Street Hospital for Children
Great Ormond Street
London
United Kingdom
WC1N 3JH

Study participating centre
St George's Hospital
St George's University Hospitals NHS Foundation Trust
Blackshaw Road
Tooting
London
United Kingdom
SW17 0QT

Study participating centre
National Institute of Neurology and Neurosurgery
University College London Hospital
University College London Hospitals NHS Foundation Trust
250 Euston Road
London
United Kingdom
NW1 2PG

Study participating centre
The Royal London Hospital
Barts Health NHS Trust
80 Newark Street
London
United Kingdom
E1 2ES

Study participating centre
Manchester Children's Hospital
Oxford Road
Manchester
United Kingdom
M13 9WL

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

Study participating centre
James Cook University Hospital
Marton Road
Middlesbrough
United Kingdom
TS4 3BW

Study participating centre
Royal Victoria Infirmary
Queen Victoria Road
Newcastle upon Tyne
United Kingdom
NE1 4LP

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

Study participating centre
Royal Hallamshire Hospital
Glossop Road
Sheffield
United Kingdom
S10 2JF

Study participating centre
University Hospital Southampton
Southampton University Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre

Royal Stoke University Hospital
Newcastle Road
Stoke-on-trent
United Kingdom
ST4 6QG

Study participating centre
University Hospital of Wales
Heath Park
Cardiff
United Kingdom
CF14 4XW

Study participating centre
Bristol Royal Hospital for Children
Paul O'Gorman Building
Upper Maudlin Street
St Michael's Hill
Bristol
United Kingdom
BS2 8BJ

Study participating centre
Sheffield Childrens Hospital
Western Bank
Sheffield
United Kingdom
S10 2TH

Study participating centre
Queen Elizabeth Hospital Birmingham
Mindelsohn Way
Edgbaston
Birmingham
United Kingdom
B15 2GW

Study participating centre
Queen's Hospital
Rom Valley Way
Romford

United Kingdom
RM7 0AG

Study participating centre
Leeds General Infirmary
Great George Street
Leeds
United Kingdom
LS1 3EX

Sponsor information

Organisation
University of Edinburgh

ROR
https://ror.org/01nrxwf90

Organisation
NHS Lothian

ROR
https://ror.org/03q82t418

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype

National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
Current Individual participant data (IPD) sharing plan as of 22/04/2024:

A de-identified version of the dataset used for analysis with individual participant data and a data dictionary will be available for other researchers to apply for use 1 year after publication, via ECTUdatashare@ed.ac.uk. Written proposals will be assessed by members of the Edinburgh Clinical Trials Unit Portfolio Management committee, and a decision made about the appropriateness of the use of data will be made. A data sharing agreement might need to be put in place before any data are shared.

———

Previous Individual participant data (IPD) sharing plan:

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request. Data access requests will be reviewed by the Chief Investigator and the Edinburgh Clinical Trials Unit (Rustam.Al-Shahi@ed.ac.uk). Researchers will be asked to outline in their request to use the data the purpose for which it is being requested. Study participants will be invited to consent to the use of their de-identified data, brain imaging and blood sample in future research. It has not been decided at this point what data will be available and for how long. Researchers using the data will be responsible for seeking the relevant approvals for the research.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		18/04/2024	22/04/2024	Yes	No
Protocol article		09/08/2023	11/08/2023	Yes	No
HRA research summary			28/06/2023	No	No
Other publications		18/04/2024	30/05/2024	Yes	No
Participant information sheet	Participant information sheet version 1.0	11/11/2025	11/11/2025	No	Yes
Statistical Analysis Plan		08/12/2022	22/04/2024	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes