BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-075187
Article Type:	Protocol
Date Submitted by the Author:	28-Apr-2023

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Keywords:	Neurosurgery < SURGERY, Stroke < NEUROLOGY, NEUROSURGERY, Paediatric neurology < NEUROLOGY, Adult neurology < NEUROLOGY, Clinical Trial

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

Protocol version:

Published summary of V2.0 (22 March 2021)

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Keywords:

Cavernous Malformation, Cavernoma, Randomised controlled trial, Neurosurgery, Stereotactic radiosurgery, Protocol

Registration: ISRCTN registration number 41647111

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Number of words in abstract: 266/300

Word Count: 4000/4000

Number of references: 27

Number of figures: 1

Number of tables: 1

Number of supplementary files: 6

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ABSTRACT

Introduction: The top research priority for cavernoma, identified by a James Lind Alliance Priority setting partnership was “Does treatment (with neurosurgery or stereotactic radiosurgery) or no treatment improve outcome for people diagnosed with a cavernoma?” This pilot randomised controlled trial (RCT) aims to determine the feasibility of answering this question in a main phase RCT.

Methods and analysis: We will perform a pilot phase, parallel group, pragmatic RCT involving approximately 60 children or adults with mental capacity, resident in the UK or Ireland, with an unresected symptomatic brain cavernoma. Participants will be randomised by web-based randomisation 1:1 to treatment with surgery (neurosurgery or stereotactic radiosurgery) and medical management versus medical management alone, stratified by pre-randomisation preference for type of surgery. In addition to 13 feasibility outcomes, the primary clinical outcome is symptomatic intracranial haemorrhage or new persistent/progressive focal neurological deficit measured at six monthly intervals. An integrated QuinteT recruitment intervention (QRI) evaluates screening logs, audio recordings of recruitment discussions, and interviews with recruiters and patients/parents/carers to identify and address barriers to participation. A Patient Advisory Group has co-designed the study and will oversee its progress.

Ethics and dissemination: This study was approved by the Yorkshire and The Humber – Leeds East Research Ethics Committee (21/YH/0046). We will submit manuscripts to peer reviewed journals, describing the findings of the QRI and the CARE pilot trial. We will present at national specialty meetings. We will disseminate a plain English summary of the findings of the CARE pilot trial to participants and public audiences with input from, and acknowledgement of, the Patient Advisory Group.

Registration: ISRCTN registration number 41647111

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This pilot trial addresses the top uncertainty about the management of brain cavernoma.
- Extensive patient, carer and public involvement in the prioritisation of the study question, protocol design, study oversight, support for participants, and understanding of barriers to participation.
- A QuinteT recruitment intervention (QRI) is refining approaches to participant recruitment and consent processes to maximise participation.
- Patients will not be blinded to treatment allocation. This introduces potential risks of performance bias. We will minimise information bias by blinded outcome adjudication.

INTRODUCTION

Symptomatic brain cavernomas are diagnosed in approximately 160 people in the UK annually and cause intracranial haemorrhage and epilepsy.[1–3] Systematic reviews of treatments for cavernomas from 2019 and 2022 have identified only observational studies.[4–7] A randomised controlled trial (RCT) is required to determine whether treatment with surgery or stereotactic radiosurgery (SRS) improves outcome, compared with medical management alone, for patients with symptomatic brain cavernoma.[8] We aim to conduct Cavernomas: A Randomised Evaluation (CARE) pilot trial to address this. This paper is a published summary of the full protocol (Supplementary material 1).

Objectives

The primary objective is to assess the feasibility of performing a definitive main phase of a RCT comparing medical management to medical and surgical management (with neurosurgery or SRS) for improving outcome for people with symptomatic brain cavernoma. Secondary objectives are: (1) to set up a collaborative network of patient advocacy organisations and professional representatives at neuroscience centres in the UK and Ireland; (2) to understand recruitment processes and barriers and optimise informed consent and recruitment as part of a QuinteT recruitment intervention (QRI); and (3) conduct the CARE pilot trial for approximately 60 people with symptomatic brain cavernoma.

METHODS AND ANALYSIS

Design

Two-arm, parallel group randomised feasibility trial with an integrated QRI comparing medical management to medical and surgical management stratified by preferred type of surgical management (figure 1).

Setting

Participants will be recruited in secondary care settings in the UK and Ireland, from a collaborative network of research sites, with input from the patient advocacy organisation Cavernoma Alliance UK (CAUK). Neurosurgery and follow-up will be conducted by regional neuroscience centres in the United Kingdom and Ireland. SRS will be performed at the National Centre for Stereotactic Radiosurgery in Sheffield or the Queen Square Radiosurgery Centre.

Eligibility

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.[9,10]
3. Clinical history attributable to a brain cavernoma of:[11,12]
    a. Symptomatic stroke due to haemorrhage or
    b. Symptomatic stroke due to a persistent or progressive non-haemorrhagic, or not otherwise specified, focal neurological deficit, or
    c. 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).

There is no time limit on when a patient may be recruited following the presentation and diagnosis of a brain cavernoma. Patients who have previously received surgical management

may be included so long as the symptomatic brain cavernoma has not been completely removed/obliterated.

Exclusion criteria

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

Co-enrolment

Inclusion in another RCT or observational study does not preclude participation in the CARE pilot trial as long as: participants are not overburdened; their inclusion would be unlikely to confound the CARE pilot trial's results or complicate attribution of serious adverse events and outcomes; the protocol of the other study does not preclude co-enrolment in the CARE pilot trial; and co-enrolment has been agreed with the Chief Investigators of all studies involved in co-enrolment.

Interventions

Patients randomised to medical and surgical management will receive neurosurgical excision or Gamma Knife SRS for their brain cavernoma, in addition to medical management (see comparator), according to what is available in standard clinical practice in the participant's health service.

Neurosurgical excision

Surgery will be undertaken by a consultant neurosurgeon who will be responsible for neurosurgical aspects of clinical care of that patient in CARE. The neurosurgical technique to

resect the cavernoma, including any operative adjuncts, will be that used by that consultant neurosurgeon in usual clinical practice and tailored to each patient according to the consultant neurosurgeon's discretion. Post-operative MRI scan performed within 72h of surgery is recommended, but not mandated, to confirm resection completeness.

Stereotactic radiosurgery

Standard clinical treatment protocols will be used to target the brain cavernoma but not surrounding haemosiderin. Treatment dosages will range from 12-16Gy depending on the size, shape, definition and site of the cavernoma. If intracerebral haemorrhage has occurred from the cavernoma, radiosurgery will be performed once the haematoma is judged to have been reabsorbed to minimise radiation exposure and treatment volume.

Comparator

Medical management constitutes standard medical care for brain cavernoma according to UK guidelines.[13] This may include anti-epileptic drug therapy, rehabilitation of neurological deficits, medical treatment of other neurological symptoms, psychological support, and MRI monitoring, according to clinicians involved in each patient's care.[11]

Ancillary and post-trial care

There are no provisions for ancillary or care for participants after the trial ends. Because interventions in the CARE pilot trial are provided in standard clinical practice aftercare will occur as standard practice.

QuinteT recruitment intervention

Phase 1

Prior to recruitment to study commencement, the QRI researcher qualitatively evaluated factors that may influence recruitment using focus groups comprised of healthcare professionals. The Patient, carer and public Advisory Group (PAG) provided further relevant

input. The QRI researcher observed all CARE pilot trial management group (TMG) and trial steering committee (TSC) meetings during protocol development.

During recruitment, the QRI researcher used screening logs, recruitment consultation recordings, interviews with CARE researchers and participants, and observation of trial meetings to investigate recruitment obstacles.

Phase 2

In parallel, findings from phase 1 were presented to the Chief Investigator (CI) and TMG and used to implement measures to improve recruitment and information provision.

Outcomes

Primary outcome

We will estimate these measures of feasibility:

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 are 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.

Secondary clinical outcomes

1. Death not due to a primary clinical outcome
2. Liverpool Seizure Severity Scale plus epileptic seizure frequency (number of seizures in the preceding four weeks, and attainment of one-year seizure freedom)
3. Modified Rankin Scale (mRS) score
4. National Institute of Health Stroke Scale Score (NIHSS; adult or paediatric)
5. EQ-5D-5L in adults and EQ-5D-Y in children
6. Karnofsky Performance Status (KPS) scale in adults and Lanksy Play-Performance Scale (LPS) in children

We will also collect data to estimate health service use and healthcare and socioeconomic costs during the entire duration of follow-up.

Participant timeline

A detailed timeline for data collection is provided in table 1.

Identification and screening

The research team will identify eligible patients from the UK and Ireland from multiple sources including data on admissions, outpatient appointments, referrals, and routine brain imaging. Diagnoses may be made at any time during or prior to recruitment. CAUK and affiliated groups will share study information and direct interested patients to Consultant Cavernoma Contacts at CARE pilot trial sites or to their own clinician.

Assessment of eligibility

Eligibility will be confirmed following discussion with the patient and a specialist in the type of treatment that is thought to be most effective for surgical management. Eligibility may be informed by multidisciplinary discussion.

Baseline visit and consent

There is no specific time window for approaching eligible patients for consent. The baseline visit and consent meeting may be conducted remotely or in person, at the time of randomisation or shortly prior to this. The research team will collect a venous blood sample of up to 10mL into an EDTA blood tube for genetic analysis during face-to-face visits.

Surgical treatment

It is expected, but not mandated, that surgical management will be delivered within three months of randomisation. Adherence will be assessed remotely by the Trial Coordinating Centre (TCC) at three months.

Qualitative interviews

In-depth interviews will be conducted by the QRI researcher in a sample of eligible patients from a variety of sites who have been approached to take part in the trial, including those accepting or declining participating, with priority given to those declining so as to explore reasons why. Purposive sampling will be used to identify patients. Interviews will take place within three months of the decision about participation.

Six-month follow-up visit

Participants will be asked to attend for their first six-month follow-up visit in person to perform a brain MRI. Outcome questionnaires will be completed. If not collected at the baseline visit, a blood sample will be obtained.

Six-monthly central follow-up

The TCC will subsequently perform six-monthly postal follow-up, including completion of outcome questionnaires, after checking the patient's vital status with their general practitioner. A researcher will contact non-responders electronically.

Long-term follow-up

We will ask study participants to consent to long-term follow-up, beyond the planned follow-up in the CARE pilot trial, including the use of routinely collected data in case the CARE pilot proceeds into a definitive main phase trial.

Table 1: Table of assessments.

Assessment	Identification and Screening	Baseline visit	Within 3 months of baseline	6-month local in-person follow-up	6-monthly central follow-up
Assessment of eligibility	X				
Screening end enrolment logs	X				
Consent to recruitment conversation recordings	X [1]				
Consent to qualitative interview	X				
Recording of patient recruitment conversations	X [2]	X [2]			
Consent to randomisation	X [3]	X [3]			
Demographic, clinical, socio-economic, medication, and radiographic data		X			
DNA sample		X			
Provision of diagnostic brain imaging		X			
Questionnaires		X		X	X
Randomisation		X			
Cavernoma surgical management			X		
Repeat brain MRI				X	
Outcomes and adverse events				X	X
Qualitative interview			X [4]		

1 – Research teams will be asked to capture verbal consent to audio-recordings of recruitment conversations when the approach is made to the participant. If this is not possible at this time, consent may be captured during subsequent recruitment conversations.

2 – Recordings of recruitment conversations with patients should be captured (as requested) wherever the CARE pilot trial is discussed (illustrated here but not restricted to Screening and Baseline Visit).

3 – Consent to participation in CARE may be collected at the Baseline Visit or in advance, during the Screening stage.

4 – Interviews with patients will take place within 3 months of being invited to take part in the trial.

Sample size

Approximately 240 people will be newly-diagnosed with symptomatic brain cavernoma during 18 months of recruitment.[3] We aim for all of these patients to be screened, but if 10% are missed and 10% decline to participate, we expect research teams to identify 190 patients. In the ARUBA trial, 226/726 (31%) of the eligible patients approached were randomised, so we expect at least 60 patients with symptomatic brain cavernoma to be randomised in the CARE pilot trial.[14]

Recruitment and consent

Eligible patients will be approached for recruitment during or following discussion with relevant secondary care specialists by research staff who are members of or affiliated to the clinical team and have undergone standardised training on trial-related procedures. An invitation letter may be sent to the patient in advance. Participant information leaflets and informed consent forms will be provided (supplementary material 2). For children, participant information leaflets are available for children 0-5 years old, 6-10 years old and 11-15 years old. The patient or the parent/guardian will be given as much time as they require to consider the study information and ask questions. Written informed consent may be recorded in paper forms, electronic copies thereof, or an online electronic consent form. Children aged 6-15 who can understand it will be given the option of providing assent.

When a child recruited into the trial reaches the age of 16 years (or 18 years old in the Republic of Ireland) and is therefore competent to provide consent, they should be re-consented at their next 6-month follow-up review. No further data will be collected until a signed consent form has been received.

Consent to be contacted for an interview exploring reasons for declining participation

Patients or their parents/carers who decline participation in the CARE pilot trial will be invited to consent to participate in an interview with the QRI researcher, exploring their experiences

of being approached and invited to participate. Where parents/carers consent to take part in an interview, the child/young person may attend and contribute.

Allocation

The consensus preference agreed between each patient and their clinician for neurosurgery or SRS, should randomisation allocate them to medical and surgical management, will be recorded at the baseline visit. If there is no clear preference and both are available, the patient will be randomly allocated to the type of surgical treatment they will receive, if allocated to surgical treatment (figure 1). Participants in these two strata will be assigned 1:1 to medical management or medical and surgical management using permuted blocks. Allocation will be concealed until participants are enrolled and assigned using central web-based randomisation. Patients will be informed of their treatment allocation following randomisation.

Blinding

Treatment allocation in the CARE pilot trial is not blinded, and is therefore open to participants, treating clinicians and research staff.

We will aim to keep outcome event assessors blind to treatment allocation. We will measure how often assessors are unblinded to treatment allocation during the process of event adjudication.

Data collection

Data concerning demographic, socioeconomic, medical history will be collected at baseline visit alongside the following patient-reported questionnaires: EQ5D-5L for adults and EQ5D-3Y for children and the Liverpool Seizure Severity Scale. Research staff will assess modified mRS score, NIHSS (adult or paediatric, if examined in person), KPS (adults) and LPS (children). Research teams will upload pseudo-anonymised DICOM images of diagnostic brain imaging for validation by a senior neuroradiologist to confirm or refuse eligibility.

In-depth interviews will be conducted by the qualitative researcher within three months of their participation decision.

Participants will be asked to attend their six-month follow-up visit in person for brain MRI to assess cavernoma presence and size, as a measure of treatment efficacy. As a minimum standard, T1-weighted, T2-weighted, and haem-sensitive gradient recalled echo or susceptibility-weighted imaging will be required. We will collect any other sequences performed. Images will be uploaded to the trial database and radiology department of each site will issue a clinical report. The research team will record clinical outcome events since randomisation and the details of surgery or SRS. Imaging studies performed because of an outcome event will be uploaded. The same patient reported questionnaires and standardised assessments used at baseline will be assessed at the first six-month visit.

After this the TCC will undertake six-monthly postal, telephone or email follow-up. Questionnaires will ask about disability, health-related quality of life, the occurrence of primary or secondary clinical outcomes, serious adverse events, the occurrence of surgical management of the brain cavernoma (described above), and relevant concomitant medications (anti-epileptic drugs, propranolol, antiplatelet agents, anticoagulant agents, and statins).

Retention

We aim for >95% retention of participants at six months with <10% treatment group switches or loss to follow-up.

Data management

Personal data will be processed by site research teams, the TCC at the University of Edinburgh (UoE) and qualitative research staff at the University of Bristol (UoB). Personal data

will be stored securely at sites and the secure trial database, hosted on a UoE server. Brain imaging will be managed by the Systematic Management, Archiving & Reviewing of Trial Images Service (SMARTIS) at the UoE. Audio-recordings will be securely transferred by qualitative research team members onto a secure drive at the UoB for long-term storage and analysis. Audio-recordings will be labelled with the participant identification number but not identifiable patient details. Audio-recordings will undergo targeted transcription and editing to protect respondents' anonymity. This data will be managed using NVivo software and stored on encrypted UoB drives.

Data analysis

Statistical analyses

In this pilot phase, analyses are descriptive only, and there will be no formal statistical tests. A detailed statistical analysis plan is described in Supplementary Material 3. We will quantify the number and proportions (with 95% confidence intervals to reflect their precision) of patients who are screened, eligible, approached, provide consent and are randomised.[15] We will construct a CONSORT diagram to summarise the distribution and progress of participants in the trial including the numbers of withdrawals.[16] We will report descriptively the following: the number and the proportion of the collaborating sites that take part and recruit participants to the CARE pilot trial; research teams' implementation of trial procedures measured by number and type of protocol deviation; the numbers of participants allocated to neurosurgery and stereotactic radiosurgery; adherence to the allocated intervention; completeness of follow-up that would be due at each 6-month interval; completeness of baseline, imaging and outcome data; the frequency of outcome events overall and in an intention-to-treat analysis keeping patients in the treatment group to which they were allocated during all available follow-up.

We will also compare descriptively the characteristics of eligible patients who are screened and do not participate in the CARE pilot trial to eligible patients who are randomised using the characteristics recorded on the screening logs to assess generalisability (external validity) and

any recruitment bias. We will assess measures of functional outcome, to assess which has suitable statistical properties for use in a main phase trial (such as lack of floor/ceiling effects). We will assess whether such a measure (like the method we have used before[17]) would be more suitable as a primary outcome in place of intracranial haemorrhage.

Quintet Recruitment Intervention data analysis

The QuinteT researcher will analyse data using the SEAR framework to observe differences between sites in recruitment patterns as new sites open.[15,16] Descriptive analyses will identify where patients are lost to recruitment and the reasons why.

Audio recordings of recruitment conversations will be sought from a purposive sample of recruiting sites. The audio recordings will explore information provision, management of patient treatment preferences, and randomisation decisions to identify recruitment difficulties and improve information provision. Analysis will employ content, thematic, and novel analytical approaches, including targeted conversation analysis and quanti-qual appointment timing.[18–21] Interview data will be analysed thematically using constant comparative approaches derived from Grounded Theory methodology.[22]

Findings from the QRI will be fed back to the CI and TMG, to determine a plan of actions to optimise recruitment.

Health economics analysis

The full health economic analysis plan (HEAP) is in supplementary materials 4.[23,24] We will collect self-reported health service use and social/economic outcomes using bespoke question sets that will inform future economic analyses.[17,25] If data collection is confirmed as feasible, then a previously developed decision model will be updated and further developed to incorporate data collected within this study to provide a putative estimate of cost-effectiveness and its drivers.[26] In the context of the CARE pilot trial, the health economics

objectives are to: (i) design and test an optimal mechanism for the capture of resource use and cost data in community NHS settings, NHS secondary care, participants' out of pocket expenses and carer costs, (ii) estimate expected effect size and variance of relevant outcomes including health-related utility and quality-adjusted life years, and (iii) identify and measure the potential cost implications of surgical management of cavernomas.

We will measure health-related utility, healthcare-related resource use and costs using participant questionnaires before randomisation and at each follow-up timepoint.[19,27] These costs will be ratified by the study team through scrutiny of the patient pathway in both arms of the trials using available medical records to populate CRFs. We will assign unit costs using standard national costing sources where available, or through consultation with relevant service business managers. Costs will be summarised from the perspectives of the NHS and personal social services, and wider society (including participants' and their carers' out-of-pocket costs and lost productivity).

Data Monitoring

Data monitoring committee

An independent Data Monitoring Committee (DMC) has been established to oversee the safety of participants in the trial. No formal interim analyses are planned during the conduct of the pilot trial.

Adverse events

Participants will be instructed to contact their local research team if any symptoms develop at any time after being randomised. Participants will be asked about the occurrence of serious adverse events (SAEs) whenever contact is made with them between randomisation and the final central six-monthly follow-up. SAEs may be identified via information from support departments e.g. laboratories. Only events which are clinical outcomes on the trial or are related to medical and surgical management and occur between randomisation and the final

6-month follow-up review will be recorded as adverse events (AEs) or SAEs. Only AEs or SAEs that are clinical outcomes or SAEs related to medical and surgical management will be recorded in the electronic case report form. If there is any doubt as to whether a clinical observation is an SAE, the event will be recorded.

When an SAE occurs, site research staff will review all documentation related to the event, assess whether an AE is an outcome in the trial and record all relevant information. If the AE is detected by central means of follow-up, the TCC will initiate the collection of this information but enlist the help of local site research staff. This information will be reported to the ACCORD (Academic and Clinical Central office for Research and Development) Edinburgh Research Governance & Quality Assurance (QA) Office immediately or within 24 hours. The Investigator will follow-up each event until resolution. All reports sent to ACCORD and any follow-up information will be retained in the Investigator Site File. The sponsor is responsible for reporting SAEs that are "possibly related" to the treatment allocation and "unexpected", to the REC within 15 days of becoming aware of the event. The TCC will provide SAE line listings from ACCORD for circulation prior to DMC meetings.

Audit

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, ACCORD, research ethics committee review, and regulatory inspection(s). Risk assessment, if required, will determine if audit by the ACCORD QA group is required. If required, audit details will be captured in an audit plan.

ETHICS AND DISSEMINATION

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). Prior to study

commencement all required approvals were obtained, including that of the Yorkshire and The Humber – Leeds East Research Ethics Committee (REC; 21/YH/0046).

Protocol amendments

Any changes in research activity, except those necessary to remove a hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the CI. Amendments will be submitted to the sponsor for review and authorisation before being submitted to the appropriate REC and local Research and Development team for approval.

Data sharing

Following publication of the primary paper, a de-identified individual participant data set will be prepared for sharing purposes. All data requests should be submitted to the CI for consideration. Deidentified data collected during the QRI will be made available by the QuinteT research group to the CAUK. Other individuals wishing to access deidentified QRI data may apply to an independent committee.

Publication and dissemination

We will submit manuscripts to peer reviewed journals for open access publication. We will present our findings at meetings of relevant professional associations. We will disseminate a plain English summary of the findings of the CARE pilot trial to participants and public audiences. We will offer to present our project and its findings to the annual meetings of CAUK.

Insurance and indemnity

The UoE has insurance in place for negligent harm caused by poor protocol design by researchers employed by the UoE. 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. Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.

CONCLUSIONS

British and Irish Neurosurgery has this opportunity to demonstrate the feasibility of resolving the top uncertainty about brain cavernoma in a definitive main phase trial. Rapid site activation and engagement will be essential.

FUNDING

The CARE pilot trial is funded by the National Institute for Health and Care Research (NIHR128694), which requires publication of the trial protocol but had no other role in manuscript preparation or the decision to publish.

ROLES AND RESPONSIBILITIES

Trial co-ordinating centre: Prof Rustam Al-Shahi Salman, Dr Laura Forsyth, Dr Morag Maclean, Katherine Lewis, Dr Jacqueline Stephen, Professor Steff Lewis, Aileen Neilson, Dr Peter Hall, Garry Milne, Eleni Sakka, Chris Linsley, Dr Julia Wade and Debbie Alexander.

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DECLARATION OF CONFLICTING INTERESTS

PW declares institutional unrestricted educational grant funding for stroke reperfusion course from Stryker, Penumbra and Medtronic. MR declares that he is a Senior Clinician of the National Centre for Stereotactic Radiosurgery.

FIGURE LEGENDS

Figure 1: Participant flow diagram

SUPPLEMENTARY MATERIALS

1. Full CARE protocol v2.0 (22 March 2021)
2. Participant information leaflets and consent forms
3. Statistical analysis plan
4. Health economics analysis plan
5. Trial steering committee charter
6. Data monitoring committee charter

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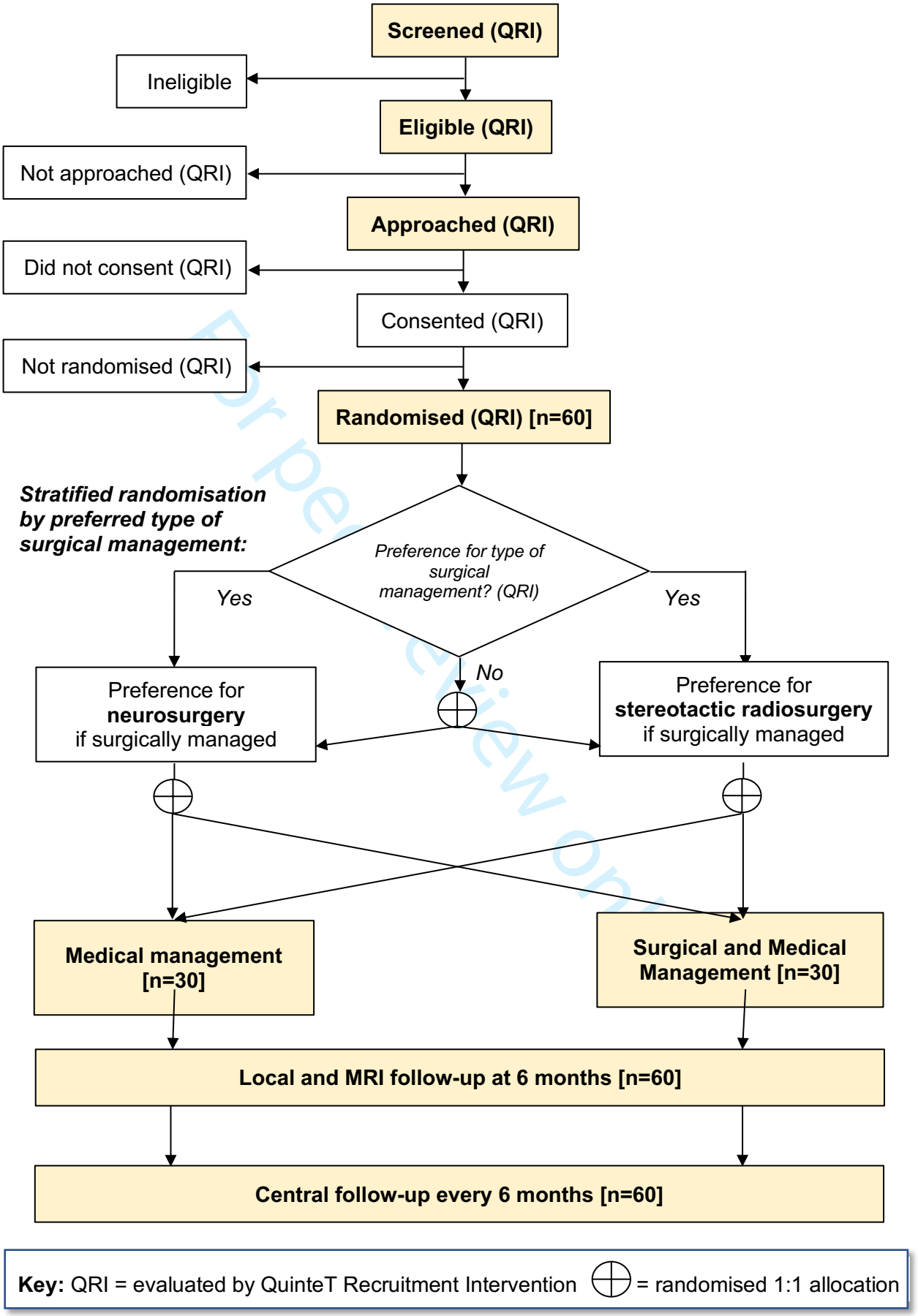

Academic and Clinical Central Office for Research and Development

Study Protocol

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

Co-sponsors	The University of Edinburgh and/or Lothian Health Board ACCORD The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ
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Funder	National Institute for Health Research Health Technology Assessment Programme
Funding Reference Number	NIHR128694

Chief Investigator	Prof Rustam Al-Shahi Salman
Sponsor number	AC20171
REC Number	21/YH/0046
Project registration	To be confirmed
Version Number and Date	V2.0 (22Mar 2021)

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LIST OF ABBREVIATIONS

95% CI	95% confidence interval
ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
CARE	Cavernomas A Randomised Effectiveness trial
CAUK	Cavernoma Alliance UK
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
DWI	Diffusion-Weighted Imaging
eCRF	Electronic Case Report Form
ECTU	Edinburgh Clinical Trials Unit
FLAIR	Fluid Attenuated Inversion Recovery
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH GCP	International Conference on Harmonisation for Good Clinical Practice
MRI	Magnetic Resonance Imaging
PAG	Patient, carer and public involvement Advisory Group
PI	Principal Investigator
PIL	Patient Information Leaflet
QA	Quality Assurance
QRI	QuinteT Recruitment Intervention
QuinteT	Qualitative Research Integrated within Trials
RaDAR	Rare Disease Ascertainment and Recruitment
REC	Research Ethics Committee
RCT	Randomised controlled trial
SAIVMs	Scottish Audit of Intracranial Vascular Malformations
SOP	Standard Operating Procedure
TCC	Trial Coordinating Centre

TMG	Trial Management Group
TSC	Trial Steering Committee

SCIENTIFIC ABSTRACT

This is a pilot randomised controlled trial (RCT) to assess the feasibility of conducting a definitive main phase RCT to address the research question commissioned by the NIHR HTA, "How effective is active treatment (with neurosurgery or stereotactic radiosurgery) versus conservative management in people with symptomatic brain cavernoma?" The terms ‘conservative management’ and ‘active treatment were used in the commission, but throughout this protocol we will refer to ‘conservative management’ as ‘medical management’ and ‘active treatment’ as ‘medical and surgical management’. We will assess: collaborator engagement; proportions of screened patients who are eligible, approached, consented, or randomised; barriers to recruitment; RCT procedure implementation; adherence; data completeness; outcome event rates; and generalisability.

At least 160 people with brain cavernomas are newly diagnosed after symptoms due to stroke or epilepsy in the UK each year. A James Lind Alliance Priority Setting Partnership found that the top research priority for cavernoma was, “Does treatment (with neurosurgery or stereotactic radiosurgery) or no treatment improve outcome for people diagnosed with a cavernoma?”. A RCT is required to answer this question, but systematic reviews and trial register searches have not revealed any such RCTs.

The Cavernomas A Randomised Effectiveness (CARE) pilot trial aims to:

1. Engage a collaboration of specialists and patient advocacy groups in the UK and Ireland.

2. Establish a pilot RCT, with an embedded qualitative study to understand the anticipated recruitment processes and address any barriers.

3. Assess the feasibility of performing a definitive main phase of the RCT.

The CARE pilot trial will include:

I. A pilot phase parallel group RCT for patients with symptomatic brain cavernoma, comparing medical management versus medical and surgical management (with neurosurgery or stereotactic radiosurgery), with randomisation stratified by preferred type of surgical management. Collaborators will keep screening logs to capture characteristics of patients screened, eligible, approached, consented and randomised. This prospective randomised open blinded end-point RCT will recruit ~60 participants.

II. A QuinteT recruitment intervention (QRI) will evaluate screening logs and incorporate qualitative research to understand recruitment processes and barriers and identify actions to address barriers.

We will use (I) and (II) to estimate the feasibility and generalisability of a definitive main phase of the CARE RCT by extending the UK collaboration to other patient support organisations and clinical communities elsewhere in the world.

PLAIN ENGLISH SUMMARY

A cavernoma is a cluster of blood vessels that form blood-filled ‘caverns’ in the brain that look like a raspberry. Cavernomas can bleed into the brain and cause a stroke. Cavernomas can also cause a seizure or epilepsy. About 160 people in the UK each year are diagnosed with a cavernoma that has caused symptoms. Stroke and seizure may lead to disability, handicap and occasionally death. In standard practice 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. Surgical management can cause death, disability, and handicap.

The pros and cons of medical management versus medical and surgical management are finely balanced. The most reliable way of finding out which management is best is to do a randomised trial, in which suitable patients are allocated to medical management or medical and surgical management at random. This has never been done with cavernomas, and this was the top priority identified by a Priority Setting Partnership for cavernoma.

The NIHR wants research to be done 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.

In three years, we will:

(1) Create a network of specialists to do this study. We will include the UK and Ireland patient support organisations for people with cavernoma (Cavernoma Alliance UK - CAUK) and doctors representing the relevant specialties at all the major hospitals specialising in decisions about cavernoma treatment in the UK and Ireland.

(2) Invite newly diagnosed patients to join a pilot phase of a randomised controlled trial. Of 190 people diagnosed with brain cavernoma in 18 months, we estimate that 60 of them will enrol in the randomised trial. We will study why some patients take part in the randomised trial and others don't. We will use this information to change the methods of the trial if recruitment to the randomised trial goes slowly.

(3) Estimate whether enough patients can be found for a full-scale randomised trial to be done to find out whether medical management or medical and surgical management of symptomatic brain cavernomas is best.

We involved people with cavernoma, carers, and representatives of CAUK with patients and carers on 6 July 2019: all approved the design of the project and the extent of patient and public involvement. The focus group wanted the trials to be as inclusive of patients as possible. The focus group recognised how the project would benefit from them contributing their 'lived experience' of brain cavernoma.

People with cavernoma, carers, and representatives of CAUK will also keep an eye on the research by forming an advisory group and meeting regularly to discuss the research. Two representatives of this group will join and advise the steering committee.

We will publish our findings in medical journals. We will work with CAUK to produce a plain English summary and circulate it to patients via newsletters, email, the web, and social media.

1 INTRODUCTION

1.1 BACKGROUND

1.1.1 What are brain cavernomas?

Cerebral cavernous malformations or 'cavernomas' are intracranial vascular malformations that are diagnosed using histopathological examination or magnetic resonance imaging (MRI). Although most cavernomas are solitary and sporadic, around one-fifth are multiple with autosomal dominant inheritance due to mutations in three genes (1), so there are implications for relatives as well.

Large brain MRI cohorts have shown that the asymptomatic prevalence of brain cavernomas is 0.16%, currently affecting ~106,000 people in the UK (2). Some of these people present to medical attention with symptoms such as epileptic seizures or stroke due to either intracranial haemorrhage or 'focal neurological deficits' anatomically related to the cavernoma that do not appear to be due to haemorrhage (3). The incidence of symptomatic cavernoma in the UK was 0.24 per 100,000 per year at the turn of the millennium (4), so approximately 160 people are newly-diagnosed with symptomatic cavernoma in the UK annually. The impact of cavernoma is disproportionately high in comparison to their frequency, because they are usually diagnosed in children and young adults of working age (4).

People with cavernoma face a considerable risk of recurrent stroke due to intracranial haemorrhage, which is reliably known over five years after diagnosis (5), but is likely to continue for their lifetime. The 5-year risk of intracranial haemorrhage ranges from ~3.8% for people with non-brainstem cavernoma who have presented without a stroke to ~30.8% for people with brainstem cavernoma who have presented with stroke due to intracranial haemorrhage or focal neurological deficit.

People with cavernoma who present with an epileptic seizure almost inevitably develop epilepsy within one year, and only half of people with cavernoma-related epilepsy achieve two-year seizure-freedom (6).

These persistent symptoms also cause economic consequences for people with cavernoma, carers, the NHS, social services, and lost productivity in the UK workforce (7).

1.1.2 What treatments are available in standard clinical practice for brain cavernoma?

'Medical management' constitutes standard medical care alone (e.g. prevention of epileptic seizures with anti-epileptic drugs, and rehabilitation of neurological deficits, according to UK guidelines (8)). This is the most frequently used management plan for people with brain cavernoma in the UK (9).

Surgical management of brain cavernoma with neurosurgical excision or stereotactic radiosurgery is used in standard clinical practice for some patients to try to prevent recurrent epileptic seizures and stroke due to intracranial haemorrhage or non-haemorrhagic focal neurological deficit, which can result in death, disability,

handicap, and psychological consequences for patients and carers (10). Surgical management is given in addition to medical management in standard clinical practice, as described above, so throughout this protocol we will refer to this as 'medical and surgical management' for clarity.

Medical and surgical management in the CARE pilot trial involves health technologies that are available in standard clinical practice in the UK and Republic of Ireland; these are either neurosurgical excision (performed by neurosurgeons at 37 regional adult or paediatric neuroscience centres) or stereotactic radiosurgery (using Gamma Knife performed at the National Centre for Stereotactic Radiosurgery in Sheffield or the Queen Square Radiosurgery Centre). Neurosurgical excision is the most frequently-used form of surgical treatment for brain cavernoma in the UK, but it involves a craniotomy and the risk of complications is much higher for some cavernomas deep within the brain or brainstem that cannot be accessed without traversing brain tissue with important functions. 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. There are some emerging technologies for the surgical treatment of brain cavernomas, including minimally invasive therapeutic approaches for brain cavernoma such as magnetic resonance thermography-guided laser interstitial thermal therapy, or stereotactic laser ablation (11). Although medical and surgical management in the CARE pilot trial will continue to be neurosurgical excision or Gamma Knife stereotactic radiosurgery plus medical management, we will collect details of each type of surgical treatment used after randomisation to allow us to quantify the use of emerging technologies.

Medical and surgical management can have complications that can be fatal or disabling (9; 12; 13), and there are few reliable data about the benefits and risks of medical management versus medical and surgical management (8; 14; 15), so most patients have medical management (9).

Although drugs like propranolol, antiplatelet agents, anticoagulant agents and statins are not licensed for the treatment of brain cavernoma, some clinicians may use them off-label for patients who are unsuitable for medical and surgical management because these drugs may have disease-modifying effects (16).

1.1.3 What evidence supports medical management vs. medical and surgical management of brain cavernoma?

A search of ClinicalTrials.gov trial register on 17 November 2020 using the terms, "cavernoma OR cavernous angioma OR cavernous malformation" revealed five RCTs of drug therapies for brain cavernoma, but no completed, ongoing, or planned RCTs comparing medical management with medical and surgical management.

In several systematic reviews of observational cohort studies comparing medical management to medical and surgical management of brain cavernoma, or one form of surgical management to another, there were no studies at low risk of bias that demonstrated sufficiently "dramatic" associations between medical management versus medical and surgical management of brain cavernoma and clinical outcomes that would make a RCT unnecessary (14; 17).

We performed or updated (to 2018-2019) several systematic reviews and meta-analyses including:

i. observational cohort studies that compared medical and surgical management involving stereotactic radiosurgery or neurosurgery against medical management in a concurrent or historical control group and reported clinical outcome (14; 18)

ii. observational cohort studies without comparison groups reporting clinical outcomes after either medical management (5), neurosurgery (9; 19), or stereotactic radiosurgery (18; 19); and
iii. decision analysis comparing all management strategies using a Markov model with a time horizon of five years (20)

The best available evidence from observational studies comparing medical management with medical and surgical management is summarised in a table (see 1.1.4 below) and in more detail in the following paragraphs.

1.1.3.1 Neurosurgery versus medical management

There are seven observational cohort studies that compare neurosurgery and medical management (9; 21; 22; 23; 24; 25; 26). The best available comparative data on an entire incident brain cavernoma population found neurosurgery to be associated with harm over five years (hazard ratios 2.2-3.6) (9)), although other comparative studies restricted to brainstem/deep cavernomas have suggested both harm (risk ratios 1.9-7.8) and benefit (risk ratios 0.5-0.6) on the risk of intracranial haemorrhage over 4-6 years (21; 22; 23; 24), but the long-term difference in risk is unknown and might favour neurosurgery.

1.1.3.2 Stereotactic radiosurgery versus medical management

In the only observational cohort study comparing stereotactic radiosurgery with medical management at one hospital in Korea (27) (see table below), stereotactic radiosurgery might have been harmful, but the risk ratio was incalculable because of the paucity of outcomes. Indirect comparisons imply that stereotactic radiosurgery might be superior to medical management over five years. In a systematic review and meta-analysis of 30 cohort studies of patients undergoing stereotactic radiosurgery for brain cavernoma (median 61% of whom had brainstem cavernoma and median 91% of whom had presented with intracranial haemorrhage), during a median follow-up of 48 (IQR 35-62) months after stereotactic radiosurgery, the annual incidence of the composite of death, intracranial haemorrhage or focal neurological deficit was 3.6% (95% CI 3.17-4.16) (18). Using these data to estimate the five-year risk (16.9%) after stereotactic radiosurgery and comparing the risk indirectly to the cumulative 5-year risks of intracranial haemorrhage with medical management that range from ~18% to ~31% for comparable patient groups (5), suggests that stereotactic radiosurgery might be superior to medical management over five years. A systematic review of stereotactic radiosurgery restricted to brainstem cavernoma suggested that treatment was beneficial by comparing intracranial haemorrhage risks before and after treatment (13), but their findings are unreliable because they may simply reflect the untreated clinical course of brain cavernoma in which intracranial haemorrhage risk declines over time (5).

Our summary of the procedures, benefits and risks for patients and carers is also summarised in a table (see1.1.5 1.1.5 below).

1.1.4 Observational studies comparing medical management with medical and surgical management for brain cavernoma.

Study	Population	Medical management: Intervention	Medical and surgical management: Comparator	Outcomes / Time	Medical vs. medical and absolute &/or relative risk(s) of ICH
Neurosurgery vs. medical management					
Brain cavernomas in any location					
Moultrie *et al.* 2014 (9)	134 adults (40 had caused ICH/FND)	Surgery (n=25)	Medical management (n=109)	Functional outcome (at least 2 successive ratings of >1 on the mRS), or new ICH/FND during 5y follow-up	Functional outcome: 13/25 vs. 40/109 (**aHR 2.2, 95% CI 1.1–4.3**) ICH/FND: 8/25 vs. 17/109 (**aHR 3.6, 95% CI 1.3–10.0**)
Kida *et al.* 2015 (25)	78 adults (53 had caused ICH)	Surgery (n=29)	Medical management (n=49)	ICH during 3.8-4.6y follow-up	2/29 vs. 16/49 (**RR 0.6, 95% CI 0.1–2.6**)
Brainstem/deep cavernomas					
Esposito *et al.* 2003 (20)	30 adults (26 had caused ICH/FND)	Surgery (n=13)	Medical management (n=17)	ICH/FND over average 3.9y	6/13 vs. 1/17 (**RR 7.8, 95% CI 1.1–57.4**)
Mathiesen *et al.* 2003 (21)	68 adults (48 had caused ICH/FND)	Surgery (n=29)	Medical management (n=34)	ICH over average 4.6y	4/29 vs. 8/34 (**RR 0.6, 95% CI 0.2–1.7**)
Tarnaris *et al.* 2008 (22)	21 adults (17 had caused ICH/FND)	Surgery (n=6)	Medical management (n=15)	ICH over average 6.5y	3/6 vs. 4/15 (**RR 1.9, 95% CI 0.6–6.0**)
Huang *et al.* 2010 (23)	30 adults (30 had caused ICH/FND)	Surgery (n=22)	Medical management (n=8)	"Deterioration" over average 4y	3/22 vs. 2/8 (**RR 0.5, 95% CI 0.1–2.7**)
Brain cavernomas not in brainstem/deep locations					
Kivelev *et al.* 2009 (24)	33 adults (15 had caused ICH)	Surgery (n=18)	Medical management (n=15)	ICH over average 7.7y	0/18 vs. 4/15 (RR incalculable)
Stereotactic radiosurgery vs. medical management					
Yoon *et al.* 1998 (26)	41 adults with cavernomas in any location (20 had caused ICH/FND)	Gamma Knife stereotactic radiosurgery (n=22)	Medical management (n=19)	ICH, adverse radiation effects (ARE) over 2-3.5y	ICH: 2/22 vs. 0/19 (RR incalculable) ARE 5/22 vs. 0/19 (RR incalculable)

aHR = adjusted hazard ratio; ARE = adverse radiation effects; FND = focal neurological deficit; ICH = intracranial haemorrhage; mRS = modified Rankin Scale; RR = risk ratio (estimated from aggregate data).

		Neurosurgery	Stereotactic radiosurgery
What may be involved?	• Treat symptoms • Prevent seizures • Rehabilitation • Brain scan	• Treat symptoms • Prevent seizures • Rehabilitation • Brain scan	• Treat symptoms • Prevent seizures • Rehabilitation • Brain scan
		• Hospital admission for days • General anaesthetic • Opening in the skull • Operation to remove cavernoma • Follow-up brain scan • Must not drive for 6 months	• Hospital attendance for a day • Anaesthetic not needed • Head fixed in a temporary frame • Focussed radiation given once • Follow-up brain scans
What are the possible benefits?	• Bleed/stroke risk reduces as time passes • Avoids risks of neurosurgery or radiosurgery	• Risk of bleed/stroke lower if cavernoma removed • Less worry about symptoms returning	• Risk of bleed/stroke may be lower if cavernoma stabilised, but these benefits are uncertain • Less worry about symptoms returning

What are the possible risks?	• Future bleed/stroke due to cavernoma
	  ○ Can be mild
	  ○ May be disabling
	  ○ Rarely be fatal
	  ○ Risk higher for cavernoma in brainstem
	• Epileptic seizures, which may be difficult to control
	• Cavernoma remains in the brain, so the risks of stroke and seizure may never go away
	• Worry about symptoms returning
		• Bleed/stroke due to neurosurgery
		  ○ Can be mild
		  ○ May be disabling
		  ○ Rarely be fatal
		  ○ Risk higher for cavernoma in brainstem
		• Epileptic seizures may not go away
		• Complications of treatment (e.g. infection or damage to brain around the cavernoma)
		• Cavernoma may come back
			• Bleed/stroke despite radiosurgery
			  ○ Can be mild
			  ○ May be disabling
			  ○ Rarely be fatal
			  ○ Risk higher for cavernoma in brainstem
			• Epileptic seizures may not go away
			• Complications of treatment (e.g. damage to brain around the cavernoma)
			• Cavernoma not removed

1.1.5 Summary of procedures, benefits and risks with medical management or medical and surgical management for brain cavernoma

1.2 RATIONALE FOR STUDY

1.2.1 The therapeutic dilemma

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 medical management or medical and surgical management for brain cavernomas (8; 15). These uncertainties were confirmed by patients and carers in a James Lind Alliance Priority Setting Partnership in the UK, which found that the top research priority for cavernoma was, “Does treatment (with neurosurgery or stereotactic radiosurgery) or no treatment improve outcome for people diagnosed with brain or spine cavernoma?” (28).

Therefore, in 2018 the NIHR HTA commissioned research to address the question, “How effective is treatment (with neurosurgery or stereotactic radiosurgery) versus conservative management in people with symptomatic brain cavernoma?” The NIHR’s commissioning brief reported that feedback from experts suggested that a randomised controlled trial (RCT) with at least 10 years of follow-up would be needed to better guide clinical care and that it would be necessary to conduct a multinational trial in countries with similar healthcare settings to the UK to ensure sufficient numbers for a robust trial.

1.2.2 Understanding recruitment barriers with a QuinteT recruitment intervention (QRI)

Resolving this therapeutic dilemma is likely to be challenging because of the low incidence of symptomatic brain cavernoma despite a high prevalence, because the availability of surgical management varies in everyday clinical practice (8; 15), and because accumulated expertise in specialist centres has guided clinical practice hitherto despite the lack of high quality evidence (29). Recruitment to the CARE pilot trial is likely to remain challenging given the history of RCTs comparing medical management versus medical and surgical management of intracranial vascular malformations with invasive procedures (30; 31). The reasons for poor recruitment to such trials have not been studied, so qualitative research is needed to investigate the potential barriers to recruitment and optimise recruitment processes in the CARE pilot trial. Many RCTs experience recruitment challenges due to difficulties that recruiters have in explaining concepts like uncertainty, equipoise and randomisation (32). Discussions with members of our collaboration during the development of this proposal have raised concerns about clinical equipoise amongst neurosurgeons, partly due to treatment preferences according to the anatomical location of the brain cavernoma, concerns about exposing children to radiation, scepticism about the effects of stereotactic radiosurgery, and the availability of stereotactic radiosurgery in the NHS for brain cavernoma at only two sites in the UK (although patients may be referred from any hospital) (29). Also, patients may have treatment preferences (e.g. for less invasive procedures), and patient/family preferences may affect RCTs involving children in particular (33).

An integrated QRI 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 CARE pilot trial (32; 33; 34). Embedding a QRI allows the identification and understanding of generic and trial-specific recruitment challenges (35; 36; 37), and enables the development of tailored plans to address these issues. A QRI (38) has been integrated into over 30

RCTs, including trials comparing surgery and medical management (39) and there is observational evidence of the benefits associated with a QRI in at least five RCTs (40).

1.2.3 This feasibility study and pilot trial will inform the feasibility of a definitive main phase trial

The NIHR HTA commissioned a UK feasibility study and pilot phase RCT to demonstrate the ability to recruit enough patients to answer the research questions and sufficient numbers in the UK such that the trial results would be applicable to the NHS. The CARE pilot trial was funded by this NIHR HTA commissioned call. A decision about whether to proceed a definitive main phase trial will be made in light of the results of the CARE pilot trial.

1.2.4 Patient, carer and public involvement (PCPI)

Between August 2014 and November 2015 we worked with people with cavernoma, carers, and representatives of the patient support organisation Cavernoma Alliance UK (CAUK) on the Steering Group of the James Lind Alliance Priority Setting Partnership that identified and prioritised the topic of this application as the top priority for further research into cavernoma. Since November 2015, individuals in the Steering Group of the James Lind Alliance Priority Setting Partnership – including patients and carers – were involved in reviewing the commissioning brief for the NIHR HTA commissioned call for research. In May-June 2016, we worked with CAUK to gather the views of patients and carers who are members of the organisation, about research to address this top priority for further research into cavernoma. We consulted 731 CAUK members affected by cavernoma or parents/guardians of affected children, by emailing them a link to a web-based survey describing the CARE trial. 70% of respondents had not received surgical management for a cavernoma and a minority (28%) of these respondents indicated that they would not participate in the RCTs proposed. Between December 2018 and June 2019, we consulted representatives and members of CAUK, including patients with the condition, who have reviewed and shaped the design of the CARE pilot trial. In July 2019, all members of CAUK were invited by the Chief Executive of the organisation to participate in a focus group on 6th July. Four carers, six patients, the Chief Executive Officer of CAUK and the Chief Investigator (CI) attended the meeting. This focus group of patients, carers, and family members considered the overall design of this project. The main themes of the discussion were: (1) The group recognised that, "many people have had to make difficult decisions without the information they need" and that in addressing this "difficult dilemma", their involvement could improve participation by contributing their 'lived experience' of brain cavernoma to the clinical experience of the co-applicants and the planned qualitative research; (2) The group approved the extent of the patient and public involvement that is planned; (3) The group wanted the CARE pilot trial to be as inclusive of patients as possible. In particular, they wanted the CARE pilot trial to include patients who have: (a) first presented with symptoms or been diagnosed some time ago, (b) multiple cavernomas (one of which might have been treated), and (c) partially treated cavernoma (for whom there is uncertainty about further treatment); (4) All participants approved the project's design. In particular, they approved a choice of the safest treatment according to cavernoma location, using the "wealth of experience" of the clinical community in the UK, permitting patient preferences, and allowing treatment if needed during follow-up; (5) The group accepted that participants would receive standard care; (6) The group asked not only that the project should include a diverse sample of patients with brain cavernoma, but

also that the analyses should account for this diversity (e.g. age, time since symptoms, single vs. multiple cavernoma, and genetic mutations).

2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary objective

Assess the feasibility of performing a definitive main phase of a RCT comparing medical management to medical and surgical management (with neurosurgery or stereotactic radiosurgery) for improving outcome for people with symptomatic brain cavernoma.

2.1.2 Secondary objectives

- Set up a collaboration of the patient advocacy organisations for cavernoma in the UK and Ireland and representatives of clinical neurology, neurosurgery, and stereotactic radiosurgery at neuroscience centres throughout the UK and Ireland.
- Evaluate screening logs and conduct qualitative research with patients and clinicians to understand recruitment processes and barriers, as well as actions to address any barriers, as part of a QuinteT recruitment intervention (QRI) to optimise informed consent and recruitment.
- Conduct the CARE pilot trial for approximately 60 patients with symptomatic brain cavernoma, comparing medical management of the brain cavernoma versus medical and surgical management (neurosurgery or Gamma Knife stereotactic radiosurgery) for improving outcome.

2.2 OUTCOMES

2.2.1 Primary outcome

We will estimate these measures of feasibility to inform the extent to which international cooperation would be needed to recruit an adequate sample size in a CARE definitive main phase RCT, and what proportion of participants might be recruited from the UK during the study:

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?

2.2.2 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.

2.2.2.1 Intracranial haemorrhage

The definition of an intracranial haemorrhage attributable to brain cavernoma is, “a clinical event involving both acute or subacute onset symptoms (any of headache, epileptic seizure, impaired consciousness, new/worsened focal neurological deficit referable to the anatomic location of the cavernous malformation as well as radiological, pathological, surgical, or rarely only cerebrospinal fluid evidence of recent extra- or intra-lesional haemorrhage. The mere existence of a haemosiderin halo, or solely an increase in cavernoma diameter without other evidence of recent haemorrhage, are not considered to constitute haemorrhage” (3).

2.2.2.2 New persistent/progressive focal neurological deficit

The definition of a non-haemorrhagic focal neurological deficit attributable to brain cavernoma is, “a new or worsened focal neurological deficit referable to the anatomic location of the brain cavernoma, which may present with other clinical features of intracranial haemorrhage, but without evidence of recent blood on timely brain imaging or pathological examination, or examination of the cerebrospinal fluid. These cases may be accompanied by an increase in cavernoma diameter alone or oedema on brain MRI (3).

The definition of a focal neurological deficit (not otherwise specified) attributable to brain cavernoma is identical to non-haemorrhagic focal neurological deficit, with the exception that pathological investigation, cerebrospinal fluid examination, or timely brain imaging have not been performed at all or at the correct time to establish whether haemorrhage, oedema, or cavernoma growth underlie the clinical deterioration (3). These focal neurological deficits may be persistent (lasting >24 hours, and staying static or improving), or progressive (lasting >24 hours with further deterioration) (3).

New persistent/progressive focal neurological deficits attributable to brain cavernoma treatment may be referrable to the anatomic location of the brain cavernoma (e.g. haemorrhage after neurosurgical treatment, or radionecrosis from stereotactic radiosurgery) or referrable to other regions of the brain (e.g. intracranial abscess following neurosurgical excision).

2.2.3 Secondary clinical outcomes

During the CARE pilot trial, investigators will collect data on the risk of several clinical primary and secondary outcomes to inform the design of a main phase RCT. The following secondary clinical outcomes will be measured at each 6-month follow-up review:

1. Death not due to a primary clinical outcome
2. Liverpool Seizure Severity Scale plus epileptic seizure frequency (number of seizures in the preceding four weeks, and attainment of one-year seizure freedom)
3. Modified Rankin Scale (mRS) score
4. National Institute of Health Stroke Scale Score (adult or paediatric)
5. EQ-5D-5L in adults and EQ-5D-Y in children
6. Karnofsky Performance Status (KPS) scale in adults and Lanksy Play-Performance Scale (LPPS) in children

We will also collect data to estimate health service use and healthcare and socioeconomic costs during the entire duration of follow-up.

2.2.4 Feasibility metrics proposed to the funder

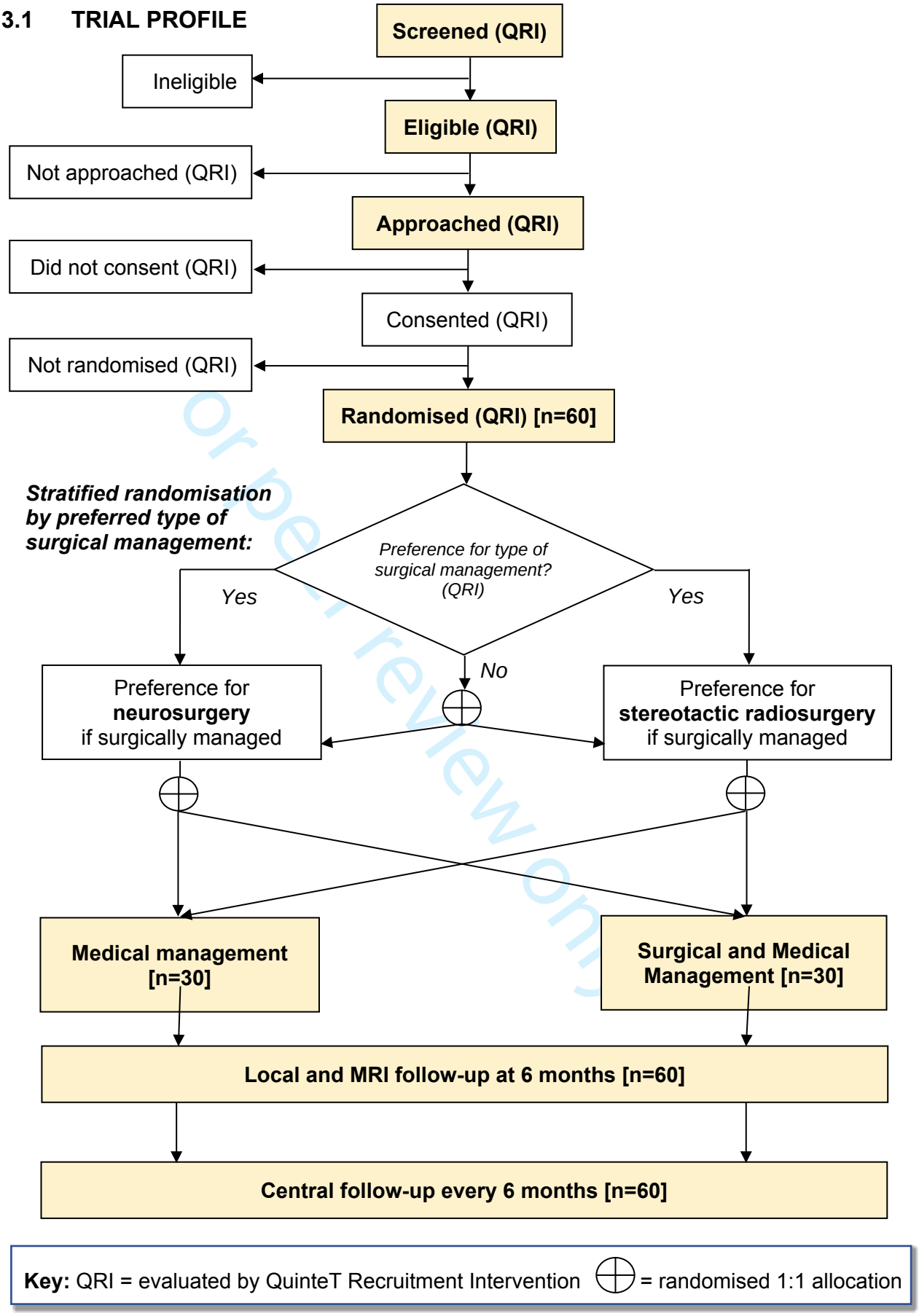
The NIHR HTA has been provided with the following criteria for success, although these are not specific secondary outcomes of the CARE pilot trial:

- At least 30 sites in the UK and Ireland collaborate
- Project delivered according to the major milestones identified in the NIHR HTA project management plan
- Recruitment to within 10% of target
- Brain cavernoma radiographic diagnosis confirmed by expert neuroradiologist review in >95% of participants recruited
- Retention of >95% of participants at six months
- <10% treatment group switches or loss to follow-up
- QuinteT recruitment intervention is associated with an improvement in recruitment
- CARE definitive main phase trial appears feasible and affordable

3 STUDY DESIGN

The CARE pilot trial is a two-arm, parallel group randomised feasibility trial which 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 outcomes for people with symptomatic brain cavernoma. An integrated QRI aims us 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 CARE pilot trial (32; 33; 34). Participants will be recruited in secondary care settings in the UK and Ireland, from a collaborative network of research sites, with input from the patient advocacy organisation CAUK. Randomisation will allocate participants to groups in a 1:1 ratio, stratified by preferred type of surgical management, but if there is no clear preference for the type of surgical management, and both are available, the patient will be allocated to either neurosurgery or stereotactic radiosurgery (see section 3.1).

3.1 TRIAL PROFILE



3.1.1 QuinteT recruitment intervention

The QuinteT recruitment intervention (QRI) has been presented as two distinct stages for clarity (data collection followed by feedback and training). In reality these are likely to overlap or run in tandem. For instance, new avenues of enquiry may emerge through feedback meetings, which can be a route to investigating recruitment difficulties in their own right. Insights into recruitment can emerge at any point during the RCT and instigate further investigations or intervention.

3.1.1.1 Phase 1

3.1.1.1.1 Before the CARE pilot trial begins recruitment

The QuinteT researcher will conduct a qualitative evaluation of what may influence recruitment during study set-up, combining evidence from previous QuinteT recruitment interventions (35; 36; 37; 38; 39; 40) and training programmes (41; 42), with data collected from patient and professional groups involved in CARE.

Qualitative work will include focus groups with healthcare professionals to explore views on eligibility and equipoise. Healthcare professionals' views will be explored in online workshops, to which we will invite relevant clinical members of the Trial Management Group (TMG), 'Consultant Cavernoma Contacts' and investigators at collaborating sites. These workshops will explore differences in views between individuals and clinical specialties regarding equipoise and identify criteria to determine patient suitability for neurosurgery or stereotactic radiosurgery, previously identified by the study team as difficult to operationalise. Discussions will also cover patient pathways into the trial, processes and management options for those declining participation, what each intervention arm involves, including potential risks and benefits, plans for follow up within the CARE pilot trial and possible advantages and disadvantages of taking part. We will organise these workshops with clinicians to maximise attendance, convenience, and efficiency by holding them virtually. The work described in this paragraph is for information only and is covered by a separate Research Ethics Committee (REC) approval (University of Bristol, Faculty of Health Sciences Research Ethics Committee Reference 111186). Qualitative work involving focus groups with healthcare professionals is therefore not covered under this protocol.

Insights into patient views to inform development of patient-facing materials, inform the design of the pathway into the trial and provide insight into the acceptability of participation in the CARE pilot trial will be obtained through the QuinteT researcher observing all CARE pilot trial Patient, carer and public involvement Advisory Group (PAG) meetings at which such issues are discussed.

A QuinteT researcher will observe all TMG and TSC meetings during which the study protocol is developed and finalised, with a focus on discussions and final presentation of equipoise and eligibility criteria.

Insights from focus groups with professionals and observation of the TMG, TSC and PAG discussions will inform the content of patient-facing information for the CARE pilot trial and site initiation visits for recruiters. The QuinteT team will provide guidance for recruiters to present CARE pilot trial information to eligible patients, carers and families during site training and initiation (see section 16.2.5.1). Guidance will raise recruiter awareness of key 'hidden' challenges when trying to recruit patients to trials comparing medical management with medical and surgical management and how these can be addressed (35; 42), as well as including insights into particular issues identified as relevant to the CARE pilot trial in how to deal with

preferences and convey equipoise between medical management and medical and surgical management.

3.1.1.1.2 During CARE pilot trial recruitment

As recruitment to the CARE pilot trial begins, recruitment processes will be investigated in-depth at study sites as they open. A QuinteT researcher will use a multi-faceted, flexible approach using triangulation of the following data to investigate site-specific or more general recruitment obstacles (34): screening logs (section 5.3); recording of recruitment consultations between recruiters and patients (section **Error! Reference source not found.**); in-depth interviews with members of the TMG, recruiters, and participants (section 9.4.3); review of study documents (section 9.4.5) and observation of monthly TMG meetings (section 9.4.4).

3.1.1.2 Phase 2

Findings from phase 1 will be presented to the CI and TMG. If recruitment difficulties are evident across the trial or at particular sites, the CI/TMG and QuinteT team will formulate a 'plan of action' to improve recruitment and information provision. The specific plan implemented will be grounded in the findings from analysis of the data above, with its format dependent on the nature of the recruitment barriers identified (see section 16.2.5.1).

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

We aim to enrol approximately 60 participants over an estimated 18 months at approximately 45 sites in the UK and Ireland. Patient follow-up will end approximately 6 months after recruitment finishes.

4.2 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 (15; 43)
3. Clinical history attributable to a brain cavernoma of:
    a. Symptomatic stroke due to intracranial haemorrhage (3), or
    b. Symptomatic stroke due to a persistent or progressive non-haemorrhagic, or not otherwise specified, focal neurological deficit (3), or
    c. Epileptic seizure(s) meeting the definition of definite or probable cavernoma-related epilepsy (44)
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).

There is no upper time limit on when a patient may be recruited following the symptomatic presentation and diagnosis of a brain cavernoma.

Patients with multiple brain cavernomas, at least one of which has been symptomatic and not undergone removal/obliteration by surgical management, may be included.

In the case of prior surgical management (with neurosurgery or stereotactic radiosurgery), patients with a symptomatic brain cavernoma that has not been completely removed/obliterated by prior surgical management may be included.

4.3 EXCLUSION CRITERIA

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

4.4 CO-ENROLMENT

Inclusion in another RCT or observational study does not preclude participation in the CARE pilot trial as long as: participants are not overburdened; their inclusion would be unlikely to confound the CARE pilot trial's results or complicate attribution of serious adverse events and outcomes; the protocol of the other study does not preclude co-enrolment in the CARE pilot trial; and co-enrolment has been agreed with the Chief Investigators of all studies involved in co-enrolment. Research staff should obtain permission to enrol patients who are participants in other trials from the CI. A record of participants who are known to have been co-enrolled in other studies will be maintained by the TCC.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING AND SCREENING PARTICIPANTS

For a patient to be eligible for the trial, the patient and doctor must be uncertain about medical management or medical and surgical management of the symptomatic brain cavernoma. In standard clinical practice, decisions about medical management or medical and surgical management of symptomatic brain cavernomas are usually made with patients and neurologists or neurosurgeons, following discussions at multi-disciplinary meetings that may involve any or all of neurologists, neurosurgeons, stroke physicians, and radiologists. We expect uncertainty about medical management or medical and surgical management to be established during discussion between a patient and their doctor. In clinical practice, multidisciplinary meetings involving neurologists and neurosurgeons may confirm this uncertainty as well as suitability for either type of surgical management; sometimes, these multidisciplinary meetings manage this uncertainty by arriving at a consensus opinion, but investigators should note that this may make recruitment to the CARE pilot trial less likely.

The principal investigator (PI), or another clinician with delegated responsibility, is responsible for confirming eligibility for the trial, however delegated research team members can identify eligible patients. Research team members delegated this role should be members of, or affiliated to, the clinical care team. These people may identify potentially eligible patients using several sources at their site, including but not limited to data on admissions, outpatient appointments, referrals, and brain imaging that record:

- New diagnoses of symptomatic brain cavernoma made in everyday clinical practice during the recruitment period.
- Diagnoses of symptomatic brain cavernoma made at any time before the recruitment period, identified by searches of clinical or imaging databases, or clinicians' own records.
- Referrals from colleagues at other hospitals in the UK and Ireland.

Verification of eligibility will require delegated research staff to access patient medical notes.

The TMG will apply to use the Association of British Neurologists' Rare Diseases Ascertainment and Recruitment platform (RaDAR; https://www.theabn.org/general/custom.asp?page=radar), which is used by neurologists to indicate that they have seen a patient with a specified rare neurological disease (such as brain cavernoma). Once a neurologist notifies RaDAR that they have seen a patient, the neurologist will be sent the patient information leaflet about the trial to send to the patient, who can be referred to their local trial site if they are interested in discussing participation.

CAUK (and affiliated groups such as Cavernoma Ireland and Cavernoma Scotland) will share information about the trial through their website, social media platforms and any other communications channels used by them. Patients who contact, or are members of, one of the patient support organisations will be made aware of the CARE pilot trial and informed about what the CARE pilot trial involves by a CAUK member of staff. If these patients are interested in finding out more and being screened for their eligibility, CAUK may direct them to information about a Consultant Cavernoma Contact at an appropriate CARE pilot trial site. The role of CAUK will be provision of information to patients; patients will be advised to speak with their clinician about decisions related to their medical care. CAUK will record the number of patients who they identify as potentially suitable for the CARE pilot trial and suggest referral to a Consultant Cavernoma Contact.

The CI and other members of the TMG will raise awareness of the trial amongst the clinical community through presentations at conferences and meetings. This could result in referral of patients to CARE pilot trial recruitment sites from other hospitals in the UK and Ireland.

5.2 APPROACHING AND CONSENTING PARTICIPANTS

Patients in the UK and Ireland will be approached and invited to take part in adult and paediatric neurology, neurosurgery, and stroke services in secondary care, or one of the stereotactic radiosurgery services that are commissioned to provide stereotactic radiosurgery for cavernoma (29). Eligibility may have been determined by a multidisciplinary discussion, but eligible patients should be approached for recruitment to the CARE pilot trial during or after consultation with a specialist in the type of treatment that is thought to be most effective for the surgical management of the brain cavernoma. Delegated research staff involved in approaching eligible patients should be members of, or affiliated to, the clinical care team.

Potential adult participants or the parent/guardians of potential paediatric participants may approached in person or by telephone (or another technology that supports remote consultations e.g. NHS Near Me). An invite letter may be sent in advance of approaching the patient. The short and supplementary PIL will be used to introduce and discuss the trial.

There is no specific time window for approaching eligible patients for their consent (see section 4.2 above), but they should be approached whenever uncertainty arises about whether to pursue medical management or medical and surgical management of a symptomatic brain cavernoma. The oral explanation given should be performed by the PI or another member of the research team delegated to perform this task and must cover all the elements specified in the relevant PIL and ICF. The patient or the parent/guardian will be given as much time as they require to consider the study information and given every opportunity to ask questions.

The PI or another clinician with delegated responsibility, is responsible for confirming eligibility for the trial, ensuring informed consent is obtained and that the informed consent form (ICF) is signed and dated by all parties before randomisation and any protocol-specific procedures are carried out. Local research staff should follow the laws that govern consent procedures in their jurisdiction. Members of the research team will have undergone standardised training on trial-related procedures. Health Research Authority guidance on applying a proportionate approach to seeking consent has been followed (45). Adult patients lacking mental capacity to consent for themselves will not be included in this trial (see section 4.2). If an adult patient loses mental capacity during the course of the research and subsequently regains mental capacity, their consent to continue taking part in the trial will be confirmed.

Face to face informed consent discussions with potential participants may not be feasible (e.g. due to the COVID-19 pandemic). In order to avoid patients making additional trips to hospital, written informed consent may be recorded in the following ways (in addition to being done in person):

1. Remotely

When completed remotely, the patient should return the signed form, or a scan or legible photograph of all sections of it, to a research team member at the recruiting site by email, by post or in person..

2. Electronically (using an online form)

The following options may be employed to complete consent electronically:

- The consent form may be completed and signed electronically where an approved mechanism is available such as DocuSign.
- An electronic consent form, generated via the trial database. Participants providing consent using the online form will be required to enter a typewritten signature.

In both cases, the form should be countersigned by the research team member taking consent. There is no requirement that the counter-signature date match the date of the participant signature but the counter-signatory must be satisfied that the consent is genuine.

Regardless of the method of consent, patients or parent/guardians will be provided with information in-person, by post or by email to consider before providing consent.

The information will be discussed with the patient or parent/guardian as outlined above.

Confirmation of eligibility, consent, and the version of the PILs used should be recorded in the participant's paper and/or electronic medical records for any future source data verification, including the date of consent (and child's assent if relevant), that the participant received the PILs, who obtained consent, and signed and dated confirmation that the patient was eligible for enrolment.
Patients will be given the opportunity to consent to any or all of the following:

- Consent to recording their recruitment consultation(s) to inform the QuinteT recruitment intervention
- Consent to taking part in an interview to inform the QuinteT recruitment intervention
- Consent to participate in the CARE pilot trial

5.2.1 Consent to the QRI

All eligible patients who are approached to take part will be invited to take part in an interview with the qualitative researcher about their experiences of being invited to join the CARE pilot trial.

Some study centres will also be involved in audio-recording conversations where the CARE pilot trial is discussed (including conversations held in person and by remote methods). In study centres selected to participate in collecting audio-recordings, eligible patients will be invited to consent to these conversations being audio-recorded, before discussion of the CARE pilot trial begins. Information on the rationale and process for recording recruitment discussions is covered in the relevant CARE PIL. Missed recordings of recruitment conversations are not required to be recorded as protocol deviations.

Participants will be given sufficient time to consider whether they wish to take part in the QRI. Participants will only be consented if they and the local research team feel they have had enough time to consider and ask questions about the QRI. Consent to take part will be documented on the relevant verbal and/or written consent forms. Written consent to audio-recordings will cover all future recruitment discussions. Patient participation in both interviews and audio-recordings is optional. If written consent to record conversations is given, the recordings will be transferred to the University of Bristol for analysis (see section 10.3.1). If no written consent form is received, all recordings for that participant will be deleted, no further recordings will be made and no invitation to interview extended.

5.2.2 Consent to participate in the CARE pilot trial

5.2.2.1 Adults

The participant will be asked to complete a consent form. The research team member and the participant should each sign and date the ICF to confirm that consent has been obtained. Written informed consent should always be sought from the participant where possible. If this is not possible because the participant cannot write, the member of the research team can gain witnessed verbal consent. The participant should receive a copy of the completed ICF, a copy should be filed in the patient's medical records and the original ICF should be filed in the investigator site file (ISF) along with the randomisation form. The participant should also receive a copy of the current PIL.

5.2.2.2 Children

Childrens' PILs are available for children 0-5 years old, 6-10 years old and 11-16 years old. Children aged 6-10 and 11-15 who are capable of understanding it will be given the option of providing assent.

The parent/guardian should receive a copy of the current parent/guardian short and supplementary PIL and appropriate children's PIL. If the parent/guardian wishes for the child to participate in the CARE pilot trial, then they will be asked to sign the ICF. Both the parent/guardian and the person delegated to take consent will each sign and date the ICF. The parent/guardian should receive a copy of the fully completed ICF, a copy should be filed in the patient's medical records and the original ICF should be filed in the investigator site file (ISF) along with the randomisation form. The same would apply in the case of assent being given.

5.2.2.2.1 Children and young people in England, Wales and Northern Ireland

Health Research Authority (HRA) guidance states (46):

- "There is no statute in England, Wales or Northern Ireland governing a child's right to consent to take part in research other than a Clinical Trial of an Investigational Medicinal Product (CTIMP), i.e. consent for non-CTIMPs. However common law presumes that young people aged between 16 and 18 are usually competent to give consent to treatment."
- "Case law suggests that if a young person has sufficient understanding and intelligence to understand fully what is proposed, and can use and weigh this information in reaching a decision (i.e. they are 'Gillick competent'), he or she can give consent to treatment."
- ''In the absence of law relating specifically to research, it is commonly assumed that the principle of 'Gillick competence' can be applied not only to consent for treatment, but also to consent for research."
- ''When a young person is believed to be competent, consent from those with parental responsibility is not legally necessary. However, the involvement of parents in decision-making is encouraged in most circumstances."
- "When a child or young person is not competent, the Children Act and the Children Act (Northern Ireland) Order permits parents (and those with parental responsibility) to consent to medical treatment on their behalf. Consent of only one parent is required."

5.2.2.2.2 Children and young people in Scotland

Health Research Authority (HRA) guidance states (47):

- "There is no specific provision in Scots law governing a child's right to consent to take part in research, other than a Clinical Trial of an Investigational Medicinal Product (CTIMP), i.e. consent for non-CTIMPs."
- In the case of medical treatment, "young people aged 16 and over are deemed to be competent to give consent for medical treatment unless proven otherwise. Children and young people under 16 have a statutory right to give consent to surgical, medical or dental procedures or treatments if they are deemed, by a medical practitioner, to be competent to do so."
- "It is commonly accepted that we can extrapolate a child / young person's right to give consent for treatment, to give them the right to give consent to

take part in non-CTIMP research. It is commonly assumed that they also have a legal right to object to participation."

- "The Children (Scotland) Act permits parents (or those with parental responsibility) to give consent on behalf of a young person under 16 who is not competent. Consent of only one parent is required."

The above guidance will be followed for this trial in relation to participants in Scotland under the age of 16.

5.2.2.2.3 Children and young people in the Republic of Ireland

Consent will be obtained in line with ICH-GCP and all applicable laws and regulations. In line with the HSE National Consent Policy, consent to a child's participation in a study must be obtained from a parent/legal guardian for all paediatric participants under 18 years old (48). Whenever the child has sufficient competence to provide it, a child's assent must be sought in a child-appropriate manner.

5.2.2.2.4 Re-consenting paediatric patients

When a child recruited into the trial reaches the age of 16 years (or 18 years old in the Republic of Ireland) and is therefore deemed competent to provide consent, they should be re-consented if still willing to participate at their next 6-month follow up review. No further data will be collected until a signed consent form has been received.

5.2.3 Consent to be contacted for an interview exploring reasons for declining participation

Patients or their parents/carers who decline participation in the CARE pilot trial will be invited to consent to take part in an interview with the QRI researcher, exploring their experiences of being approached and invited to take part in the study. Where parents/carers consent to take part in an interview, it will be acceptable for the child/young person to attend and contribute if they choose.

5.3 SCREENING AND ENROLMENT LOGS

Research teams at each site will use screening logs to record non-identifying demographic and clinical details of patients who are screened, including: initials, age (years), sex, brain cavernoma diagnosis (yes vs. no), brain cavernoma location (brainstem vs. other), type of brain cavernoma presentation (symptomatic [type] vs. not symptomatic), prior treatment of brain cavernoma, patient certainty about brain cavernoma treatment (yes vs. no, with preferences), clinician certainty about cavernoma treatment (yes vs. no, with preferences), eligibility for the CARE pilot trial (yes vs. no, with reasons for ineligibility), whether approached to take part (yes vs. no, with reasons for not approaching), whether consent was given to the CARE pilot trial (yes vs. no, with reasons for declining), and whether the patient was randomised in the CARE pilot trial (yes vs. no, with reasons for not being randomised and preferred management outside of CARE).

Collection of this information is essential to fulfilling the objectives of the feasibility study that will determine whether a CARE definitive main phase trial could proceed

(see section 2.2.1 above). The proportions of screened patients who are eligible, approached, agree to take part, and randomised (see trial profile, section 3.1) will be quantified to identify points in the recruitment pathway at which patients are being 'lost' to recruitment. Screening logs will be analysed according to the SEAR (Screened, Eligible, Approached, Randomised) framework (49).

5.4 RANDOMISATION

5.4.1 Randomisation procedures

If consent to randomisation in the CARE pilot trial is provided, complete baseline data must be collected by the research team at the baseline visit before randomisation. These data include demographic, clinical, and radiographic information, as well as the consensus preference agreed between each patient and their clinician for neurosurgery or Gamma Knife stereotactic radiosurgery should randomisation allocate them to medical and surgical management (if there is no clear preference for the type of surgical treatment, and both are available in clinical practice, the patient will be randomly allocated to neurosurgery or Gamma Knife stereotactic radiosurgery; see section 3.1). Participants in these two strata will be assigned 1:1 to medical management or medical and surgical management using permuted blocks. Allocation will be concealed until participants are enrolled and assigned by using central web-based randomisation.

A detailed description of the randomisation system including details on block size is held in the statistics master file by Edinburgh Clinical Trials Unit (ECTU).

5.4.2 Treatment allocation

The participant, or the parent/guardian of paediatric participants, and research team at the recruiting site will be notified of the assigned treatment allocation after randomisation.

5.4.3 Blinding (masking)

Treatment allocation in the CARE pilot trial is not blinded (masked), and is therefore open to participants, the clinicians caring for them and local research staff.

We will aim to keep outcome event assessors blind to treatment allocation. We will aim to measure how often assessors are unblinded to treatment allocation during the process of event adjudication.

5.5 WITHDRAWAL OF PARTICIPANTS

Participants are free to completely withdraw, or discontinue any individual component of the study, at any point or a participant can be withdrawn by the PI. In the case of loss of mental capacity in adult participants during the trial, researchers will follow the appropriate local regulations and guidance regarding loss of mental capacity in research (noting that these differ between nations, see below). The participant will remain in the trial unless withdrawn by their representative. Data collected until the time of withdrawal will be retained. If withdrawal occurs, the primary reason for

withdrawal must be documented in the participant's case report form (CRF). The participant will have the option of withdrawal from any or all of:

- consent to be contacted about other research studies
- consent to recording of recruitment conversation(s)
- consent to complete a recorded interview with the QuinteT researcher
- DNA sample provision
- allocated treatment policy
- in-person follow-up
- brain MRI at 6-months
- participant postal follow-up questionnaires
- participant follow-up questionnaire conducted by telephone
- long-term follow-up using record linkage
- use of de-identified data or brain imaging by other research studies

5.5.1 Loss of mental capacity in adult participants in England and Wales

In England and Wales, regulations advise that advice should be sought from the participant's representative on whether the research should be carried out in relation to the participant and what they think the wishes and feelings of the participant would be if they had mental capacity (50).

Where the participant representative (consultee) requests that the participant who has lost mental capacity be withdrawn, a delegated member of the research team will discuss with this person to determine if they think the participant should be withdrawn taking into consideration what the wishes and feelings of the participant would be thought to be if they still had the mental capacity to decide for themselves. If it is agreed that the participant should be withdrawn from the trial, the appropriate trial form will be completed.

5.5.2 Loss of mental capacity in adult participants in Scotland

In Scotland, there is no specific legal provision for adults who lose capacity while taking part in non-CTIMPs. We will respect the participant's original consent to take part however will also consider the participant's representative's views.

Where the participant representative (nearest relative, welfare attorney or welfare guardian) requests that the participant who has lost mental capacity be withdrawn, a delegated member of the research team will discuss with this person to determine if they think the participant should be withdrawn taking into consideration what the wishes and feelings of the participant would be thought to be if they still had the mental capacity to decide for themselves. If it is agreed that the participant should be withdrawn from the trial, the appropriate trial form will be completed (51).

5.5.3 Loss of mental capacity in adult participants in Northern Ireland

In Northern Ireland, section 138 of Part 8 of the Mental Capacity Act (Northern Ireland) 2016 applies which states that consent can be considered to endure provided that the study has not changed significantly since consent was given. We will respect the participant's original consent to take part however will also consider the participant's representative's views.

Where the participant representative (consultee) requests that the patient who has lost mental capacity be withdrawn, a delegated member of the research team will

discuss with this person to determine if they think the participant should be withdrawn taking into consideration what the wishes and feelings of the participant would be thought to be if they still had the mental capacity to decide for themselves. If it is agreed that the participant should be withdrawn from the trial, the appropriate trial form will be completed (52).

5.5.4 Loss of mental capacity in adult participants in the Republic of Ireland

Health Service Executive Policy (48) states that:

"Outside of clinical trials, there is currently no legal framework for a person who lacks decision-making capacity to participate in research. In the absence of any such legal regulations, it is recommended that as a matter of best practice the same principles should apply to both clinical trials and other forms of research. This means that consent for participation in any form of research on behalf of an adult lacking decision-making capacity must be obtained from the person's legal representative".

The same policy defines 'legal representative' as:

"…a person not connected with the conduct of the trial who by virtue of his/her family relationship with an adult lacking decision-making capacity, is suitable to act as the legal representative and is willing and able to do so or (if there is no such individual) a person who is not connected with the conduct of the trial, who is a solicitor nominated by the relevant health care provider.".

6 COMPARATOR

Medical management constitutes standard medical care alone for brain cavernoma, according to UK guidelines (8). This may include anti-epileptic drug therapy to prevent epileptic seizures (e.g. following the recommendations of the Surgical Task Force of the ILAE Commission on Therapeutic Strategies (44)), 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. Provision of these interventions varies because of the extent of the evidence to support their use, and their availability in everyday clinical practice around the UK and Ireland according to the nature of regional and national healthcare systems.

Some clinicians arrange repeat brain MRI for patients with brain cavernoma. This may be done with good reason in order to confirm the diagnosis following intracranial haemorrhage, in case of diagnostic doubt, to guide treatment decisions, or to investigate new symptoms as recommended by recent guidelines (15). But in other cases repeat brain MRI is done to 'monitor' brain cavernomas to reassure patients, although the evidence that this strategy is beneficial is lacking.

7 INTERVENTION

Medical and surgical management in the CARE pilot trial is defined as neurosurgical excision or Gamma Knife stereotactic radiosurgery for brain cavernoma, in addition to all components of medical management described in section 6 above. These interventions will be accessed and delivered according tco what is available in standard clinical practice in the participant's health service.

It is expected (but not mandated by the trial protocol) that surgical management will be delivered within 3 months of randomisation to the trial.

7.1 Neurosurgical excision

Surgery 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.

It is recommended (but not mandated by this protocol) that a post-operative MRI scan is performed within 72 hours of surgery and used along with the surgeon's assessment to confirm complete resection or incomplete resection. A copy of this scan will be taken by the research team and uploaded to the scan database for the trial.

7.2 Stereotactic radiosurgery

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 (29).

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.

If ICH has occurred from the cavernoma, Gamma Knife stereotactic radiosurgery will be carried out once the haematoma is judged to have been reabsorbed to minimise radiation exposure and reduce volume of treatment as much as possible.

8 STUDY ASSESSMENTS

8.1 STUDY ASSESSMENTS

This section outlines the study assessments to be completed by the research team. The schedule of study assessments is provided on the following page.

8.1.1 Table of assessments

Assessment	Identification and Screening	Baseline visit	Within 3 months of baseline	6-month local in-person follow-up	6-monthly central follow-up
Assessment of eligibility	X				
Screening end enrolment logs	X				
Consent to recruitment conversation recordings	X [1]				
Consent to qualitative interview	X				
Recording of patient recruitment conversations	X [2]	X [2]			
Consent to randomisation	X [3]	X [3]			
Demographic, clinical, socio-economic, medication, and radiographic data		X			
DNA sample		X			
Provision of diagnostic brain imaging		X			
Randomisation		X			
Questionnaires		X		X	X
Cavernoma surgical management			X		X
Repeat brain MRI				X	
Outcomes and adverse events				X	X
Qualitative interview			X [4]		

1 – Research teams will be asked to capture verbal consent to audio-recordings of recruitment conversations when the approach is made to the participant. If this is not possible at this time, consent may be captured during subsequent recruitment conversations.

2 – Recordings of recruitment conversations with patients should be captured (as requested) wherever the CARE pilot trial is discussed (illustrated here but not restricted to Screening and Baseline Visit).

3 – Consent to participation in CARE may be collected at the Baseline Visit or in advance, during the Screening stage.

4 – Interviews with patients will take place within 3 months of being invited to take part in the trial.

8.1.2 Screening

Potential participant identification and screening should be carried out as per sections 5.1 and 5.2.

Approached patients who decline to take part will be given the opportunity to take part in an interview to discuss why they decided not to participate as per section 5.2.3.

Research teams should complete screening and enrolment logs as per section 5.3.

8.1.3 Informed consent

It is likely that consent to participate in the CARE pilot trial will be captured during a clinical consultation between the patient and a clinician who is also a member of the CARE pilot trial research team. The consenting procedures outlined in section 5.2. will be followed.

8.1.4 Baseline visit

Baseline visits may be conducted remotely or in person, depending on patient, carer or parent/guardian preference, and restrictions on working practices. These visits will be conducted by research team staff who are members of, or affiliated to, the clinical care team.

Research team staff will collect the following data at the baseline visit from all study participants: demographics, socioeconomic characteristics (e.g. employment, education, and carer needs), medical history (including details of the type of presentation of the symptomatic brain cavernoma and family history) and medications (including drug therapy).

The patient reported questionnaires that should be completed are EQ5D-5L for adults or EQ5D-3Y for children and Liverpool Seizure Severity Scale (LSSS).

The patient should be assessed by the research team member (assisted by parent/guardian where required) using the following scales:

1. Modified Rankin Scale (mRS) score
2. National Institute of Health Stroke Scale Score (adult or paediatric) (if examined in person)
3. Karnofsky Performance Status (KPS) scale in adults and Lanksy Play-Performance Scale in children (LPS)

If the visit is done face to face, research team staff will collect a venous blood sample of up to 10mL from patients who consent into an EDTA tube for genetic analysis. Samples will be shipped immediately by first class post and in adherence with UN3373 guidelines to the central laboratory at the Edinburgh Clinical Research Facility.

The research team at each site is responsible for entering these data onto the study Electronic Case Report Form (eCRF). Once baseline data are complete, randomisation may proceed. After randomisation is performed, the PI and other research staff on the delegation log at the participant's site will be sent email

confirmation or randomisation and treatment allocation, with a reminder about the subsequent scheduled activities in the trial.

Research teams will upload the relevant pseudo-anonymised DICOM images of the brain imaging (including diagnostic brain MRI) that confirmed the mode of presentation and diagnosis of the symptomatic cavernoma to the trial imaging database. Images may also be copied to CD and posted to the brain imaging management team for upload. These scans will be stored for subsequent validation by a senior neuroradiologist to confirm or refute eligibility.

8.1.5 Three-month adherence check

The PI and research staff at a site where a participant was randomised will be sent an email prompt around three months after baseline to report whether surgical management was undertaken after randomisation, regardless of whether the participant was allocated to surgical management by randomisation. This will allow detection of cross-overs between the two arms of the trial.

Adherence to the randomised allocation will be assessed by comparing treatment allocation with the completion of the surgical management case report form. Lack of adherence to the randomised treatment allocation will not be recorded as a protocol deviation or violation.

8.1.6 Six-month local follow-up visit

Participants will be asked to attend for their first six-month follow-up visit in person in order to perform brain MRI (which will be permitted between 5-7 months after randomisation) to assess cavernoma presence and size as a measure of the efficacy of surgical management. These images should be uploaded to the trial imaging database or research teams may post CDs to the MRI management team for upload. The radiology department at each site will issue the clinical report of any brain MRI performed for the CARE pilot trial. A copy of MRI brain scans performed before or after surgical management (if performed) will be taken by the research team and uploaded to the scan database for the trial. A copy of the MRI performed on the day of treatment for patients undergoing stereotactic radiosurgery will be taken by the research team and uploaded to the database for the trial (or copied to CD and posted to the MRI management team for upload).

Research teams will record details of any clinical outcome events that have occurred since randomisation, whether surgical management was used, including specific operative techniques or methods of stereotactic radiosurgery. Although surgical management in the CARE pilot trial will continue to be neurosurgical excision or stereotactic radiosurgery, we will collect details of each type of surgical management used after randomisation to allow us to quantify the use of emerging technologies, such as minimally invasive therapeutic approaches for brain cavernoma such as magnetic resonance thermography-guided laser interstitial thermal therapy, or stereotactic laser ablation (41).

Imaging studies performed because of the occurrence of an outcome event will be collected by the research team and uploaded to the scan database for the trial.

The patient reported questionnaires that should be completed are EQ5D-5L for adults or EQ5D-3Y for children and Liverpool Seizure Severity Scale (LSSS).

The patient should be assessed by the research team member (assisted by parent/guardian where required) using the following scales:

1. Modified Rankin Scale (mRS) score
2. National Institute of Health Stroke Scale Score (adult or paediatric) (if examined in person)
3. Karnofsky Performance Status (KPS) scale in adults and Lanksy Play-Performance Scale in children (LPS)

If a blood sample for genetic analysis was not collected as the Baseline Visit, research team staff will collect a venous blood sample of up to 10mL from patients who consent into an EDTA tube. The sample will be shipped immediately by first class post and in adherence with UN3373 guidelines to the central laboratory at the Edinburgh Clinical Research Facility.

8.1.7 Six-monthly central follow-up visit

Thereafter, staff at the TCC, will perform six-monthly follow-up (+/- one month) by post in all patients who do not withdraw from follow-up in the CARE pilot trial, after checking the participant's vital status with their general practitioner. If a response is not received by the TCC within a fortnight, a research team member (based within ECTU) will contact non-responders and follow-up data by telephone or email.

Follow-up questionnaires will confirm participants' current domicile and general practitioner, and ask about disability, health-related quality of life, the occurrence of primary or secondary clinical outcomes, serious adverse events, and the occurrence of surgical management of the brain cavernoma (as described above). These questionnaires will also ask for information about relevant concomitant medications, such as anti-epileptic drugs. We will also record the use of drugs like propranolol, antiplatelet agents, anticoagulant agents and statins, which may have disease-modifying effects (49).

The patient reported questionnaires that should be completed are EQ5D-5L for adults or EQ5D-3Y for children and Liverpool Seizure Severity Scale (LSSS).

The patient should be assessed by the research team member (assisted by parent/guardian where required) using the following scales:

1. Modified Rankin Scale (mRS) score
2. Karnofsky Performance Status (KPS) scale in adults and Lanksy Play-Performance Scale in children

8.1.8 Patient Interviews

In-depth interviews will be conducted by the qualitative researcher with a sample of eligible patients who have been approached to take part in the trial (including those accepting or declining participation) (see section 9.4). Purposive sampling will be used to identify patients who have declined participation from a variety of study sites, to gain insight into study-wide and site-specific reasons patients may have for declining. Purposive sampling of patients accepting participation in the CARE pilot trial will also be considered if findings from analysis of recorded recruitment conversations indicates this will be helpful. Interviews will take place within three months of the decision about trial participation (see 8.1.1).

8.2 LONG TERM FOLLOW UP

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.

8.3 BRAIN MAGNETIC RESONANCE IMAGING

Participants who consent to be randomised should undergo repeat brain MRI once at six months (± one month) after randomisation.

Brain MRI is usually undertaken after surgical management in clinical practice, but not always during medical management. If a participant undergoes brain MRI with the required sequences as part of their routine clinical care before the 6-month local follow up visit, the research team will request the brain MRI and upload the scan to the trial imaging database. Otherwise, repeat brain MRI should be performed six months after randomisation (± one month), regardless of treatment allocation, treatment received, and timing of treatment, for research purposes.

As a minimum standard, T1-weighted, T2-weighted, and haem-sensitive sequences (gradient recalled echo or susceptibility weighted imaging) will be required within standard sequence parameters and with an acceptable slice thickness and voxel size. We will collect any other sequences performed (e.g. Fluid Attenuated Inversion Recovery (FLAIR) post-contrast, T1 or FLAIR, and Diffusion-Weighted Imaging [DWI] sequences) to ascertain the frequency of their use for follow-up of brain cavernoma in everyday clinical practice.

8.4 OUTCOME EVENT ADJUDICATION

Clinical outcomes including death and stroke-like events will be adjudicated by a member of the TMG using all available source data (with patient identifiers and any information about cavernoma treatment redacted by the research team before upload to trial database) including clinical correspondence, brain imaging reports, and death certificate. Brain imaging performed during follow-up will be reviewed by a consultant neuroradiologist. Outcome assessors will aim to remain blinded to the brain cavernoma treatment policy that was allocated at randomisation, and if possible any medical and surgical management of the brain cavernoma received. If blinding could not be maintained, this will be documented.

8.5 DNA SAMPLE STORAGE AND ANALYSIS

A venous blood sample of up to 10mL will be collected into an EDTA tube for genetic analysis. Samples will be shipped immediately by first class post and in adherence with UN3373 guidelines to the central laboratory at the Edinburgh Clinical Research Facility for DNA extraction and future analysis. This sample will be stored for subsequent investigation of genetic modifiers of treatment effect, which are currently unknown (1). The relevant approvals will be sought for future research involving these samples.

9 DATA COLLECTION

Data items to be collected are described in section 8. This section describes the methods of data collection.

9.1 SOURCE DATA DOCUMENTATION

Source documents are those in which information is recorded and documented for the first time. The location of source data collected from the CARE pilot trial participants is detailed in the CARE pilot trial Source Data Plan. Investigators will be required to retain paper copies of completed ICFs. Otherwise, clinical data will be entered directly into the eCRF by the research team and TCC staff based on information in the medical records, which will be regarded as source data.

9.2 CASE REPORT FORMS

Documents reflecting the data required at each study assessment will be made available to research teams, to support entry into the study database of: Screening Log, Consent to Contact form, Consent and Status Log, Baseline Visit CRF, 6-Month Follow-up CRF, Serious Adverse Events Log and Change of Status form. Site research teams will be responsible for transcribing these data into the database. Data will be transcribed by those staff delegated to do so on the delegation log held at site.

9.3 STUDY DATABASE

The study database will be created and maintained by ECTU. This database will be compliant with the relevant regulations and Sponsor Standard Operating Procedures (SOPs). Trained and delegated members of the research team will be given password-protected logins to the database. The data will be stored in a secure server in the University of Edinburgh.

9.4 QRI DATA COLLECTION

9.4.1 Screening log data

Screening logs will collect de-identified data on patients screened, identified as eligible, approached and accepting randomisation into the CARE pilot trial (see section 5.4) and identify points in the pathway where patients may be ‘lost’ to recruitment. Findings will guide data collection using the qualitative methods outlined below.

9.4.2 Recordings of recruitment conversations

Patients will be invited to consent to the recording of all conversations during which participation in the CARE pilot trial is discussed. These conversations provide insight into both how the study is presented to patients and how patients interpret that

information. Analysis of these conversations can reveal misunderstandings about that trial that can then be addressed in recruiter training.

9.4.3 Patient and staff interviews

A sample of eligible patients who have been approached to take part in the trial (including those accepting and declining participation) will be invited to take part in an in-depth interview with the qualitative researcher based at the University of Bristol. This interview will take place within three months of being invited to take part in the trial.

Interviews with patients will explore views on the presentation of trial information, understanding of study processes (e.g. randomisation), and reasons underlying decisions to consent or decline to participate in the CARE pilot trial. Numbers of interviews will be guided by the concept of 'data saturation' with final sample size (up to a maximum of 20 interviews) determined by the point at which three new interviews fail to shed insights.

Staff involved in the trial will also be invited to take part in an in-depth interview. Interviews with health professionals will use purposeful sampling. Interviews with staff will include members of the trial TMG, including the CI, and those closely involved in the design, management leadership and coordination of the trial (approximately n=4-8); clinicians or researchers involved in trial recruitment (approximately n=12-20).

Interviews with TMG members and investigators at sites will investigate their perspectives on the CARE pilot trial and experiences of recruitment (where relevant). Key topics explored will include views about the study design and protocol; understandings of the evidence on which the study is based; perceptions of uncertainty/equipoise in relation to the intervention arms; views about how the arms/protocol are delivered in clinical centres; methods for identifying eligible patients; views on eligibility, and examples of actual recruitment successes and difficulties.

Interviews will take place at a mutually convenient time by telephone or video-conferencing and will be recorded using University of Bristol approved methods for data capture and storage (this may include MS Teams and Zoom, depending on current policies).

9.4.4 Meetings

A QuinteT researcher will observe all TMG and TSC meetings during which the study protocol is developed and finalised, with a focus on discussions and final presentation of equipoise and eligibility criteria.

9.4.5 Trial documentation

The QRI team will continue to review the wording of patient information leaflets (PIL) and consent forms in line with any feedback from the above that indicates content that is unclear or potentially open to misinterpretation.

10 DATA MANAGEMENT AND TRANSFER

10.1 PERSONAL DATA

The following personal data will be collected as part of this research: contact details (including home address, telephone numbers, email address,date of birth and contact information for relatives/carers), demographic information (including age and sex), socioeconomic information, medical history (including prior symptoms from brain cavernoma, major co-morbidities, medication history, family history), and unique healthcare identifier (such as the Community Health Index [CHI] in Scotland, NHS Number, or equivalent in other nations). Unique healthcare identifiers will be collected to enable long term patient follow-up and ensure correct identification of patients when contacting GPs or sites for follow-up.

Personal data will be processed by site research teams, the TCC at the University of Edinburgh and qualitative research staff at the University of Bristol:

- Personal data will be stored at site by research teams on NHS computers (desktop and laptop). Computers will be password protected and kept in locked offices. All paper files containing personal data will be held in filing cabinets in NHS offices that will be locked when unattended. Study documentation will be accessed by the study team only.
- Personal data will also be entered into the secure trial database which will be hosted on a University of Edinburgh server and will be accessed by the TCC to perform 6-monthly follow-up with patients and long term follow up via record linkage.
- Contact information will be accessed by/passed to the qualitative researcher based at University of Bristol to contact patients for interview.
- Screening log data will be accessed by the qualitative researcher based at University of Bristol as part of the research.

Additional information on personal data in relation to the qualitative aspect of the trial is included in section 10.3.

10.2 BRAIN MRI SCANS

Diagnostic brain imaging will be managed by the Systematic Management, Archiving & Reviewing of Trial Images Service (SMARTIS) at the University of Edinburgh. We will establish a scan database (housekeeping system) using established models, to track all scan episodes, completeness and assessments; this will interface with the trial database. De-identified brain MRI scans will be uploaded to this database by research teams or by SMARTIS staff if CDs are posted to them. Scan collection, quality assurance, curation, and backup will be conducted by SMARTIS staff at the Brain Research Imaging Centre (BRIC), University of Edinburgh. Prof Phil White, or another neuroradiologist involved in the trial, will review the diagnostic and follow-up brain MR imaging using standardised review proforma derived from pre-existing validated work (Scottish Audit of Intracranial Vascular Malformations - SAIVMs).

10.3 QUINTET RECRUITMENT INTERVENTION

10.3.1 Recordings of recruitment conversations

Recruitment conversations will be recorded by a research team member using a method of secure data capture and storage in line with University of Bristol procedures (as outlined on the University of Bristol website). Audio-recordings will be transferred by secure data transfer by the approved qualitative research team members onto a secure drive at the University of Bristol for long-term storage and analysis. Audio-recordings will be labelled with the participant identification number; identifiable patient details will not be used.

Audio-recordings will be subject to targeted transcription and edited to protect the anonymity of respondent. Transcription will be undertaken by an approved transcription service/transcriber that has signed the necessary confidentiality agreements with the University of Bristol. Data will be managed using NVivo software and stored on encrypted drives at the University of Bristol, in line with the university's data storage policies and in line with GDPR legislation.

At the end of the study, audio-recordings will be kept for at least 10 years before they will be destroyed. Transcripts will be stored indefinitely in secure research data storage designated 'controlled access', so can only be accessed by approved individuals who are interested in conducting their own analyses of the data. These individuals will have to submit an application to do this, which will be assessed by an independent committee. However, all data will have identifiable information removed before they are made available, and there will be no way to identify any individuals mentioned in interviews/appointments.

10.3.2 Interviews

Approved qualitative research team members from University of Bristol will access participants' contact details via the trial database or be securely passed them by the research team for the purposes of contacting patients who have consented to interviews as part of the QRI. Team members will be provided with an individual user account for the database with restricted, password-controlled access.

Interviews with patients and staff will be recorded directly by the qualitative researcher using processes for secure data capture and storage in line with University of Bristol procedures (as outlined on the University of Bristol website). Recordings will be held on a secure drive with restricted access at the University of Bristol for long-term storage and analysis. Recordings will be labelled with the participant identification number; identifiable patient details will not be used. At the end of the trial, recordings will be held for a minimum of 10 years after which they will be destroyed.

Data from the QRI will be shared at the end of the trial as outlined in section 17.3.

10.3.3 QRI documentation

Paper or electronic documentation which is generated through the process of performing the QRI will be stored securely at the University of Bristol with access restricted only to approved personnel.

10.4 DATA CONTROLLER

The University of Edinburgh and NHS Lothian are joint data controllers.

10.5 DATA BREACHES

Any data breaches will be reported to the University of Edinburgh and NHS Lothian Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

11 STATISTICS AND DATA ANALYSIS

11.1 SAMPLE SIZE CALCULATION

Symptomatic brain cavernoma incidence data indicate that ~240 people would be newly-diagnosed during 18 months of recruitment (4). We aim for all of these patients to be screened, but if 10% are missed and 10% decline to participate, we expect research teams to identify ~190 patients. In the ARUBA trial, 226/726 (31%) of the eligible patients approached were randomised (30), so we expect ~60 patients with symptomatic brain cavernoma to be randomised in the CARE pilot trial.

11.2 PROPOSED STATISTICAL ANALYSES

In this pilot phase, analyses are descriptive only, and there will be no formal statistical tests.

We will quantify the number and proportions (with 95% confidence intervals to reflect their precision) of patients who are screened, eligible, approached, consent and are randomised. We will construct a CONSORT diagram to summarise the distribution and progress of participants in the trial including the numbers of withdrawals (50).

We will report descriptively the following: the number and the proportion of the collaborating sites that take part and recruit participants to the CARE pilot trial; research teams' implementation of trial procedures measured by number and type of protocol deviation; the numbers of participants allocated to neurosurgery and stereotactic radiosurgery; adherence to the allocated intervention; completeness of follow-up that would be due at each 6-month interval; completeness of baseline, imaging and outcome data; the frequency of outcome events overall and in an intention-to-treat analysis keeping patients in the treatment group to which they were allocated during all available follow-up.

We will also compare descriptively the characteristics of eligible patients who are screened and do not participate in the CARE pilot trial to eligible patients who are randomised using the characteristics recorded on the screening logs to assess generalisability (external validity) and any recruitment bias.

We will assess measures of functional outcome, to assess which has suitable statistical properties for use in a main phase trial (such as lack of floor/ceiling effects). We will assess whether such a measure (like the method we have used before (9)) would be more suitable as a primary outcome in place of intracranial haemorrhage.

11.3 QUINTET RECRUITMENT INTERVENTION DATA ANALYSIS

11.3.1 Screening and enrolment logs

The QuinteT researcher will analyse data using the SEAR framework to observe differences between sites in recruitment patterns as new sites open (51). Simple descriptive analyses will identify points in the recruitment pathway at which patients are lost to recruitment to the cohort or trials and the reasons why. Detailed eligibility and recruitment pathways will be compiled for sites, noting the point at which patients receive information about the study, which members of the clinical team they meet, and the timing and frequency of appointments. Recruitment pathways will be compared with details specified in the trial protocol and pathways from other sites to identify practices that are potentially more/less efficient. Numbers of eligible and recruited patients will be compared across sites and considered in relation to estimates specified in the grant application/study protocol. These data will be triangulated with qualitative findings (see below) to identify barriers and potential solutions to recruitment.

11.3.2 Recordings of recruitment conversations and interviews

Audio recordings of recruitment conversations will be sought from a purposefully sampled range of recruiting sites (showing higher and lower recruitment) to ensure maximum variation and recordings will be analysed by the QuinteT researcher. The audio recordings will be used to explore information provision, management of patient treatment preferences, and randomisation decisions to identify recruitment difficulties and improve information provision. Audio-recorded recruitment consultations will be subjected to targeted transcription with relevant sections first identified then transcribed and identifying data removed before fuller analysis. Analysis will employ content, thematic, and novel analytical approaches, including targeted conversation analysis (52) and quanti-qual appointment timing (the ‘Q-Qat method’) (53), as described in the QuinteT recruitment intervention protocol [24]. Interview data will be analysed thematically using constant comparative approaches derived from Grounded Theory methodology (54).

Findings from the investigation of recruitment to the CARE trials will be fed back to the CI, TMG, and collaborator Bauld, where appropriate, to determine a plan of actions to optimise recruitment to the pilot trials. Actions may include feedback to individuals or in groups as appropriate and will include template patient pathways, individualised or generic ‘tips’ sheets for recruiters and delivery of recruiter training. Group feedback and training will be timed to coincide with the meetings of professional associations mentioned above.

12 HEALTH ECONOMICS AND DATA ANALYSIS

We will collect self-reported health service use and social/economic outcomes using bespoke question sets that will inform future economic analyses (9; 10). If data collection is confirmed as feasible, then a previously developed decision model (20) will be updated and further developed to incorporate data collected within this study to provide a putative estimate of cost-effectiveness and its drivers. In the context of the CARE pilot trial, the health economics objectives are to: (i) design and test an optimal mechanism for the capture of resource use and cost data in community NHS

settings, NHS secondary care, participants' out of pocket expenses and carer costs, (ii) estimate expected effect size and variance of relevant outcomes including health-related utility and quality-adjusted life years, and (iii) identify and measure the potential cost implications of surgical management of cavernomas. We will measure health-related utility (55), healthcare-related resource use and costs using participant questionnaires before randomisation and at each follow-up timepoint (56). These costs will be ratified by the study team through scrutiny of the patient pathway in both arms of the trials using available medical records to populate CRFs. We will assign unit costs using standard national costing sources where available, or through consultation with relevant service business managers. Costs will be summarised from the perspectives of (a) the NHS and personal social services, and (b) wider society (including participants' and their carers' out-of-pocket costs and lost productivity).

13 ADVERSE EVENTS

The PI is responsible for the detection and documentation of events meeting the criteria and definitions detailed below. This task may also be carried out by another suitably qualified clinician in the research team at that site who has been delegated this role. Only clinical outcomes and relevant serious adverse events (SAE) related to medical and surgical management that occur after randomisation until the final 6-month follow-up review must be recorded in the eCRF. Participants will be instructed to contact their local research team if any symptoms develop at any time after being randomised.

13.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

An **adverse reaction** (AR) is any untoward and unintended response to an IMP which is related to any dose administered to that participant.

A **serious adverse event** (SAE), **serious adverse reaction** (SAR). Any AE or AR that at any dose:

- results in death of the clinical trial participant;
- is life threatening*;
- requires in-patient hospitalisation^ or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect;
- results in any other significant medical event not meeting the criteria above.

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

^Any hospitalisation that was planned prior to enrolment will not meet SAE criteria. Any hospitalisation that is planned post enrolment will meet the SAE criteria.

13.2 IDENTIFYING SAEs

Participants will be asked about the occurrence of SAEs wherever contact is made with them between randomisation and the final central six monthly follow up review. Open-ended and non-leading verbal questioning of the participant will be used to enquire about SAE occurrence. Only events which are clinical outcomes on the trial or are related to medical and surgical management will be recorded as AEs and SAEs. Participants will also be asked if they have been admitted to hospital, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an SAE, the event will be recorded. SAEs might also be identified via information from support departments e.g. laboratories.

13.3 RECORDING SAEs

When an SAE occurs, it is the responsibility of the PI, or another suitably qualified clinician in the study team who is delegated to record and report SAEs, to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. It is the PIs responsibility, or another suitably qualified clinician that has been delegated this role, to assess whether an AE is an outcome in the trial. The PI or delegated research team member will then record all relevant information in the CRF/AE log and on the SAE form (if the AE meets the criteria of serious). If the AE is detected by central means of follow-up, the TCC will initiate the collection of this information but enlist the help of local site research staff to acquire the relevant clinical and imaging information. Information to be collected includes type of event, onset date, clinical assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

13.3.1 Pre-existing medical conditions

Pre-existing medical conditions (i.e. existed prior to informed consent) should be recorded as medical history and only recorded as SAEs if medically judged to have worsened during the trial and meet the definition of an SAE.

13.3.2 Worsening of the underlying condition during the trial

Medical occurrences or symptoms of deterioration that are expected to be due to the participant's underlying condition should be recorded in the participant's medical notes and only be recorded as SAEs if medically judged to have unexpectedly worsened during the trial. Events that are consistent with the expected progression of the underlying disease should not be recorded as SAEs.

13.4 ASSESSMENT OF AEs AND SAEs

Each AE which may be a clinical outcome for the trial or may be related to surgical management must be assessed for seriousness, causality, severity and ARs must be assessed for expectedness by the PI or another suitably qualified clinician in the study team who has been delegated this role.

The CI may not downgrade an event that has been assessed by an Investigator as an SAE or a related and unexpected SAE, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate.

13.4.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 13.1.

13.4.2 Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the study intervention according to the definitions below.

Unrelated: where an event is not considered to be related to the treatment allocated at randomisation.

Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the treatment allocated at randomisation.

13.4.3 Assessment of Expectedness

If the AE is judged to be related to the study interventions, the Investigator will make an assessment of expectedness.

Expected: The type of event is expected in line with the treatment allocated at randomisation.

Unexpected: The type of event was not listed in the protocol or is not an expected clinical occurrence.

13.4.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE and record this on the CRF or SAE form according to one of the following categories:

Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.

Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: an event that prevents normal everyday activities.

Note: the term ‘severe’, used to describe the intensity, should not be confused with ‘serious’ which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

13.5 REPORTING OF SAEs

Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the ACCORD (Academic and Clinical Central office for Research and Development) Research Governance & Quality Assurance (QA) Office **immediately or within 24 hours**. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received.

The SAE form will be emailed to ACCORD via Safety@accord.scot. Only forms in a PDF format will be accepted by ACCORD via email.

The Investigator will follow up each event until resolution. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the investigator and request the missing information.

All reports faxed to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).

The sponsor is responsible for reporting SAEs that are considered to be "possibly related" to the treatment allocation and "unexpected", to the REC within 15 days of becoming aware of the event.

The TCC will provide SAE line listings from ACCORD for circulation prior to DMC meetings.

14 PREGNANCY

Although pregnancy is not considered an AE or SAE; as a matter of safety, the Investigator will be required to record any female participant's pregnancy which occurs while participating in the study. The Investigator will need to record the information on a Pregnancy Notification Form and submit this to the ACCORD office within 14 days of being made aware of the pregnancy. All pregnant female participants will be followed up until the outcome of the pregnancy.

15 OVERSIGHT ARRANGEMENTS

15.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a TMG, consisting of the CI, grant holders, Trial Manager and PAG members. The roles and responsibilities of the TMG and the names of committee members are detailed in the TMG charter.

The Trial Manager will coordinate and oversee the trial and will be accountable to the CI. The Data Manager will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the site team.

15.2 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. The terms of reference of the TSC, reporting arrangements and the names of committee members are detailed in the TSC charter.

15.3 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the trial. The terms of reference of the Data Monitoring Committee and the names of committee members are detailed in the DMC charter. The DMC Charter will be signed by the appropriate individuals before recruitment to the trial starts.

15.4 PATIENT ADVISORY GROUP

The patient advocacy organisation CAUK will organise input from a diverse Patient Advisory Group which will aim to meet bi-monthly. Two representatives of this PAG will join the TSC. The terms of reference of the Patient Advisory Group and the names of committee members are detailed in the PAG Terms of Reference.

15.5 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial 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.

15.6 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.

16 GOOD CLINICAL PRACTICE

16.1 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). Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

16.2 INVESTIGATOR RESPONSIBILITIES

The PI 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 PI. Responsibilities may be delegated to an appropriate member of study site staff. A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

16.2.1 Informed Consent

The PI 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 PILs and ICFs will be provided. The oral explanation to the participant will be performed by the PI or qualified delegated person, and must cover all the elements specified in the PIL 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).
The PI or delegated member of the research team and the participant will sign and date the ICF(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes (if applicable).

16.2.2 Study Site Staff

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

16.2.3 Data Recording

The PI is responsible for the quality of the data recorded in the CRF at each Investigator Site.

16.2.4 Investigator Documentation

The PI will ensure that the required documentation is available in local Investigator Site files.

16.2.5 Training

16.2.5.1 Recruitment site training

Research teams will be trained on the trial protocol, sponsor SOPs and QRI processes by the trial team and qualitative researcher (in person or remotely). This will be completed before the site is permitted to open to recruitment.

QRI training of PIs and recruiters will take place as needed and as indicated by QRI findings as described in 3.1.1.2 above. Findings from data collected during the QRI will be presented to the CI and TMG and a plan of action formulated to improve recruitment and information provision. Generic challenges such as how to explain study processes (e.g. randomisation) may be addressed through dissemination of 'tips and guidance' documents. Supportive feedback will be a core component of the plan of action, with the exact nature and timing dependent on the issues that arise. Site-specific feedback may cover institutional barriers, while multi-centre group feedback sessions may address widespread challenges, that would benefit from discussion. All group feedback sessions will be aided by de-identified data extracts from interviews and recorded recruitment conversations. Individual confidential feedback will also be offered, particularly where recruiters experience specific difficulties or where there is a need to discuss potentially sensitive issues. Investigator meetings and site visits may also be employed to discuss technical or clinical challenges (e.g. discomfort surrounding eligibility criteria).

16.2.5.2 GCP training

For non-CTIMP (i.e. non-drug) studies all researchers are encouraged to undertake Good Clinical Practice (GCP) training in order to understand the principles of GCP. However, this is not a mandatory requirement unless deemed so by the sponsor. GCP training status for all research team members should be indicated in their respective CVs or a GCP certificate may be provided.

16.2.6 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. The PI and research 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 information, which is confidential or identifiable, and has been 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 parties not involved in the trial.

16.2.7 Data Protection

All PIs and research team staff (including central research team staff and qualitative research staff) involved with this study must comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act) with regard to the collection, storage, processing and disclosure of personal information.

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

Published results will not contain any personal data and be of a form where individuals are not identified and re-identification is not likely to take place.

STUDY CONDUCT RESPONSIBILITIES

16.3 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 will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

16.4 MANAGEMENT OF PROTOCOL NON-COMPLIANCE

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. All protocol deviation logs and violation forms should be emailed to QA@accord.scot

Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies. An alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

The following will not be recorded as protocol deviations:

- Missed audio-recordings of conversations by research teams.
- Lack of adherence to the randomised treatment allocation.

16.5 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree: (a) the safety or physical or mental integrity of the participants of the trial; or(b) the scientific value of the trial.

If a potential serious breach is identified by the CI, a site PI or delegates, the co-sponsors must be notified via seriousbreach@accord.scot within 24 hours. It is the

responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to REC as necessary.

16.6 STUDY RECORD RETENTION

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

QRI audio-recordings will be kept for at least 10 years before they will be destroyed and electronic transcripts will be stored indefinitely in secure research data storage.

16.7 END OF TRIAL

The end of study is defined as the last participant's last visit. This will be a 6-month follow up review.

The PIs 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, and Research and Development Offices and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The PIs will inform participants if the study is closed prematurely and ensure that the appropriate follow up is arranged for all participants involved.

End of study notification will be reported to the co-sponsors via email to resgov@accord.scot.

16.8 CONTINUATION OF TREATMENT FOLLOWING THE END OF STUDY

There are no provisions for ancillary or care for participants after the trial ends, because the interventions in the CARE pilot trial are provided in standard clinical practice and aftercare will occur as normal in standard practice.

16.9 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, researchers employed by the University and the TMG. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the CI 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 National Health Service will have the benefit of NHS Indemnity.

- Sites outside the United Kingdom may be responsible for arranging their own indemnity or insurance for their participation in the study, and will be responsible for compliance with local law applicable to their participation in the study.

17 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

17.1 AUTHORSHIP POLICY AND REPORTING

On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with the International Conference on Harmonisation guidelines.

A final research report will be prepared as required by the funder. A summary report of the study will be provided to the REC within one year of the end of the study.

The success of the CARE pilot trial will be determined by the collaboration of a large number of doctors, nurses, other health professionals, patients, relatives, and the patient support organisation CAUK. For this reason, the credit for the main results will be given, not exclusively to the TMG, but to all collaborators with the trial. The primary trial publication will be drafted by a writing committee drawn from the TMG, whose membership has been approved by the TSC. Authorship will be under a group name for the CARE pilot trial collaboration and include the writing committee. People included on active sites' delegation logs will be included in any listing of collaborators in trial publications. The manuscript will be approved by the TSC before submission for publication.

17.2 PUBLICATION AND DISSEMINATION

Publications will be managed in line with funder requirements. We will submit manuscripts to peer reviewed journals, describing the findings of the QuinteT recruitment intervention and the CARE pilot trial (in addition to the final report for publication in the HTA journal). We will pay for these papers to be published open access. We will also present our findings at meetings of the Association of British Neurologists, the Society of British Neurological Surgeons, the British Paediatric Neurosurgery Society, and the British Paediatric Neurology Association.

We will disseminate a plain English summary of the findings of the CARE pilot trial to participants and public audiences with input from, and acknowledgement of, the Patient Advisory Group. We will offer to present our project and its findings to the annual meetings of CAUK, which is a national event that gives people affected by cavernoma a voice to talk about the issues that matter to them. We will produce an easy access report of our findings to share with the public and patients, and we will post it in the public domain on the CAUK website. We will keep the public, patients, and carers informed about study progress and results via social media channels (Facebook and Twitter).

17.3 DATA SHARING

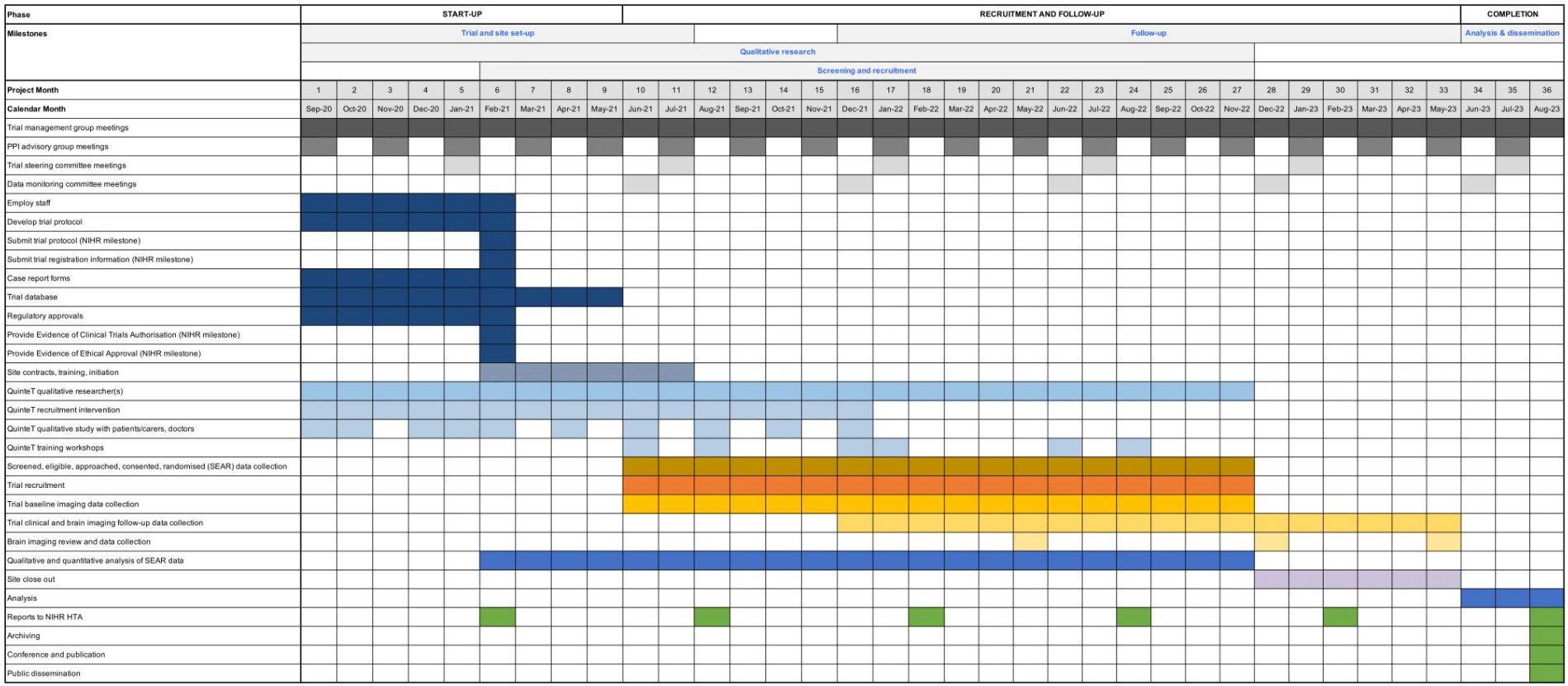
Ownership of the data arising from this study resides with the study team.

Following publication of the primary paper, a de-identified individual participant data set will be prepared for sharing purposes. All data requests should be submitted to the CI for consideration. Access to de-identified data may be granted following review by CI and TMG.

Data collected during PAG discussions or in QuinteT recruitment intervention data collection with patients may include quotes that will be useful to CAUK in producing or optimising existing patient or carer information; where participant consent has been given, these data (after removing or disguising identifiers) will be made available by the QuinteT research group in Bristol to CAUK in order to maximise their impact.

At the end of the study, QRI audio-recordings will be kept for at least 10 years before they will be destroyed. Transcripts will be stored indefinitely in secure research data storage, which can be accessed by approved individuals who are interested in conducting their own analyses of the data. These individuals will have to submit an application to do this, which will be assessed by an independent committee. However, all data will have identifiable information removed before they are made available, and there will be no way to identify individuals mentioned in interviews/appointments.

18 TRIAL TIMELINE



Footnote: Trial delivery timings are targets, variations will not be recorded as a protocol deviation/violation.

19 PROTOCOL VERSION CONTROL HISTORY

19.1 Version 1.0 (29Jan2021)

Original sponsor-approved version, submitted as part of application for REC review.

19.2 Version 2.0 (22Mar2021)

Protocol updated following REC meeting comments. Summary of changes:

- REC reference added to cover page table (page 1).
- Specific reference to Gamma Knife stereotactic radiosurgery added throughout and clarification added that neurosurgery and Gamma Knife stereotactic radiosurgery will be used according to their availability in clinical practice (section 3, 7 and throughout).
- Clarification added that imaging studies performed because of the occurrence of an outcome event will be collected by the research team and uploaded to the scan database for the trial (section 8.1.6)
- Trial timeline added (section 18).
- Version history table added (section 19).

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	24
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	24
Roles and	#5b	Name and contact information for the trial sponsor	1

responsibilities: sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	24
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	24 and supplementary
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7-8
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	8-9

		eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9-10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9-10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-12
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13-15
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	16-17
Methods: Assignment of interventions (for controlled trials)			

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	17
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	17
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	17
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	17
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17-18
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	18
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data	18-19

		entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19-21 and supplement
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19-21 and supplement
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19-21 and supplement
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	21
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	21
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	21-22
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	22
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	22-23
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to	23

		relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	16
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18-19
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	24 and 25
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	23
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	10
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	23
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	23
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	23
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	16 and supplement
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the	NA

current trial and for future use in ancillary studies, if applicable

Notes:

- 5d: 24 and supplementary
- 20a: 19-21 and supplement
- 20b: 19-21 and supplement
- 20c: 19-21 and supplement
- 32: 16 and supplement

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-075187.R1
Article Type:	Protocol
Date Submitted by the Author:	28-Jun-2023

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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Neurology, Radiology and imaging, Cardiovascular medicine
Keywords:	Neurosurgery < SURGERY, Stroke < NEUROLOGY, NEUROSURGERY, Paediatric neurology < NEUROLOGY, Adult neurology < NEUROLOGY, Clinical Trial
Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.	
Supplementary material 3 - Patient information leaflets and consent forms.zip	

TITLE:

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

Protocol version:

Published summary of V2.0 (22 March 2021)

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Keywords:

Cavernous Malformation, Cavernoma, Randomised controlled trial, Neurosurgery, Stereotactic radiosurgery, Protocol

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Number of words in abstract: 266/300

Word Count: 4000/4000

Number of references: 28

Number of figures: 1

Number of tables: 1

Number of supplementary files: 6

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ABSTRACT

Introduction: The top research priority for cavernoma, identified by a James Lind Alliance Priority setting partnership was “Does treatment (with neurosurgery or stereotactic radiosurgery) or no treatment improve outcome for people diagnosed with a cavernoma?” This pilot randomised controlled trial (RCT) aims to determine the feasibility of answering this question in a main phase RCT.

Methods and analysis: We will perform a pilot phase, parallel group, pragmatic RCT involving approximately 60 children or adults with mental capacity, resident in the UK or Ireland, with an unresected symptomatic brain cavernoma. Participants will be randomised by web-based randomisation 1:1 to treatment with surgery (neurosurgery or stereotactic radiosurgery) and medical management versus medical management alone, stratified by pre-randomisation preference for type of surgery. In addition to 13 feasibility outcomes, the primary clinical outcome is symptomatic intracranial haemorrhage or new persistent/progressive focal neurological deficit measured at six monthly intervals. An integrated QuinteT recruitment intervention (QRI) evaluates screening logs, audio recordings of recruitment discussions, and interviews with recruiters and patients/parents/carers to identify and address barriers to participation. A Patient Advisory Group has co-designed the study and will oversee its progress.

Ethics and dissemination: This study was approved by the Yorkshire and The Humber – Leeds East Research Ethics Committee (21/YH/0046). We will submit manuscripts to peer reviewed journals, describing the findings of the QRI and the CARE pilot trial. We will present at national specialty meetings. We will disseminate a plain English summary of the findings of the CARE pilot trial to participants and public audiences with input from, and acknowledgement of, the Patient Advisory Group.

Registration: ISRCTN registration number 41647111

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Extensive patient, carer and public involvement in the prioritisation of the study question, protocol design, study oversight, support for participants, and understanding of barriers to participation.
- A QuinteT recruitment intervention (QRI) will identify facilitators and barriers to recruitment to inform study materials and recommendations for the method of approach by investigators.
- Participants and investigators will not be blinded to treatment allocation, so there is a risk of non-adherence and performance bias, but blinded outcome adjudication will minimise detection bias.

INTRODUCTION

Symptomatic brain cavernomas are diagnosed in approximately 160 people in the UK annually and cause intracranial haemorrhage and epilepsy.[1–3] Systematic reviews of treatments for cavernomas published in 2019 and 2022 identified only observational studies.[4–7] These demonstrate that both medical and surgical treatments have risks and benefits.[4,5,7,8] No observational study at low risk of bias demonstrates a strong association between treatment option and outcome. A randomised controlled trial (RCT) is therefore required to determine whether treatment with surgery or stereotactic radiosurgery (SRS) improves outcome, compared with medical management alone, for patients with symptomatic brain cavernoma.[9] We aim to conduct Cavernomas: A Randomised Evaluation (CARE) pilot trial to address this. This paper is a published summary of the full protocol (Supplementary material 1).

Objectives

The primary objective is to assess the feasibility of performing a definitive main phase of a RCT comparing medical management to medical and surgical management (with neurosurgery or SRS) for improving outcome for people with symptomatic brain cavernoma. Secondary objectives are: (1) to set up a collaborative network of patient advocacy organisations and professional representatives at neuroscience centres in the UK and Ireland; (2) to understand recruitment processes and barriers and optimise informed consent and recruitment as part of a QuinteT recruitment intervention (QRI); and (3) conduct the CARE pilot trial for approximately 60 people with symptomatic brain cavernoma.

METHODS AND ANALYSIS

Design

Two-arm, parallel group randomised feasibility trial with an integrated QRI comparing medical management to medical and surgical management stratified by preferred type of surgical management (figure 1).

Setting

Participants will be recruited in secondary care settings in the UK and Ireland, from a collaborative network of research sites. Neurosurgery and follow-up will be conducted by regional neuroscience centres in the United Kingdom and Ireland. SRS will be performed at the National Centre for Stereotactic Radiosurgery in Sheffield or the Queen Square Radiosurgery Centre.

Patient and Public Involvement

The research question was developed by a Priority-Setting-Partnership with the patient advocacy organisation Cavernoma Alliance UK (CAUK).[10] A Patient, carer and public Advisory Group (PAG) guided and approved study design and scope. CAUK will share study information and direct patients to Consultant Cavernoma Contacts at CARE pilot trial sites or to their clinician. Patients will be invited to interviews to explore participation and non-participation decisions. We will disseminate a plain English summary of the study findings to participants and public audiences. We will offer to present our project to annual CAUK meetings.

Eligibility

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.[11,12]
3. Clinical history attributable to a brain cavernoma of:[13,14]
    a. Symptomatic stroke due to haemorrhage or
    b. Symptomatic stroke due to a persistent or progressive non-haemorrhagic, or not otherwise specified, focal neurological deficit, or

c. 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).

There is no time limit on when a patient may be recruited following the presentation and diagnosis of a brain cavernoma. Patients who have previously received surgical management may be included so long as the symptomatic brain cavernoma has not been completely removed/obliterated.

Exclusion criteria

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

Co-enrolment

Inclusion in another RCT or observational study does not preclude participation in the CARE pilot trial as long as: participants are not overburdened; their inclusion would be unlikely to confound the CARE pilot trial's results or complicate attribution of serious adverse events and outcomes; the protocol of the other study does not preclude co-enrolment in the CARE pilot trial; and co-enrolment has been agreed with the Chief Investigators of all studies involved in co-enrolment.

Interventions

Patients randomised to medical and surgical management will receive neurosurgical excision or Gamma Knife SRS for their brain cavernoma, in addition to medical management (see comparator), according to what is available in standard clinical practice in the participant's health service.

Neurosurgical excision

Surgery will be undertaken by a consultant neurosurgeon who will be responsible for neurosurgical aspects of clinical care of that patient in CARE. The neurosurgical technique to resect the cavernoma, including any operative adjuncts, will be that used by that consultant neurosurgeon in usual clinical practice and tailored to each patient according to the consultant neurosurgeon's discretion. Post-operative MRI scan performed within 72h of surgery is recommended, but not mandated, to confirm resection completeness.

Stereotactic radiosurgery

Standard clinical treatment protocols will be used to target the brain cavernoma but not surrounding haemosiderin. Treatment dosages will range from 12-16Gy depending on the size, shape, definition and site of the cavernoma. If intracerebral haemorrhage has occurred from the cavernoma, radiosurgery will be performed once the haematoma is judged to have been reabsorbed to minimise radiation exposure and treatment volume.

Comparator

Medical management constitutes standard medical care for brain cavernoma according to UK guidelines.[15] This may include anti-epileptic drug therapy, rehabilitation of neurological deficits, medical treatment of other neurological symptoms, psychological support, and MRI monitoring, according to clinicians involved in each patient's care.[13]

Ancillary and post-trial care

There are no provisions for ancillary or care for participants after the trial ends. Because interventions in the CARE pilot trial are provided in standard clinical practice, aftercare will occur as standard practice.

QuinteT recruitment intervention

Phase 1

Prior to recruitment to study commencement, the QRI researcher qualitatively evaluated factors that may influence recruitment using focus groups comprised of healthcare professionals and PAG members. The QRI researcher observed all CARE pilot trial management group (TMG) and trial steering committee (TSC; Supplementary material 2)) meetings during protocol development.

During recruitment, the QRI researcher used screening logs, recruitment consultation recordings, interviews with CARE researchers and participants, and observation of trial meetings to investigate recruitment obstacles.

Phase 2

In parallel, findings from phase 1 were presented to the Chief Investigator (CI) and TMG and used to implement measures to improve recruitment and information provision.

Outcomes

Primary outcome

We will estimate these measures of feasibility:

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 are 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.

Secondary clinical outcomes

1. Death not due to a primary clinical outcome

2. Liverpool Seizure Severity Scale plus epileptic seizure frequency (number of seizures in the preceding four weeks, and attainment of one-year seizure freedom)
3. Modified Rankin Scale (mRS) score
4. National Institute of Health Stroke Scale Score (NIHSS; adult or paediatric)
5. EQ-5D-5L in adults and EQ-5D-Y in children
6. Karnofsky Performance Status (KPS) scale in adults and Lanksy Play-Performance Scale (LPS) in children

We will also collect data to estimate health service use and healthcare and socioeconomic costs during the entire duration of follow-up.

Participant timeline

A detailed timeline for data collection is provided in table 1.

Identification and screening

The research team will identify eligible patients from the UK and Ireland from multiple sources including data on admissions, outpatient appointments, referrals, and routine brain imaging. Diagnoses may be made at any time during or prior to recruitment.

Assessment of eligibility

Eligibility will be confirmed following discussion with the patient and a specialist in the type of treatment that is thought to be most effective for surgical management. Eligibility may be informed by multidisciplinary discussion.

Baseline visit and consent

There is no specific time window for approaching eligible patients for consent. The baseline visit and consent meeting may be conducted remotely or in person, at the time of

randomisation or shortly prior to this. The research team will collect a venous blood sample of up to 10mL into an EDTA blood tube for genetic analysis during face-to-face visits.

Surgical treatment

It is expected, but not mandated, that surgical management will be delivered within three months of randomisation. Adherence will be assessed remotely by the Trial Coordinating Centre (TCC) at three months.

Qualitative interviews

In-depth interviews will be conducted by the QRI researcher in a sample of eligible patients from a variety of sites who have been approached to participate in the trial, with priority given to those declining participation to explore reasons why. Purposive sampling will be used to identify patients. Interviews will take place within three months of the participation decision.

Six-month follow-up visit

Participants will be asked to attend for their first six-month follow-up visit in person to perform a brain MRI. Outcome questionnaires will be completed. If not collected at the baseline visit, a blood sample will be obtained.

Six-monthly central follow-up

The TCC will subsequently perform six-monthly postal follow-up, including completion of outcome questionnaires, after checking the patient's vital status with their general practitioner. A researcher will contact non-responders electronically.

Long-term follow-up

We will ask study participants to consent to long-term follow-up, beyond the planned follow-up in the CARE pilot trial, including the use of routinely collected data in case the CARE pilot proceeds into a definitive main phase trial.

Table 1: Table of assessments.

Assessment	Identification and Screening	Baseline visit	Within 3 months of baseline	6-month local in-person follow-up	6-monthly central follow-up
Assessment of eligibility	X				
Screening end enrolment logs	X				
Consent to recruitment conversation recordings	X [1]				
Consent to qualitative interview	X				
Recording of patient recruitment conversations	X [2]	X [2]			
Consent to randomisation	X [3]	X [3]			
Demographic, clinical, socio-economic, medication, and radiographic data		X			
DNA sample		X			
Provision of diagnostic brain imaging		X			
Questionnaires		X		X	X
Randomisation		X			
Cavernoma surgical management			X		
Repeat brain MRI				X	
Outcomes and adverse events				X	X
Qualitative interview			X [4]		

1 – Research teams will be asked to capture verbal consent to audio-recordings of recruitment conversations when the approach is made to the participant. If this is not possible at this time, consent may be captured during subsequent recruitment conversations.

2 – Recordings of recruitment conversations with patients should be captured (as requested) wherever the CARE pilot trial is discussed (illustrated here but not restricted to Screening and Baseline Visit).

3 – Consent to participation in CARE may be collected at the Baseline Visit or in advance, during the Screening stage.

4 – Interviews with patients will take place within 3 months of being invited to take part in the trial.

Sample size

Approximately 240 people will be newly-diagnosed with symptomatic brain cavernoma during 18 months of recruitment.[2] We aim for all of these patients to be screened, but if 10% are missed and 10% decline to participate, we expect research teams to identify 190 patients. In the ARUBA trial, 226/726 (31%) of the eligible patients approached were randomised, so we expect at least 60 patients with symptomatic brain cavernoma to be randomised in the CARE pilot trial.[16]

Recruitment and consent

Eligible patients will be approached for recruitment during or following discussion with relevant secondary care specialists by research staff who are members of or affiliated to the clinical team and have undergone standardised training on trial-related procedures. An invitation letter may be sent to the patient in advance. Participant information leaflets and informed consent forms will be provided (Supplementary material 3). For children, participant information leaflets are available for children 0-5 years old, 6-10 years old and 11-15 years old. The patient or the parent/guardian will be given as much time as they require to consider the study information and ask questions. Written informed consent may be recorded in paper forms, electronic copies thereof, or an online electronic consent form. Children aged 6-15 who can understand it will be given the option of providing assent.

When a child recruited into the trial reaches the age of 16 years (or 18 years old in the Republic of Ireland) and is therefore competent to provide consent, they should be re-consented at their next 6-month follow-up review. No further data will be collected until a signed consent form has been received.

Consent to be contacted for an interview exploring reasons for declining participation

Patients or their parents/carers who decline participation in the CARE pilot trial will be invited to consent to participate in an interview with the QRI researcher, exploring their experiences

of being approached and invited to participate. Where parents/carers consent to take part in an interview, the child/young person may attend and contribute.

Allocation

The consensus preference agreed between each patient and their clinician for neurosurgery or SRS, should randomisation allocate them to medical and surgical management, will be recorded at the baseline visit. If there is no clear preference and both are available, the patient will be randomly allocated to the type of surgical treatment they will receive, if allocated to surgical treatment (figure 1). Participants in these two strata will be assigned 1:1 to medical management or medical and surgical management using permuted blocks. Allocation will be concealed until participants are enrolled and assigned using central web-based randomisation. Patients will be informed of their treatment allocation following randomisation.

Blinding

Treatment allocation in the CARE pilot trial is not blinded, and is therefore open to participants, treating clinicians and research staff.

We will aim to keep outcome event assessors blind to treatment allocation. We will measure how often assessors are unblinded to treatment allocation during the process of event adjudication.

Data collection

Demographic socioeconomic data and medical history will be collected at baseline visit alongside the following patient-reported questionnaires: EQ5D-5L (adults), EQ5D-3Y (children), and the Liverpool Seizure Severity Scale. Research staff will assess modified mRS score, NIHSS (adult or paediatric, if examined in person), KPS (adults) and LPS (children). Research teams will upload pseudo-anonymised DICOM images of diagnostic brain imaging for validation by a senior neuroradiologist to confirm or refuse eligibility.

In-depth interviews will be conducted by the qualitative researcher within three months of their participation decision.

Participants will be asked to attend their six-month follow-up visit in person for brain MRI to assess cavernoma presence and size, as a measure of treatment efficacy. As a minimum standard, T1-weighted, T2-weighted, and haem-sensitive gradient recalled echo or susceptibility-weighted imaging will be required. We will collect any other sequences performed. Images will be uploaded to the trial database and radiology department of each site will issue a clinical report. The research team will record clinical outcome events since randomisation and the details of surgery or SRS. Imaging studies performed because of an outcome event will be uploaded. The same patient reported questionnaires and standardised assessments used at baseline will be assessed at the first six-month visit.

After this the TCC will undertake six-monthly postal, telephone or email follow-up. Questionnaires will ask about disability, health-related quality of life, the occurrence of primary or secondary clinical outcomes, serious adverse events, the occurrence of surgical management of the brain cavernoma (described above), and relevant concomitant medications (anti-epileptic drugs, propranolol, antiplatelet agents, anticoagulant agents, and statins).

Retention

We aim for >95% retention of participants at six months with <10% treatment group switches or loss to follow-up.

Data management

Personal data will be processed by site research teams, the TCC at the University of Edinburgh (UoE) and qualitative research staff at the University of Bristol (UoB). Personal data

will be stored securely at sites and the secure trial database, hosted on a UoE server. Brain imaging will be managed by the Systematic Management, Archiving & Reviewing of Trial Images Service (SMARTIS) at the UoE. Audio-recordings will be securely transferred by qualitative research team members onto a secure drive at the UoB for long-term storage and analysis. Audio-recordings will be labelled with the participant identification number but not identifiable patient details. Audio-recordings will undergo targeted transcription and editing to protect respondents' anonymity. This data will be managed using NVivo software and stored on encrypted UoB drives.

Data analysis

Statistical analyses

In this pilot phase, analyses are descriptive only, and there will be no formal statistical tests. A detailed statistical analysis plan is described in Supplementary material 4. We will quantify the number and proportions (with 95% confidence intervals to reflect their precision) of patients who are screened, eligible, approached, provide consent and are randomised.[17] We will construct a CONSORT diagram to summarise the distribution and progress of participants in the trial including the numbers of withdrawals.[18] We will report descriptively the following: the number and the proportion of the collaborating sites that take part and recruit participants to the CARE pilot trial; research teams' implementation of trial procedures measured by number and type of protocol deviation; the numbers of participants allocated to neurosurgery and stereotactic radiosurgery; adherence to the allocated intervention; completeness of follow-up that would be due at each 6-month interval; completeness of baseline, imaging and outcome data; the frequency of outcome events overall and in an intention-to-treat analysis keeping patients in the treatment group to which they were allocated during all available follow-up.

We will also compare descriptively the characteristics of eligible patients who are screened and do not participate in the CARE pilot trial to eligible patients who are randomised using the characteristics recorded on the screening logs to assess generalisability (external validity) and

any recruitment bias. We will assess measures of functional outcome, to assess which has suitable statistical properties for use in a main phase trial (such as lack of floor/ceiling effects). We will assess whether such a measure (like the method we have used before[8]) would be more suitable as a primary outcome in place of intracranial haemorrhage.

Quintet Recruitment Intervention data analysis

The QuinteT researcher will analyse data using the SEAR framework to observe differences between sites in recruitment patterns as new sites open.[17,18] Descriptive analyses will identify where patients are lost to recruitment and the reasons why.

Audio recordings of recruitment conversations will be sought from a purposive sample of recruiting sites. The audio recordings will explore information provision, management of patient treatment preferences, and randomisation decisions to identify recruitment difficulties and improve information provision. Analysis will employ content, thematic, and novel analytical approaches, including targeted conversation analysis and quanti-qual appointment timing.[19–22] Interview data will be analysed thematically using constant comparative approaches derived from Grounded Theory methodology.[23]

Findings from the QRI will be fed back to the CI and TMG, to determine a plan of actions to optimise recruitment.

Health economics analysis

The full health economic analysis plan (HEAP) is in Supplementary material 5.[24,25] We will collect self-reported health service use and social/economic outcomes using bespoke question sets that will inform future economic analyses.[8,26] If data collection is confirmed as feasible, then a previously developed decision model will be updated and further developed to incorporate data collected within this study to provide a putative estimate of cost-effectiveness and its drivers.[27] In the context of the CARE pilot trial, the health economics

objectives are to: (i) design and test an optimal mechanism for the capture of resource use and cost data in community NHS settings, NHS secondary care, participants' out of pocket expenses and carer costs, (ii) estimate expected effect size and variance of relevant outcomes including health-related utility and quality-adjusted life years, and (iii) identify and measure the potential cost implications of surgical management of cavernomas.

We will measure health-related utility, healthcare-related resource use and costs using participant questionnaires before randomisation and at each follow-up timepoint.[20,28] These costs will be ratified by the study team through scrutiny of the patient pathway in both arms of the trials using available medical records to populate CRFs. We will assign unit costs using standard national costing sources where available, or through consultation with relevant service business managers. Costs will be summarised from the perspectives of the NHS and personal social services, and wider society (including participants and their carers).

Data Monitoring

Data monitoring committee

An independent Data Monitoring Committee (DMC) has been established to oversee the safety of participants in the trial (Supplementary material 6). No formal interim analyses are planned during the conduct of the pilot trial.

Adverse events

Participants will be instructed to contact their local research team if any symptoms develop at any time after being randomised. Participants will be asked about the occurrence of serious adverse events (SAEs) whenever contact is made with them between randomisation and the final central six-monthly follow-up. SAEs may be identified via information from support departments e.g. laboratories. Only events which are clinical outcomes on the trial or are related to medical and surgical management and occur between randomisation and the final 6-month follow-up review will be recorded as adverse events (AEs) or SAEs. Only AEs or

SAEs that are clinical outcomes or SAEs related to medical and surgical management will be recorded in the electronic case report form. If there is any doubt as to whether a clinical observation is an SAE, the event will be recorded.

When an SAE occurs, site research staff will review all documentation related to the event, assess whether an AE is an outcome in the trial and record all relevant information. If the AE is detected by central means of follow-up, the TCC will initiate the collection of this information but enlist the help of local site research staff. This information will be reported to the ACCORD (Academic and Clinical Central office for Research and Development) Edinburgh Research Governance & Quality Assurance (QA) Office immediately or within 24 hours. The Investigator will follow-up each event until resolution. All reports sent to ACCORD and any follow-up information will be retained in the Investigator Site File. The sponsor is responsible for reporting SAEs that are “possibly related” to the treatment allocation and “unexpected”, to the REC within 15 days of becoming aware of the event. The TCC will provide SAE line listings from ACCORD for circulation prior to DMC meetings.

Audit

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, ACCORD, research ethics committee review, and regulatory inspection(s). Risk assessment, if required, will determine if audit by the ACCORD QA group is required. If required, audit details will be captured in an audit plan.

ETHICS AND DISSEMINATION

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). Prior to study commencement all required approvals were obtained, including that of the Yorkshire and The Humber – Leeds East Research Ethics Committee (REC; 21/YH/0046).

Protocol amendments

Any changes in research activity, except those necessary to remove a hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the CI. Amendments will be submitted to the sponsor for review and authorisation before being submitted to the appropriate REC and local Research and Development team for approval.

Data sharing

Following publication of the primary paper, a de-identified individual participant data set will be prepared for sharing purposes. All data requests should be submitted to the CI for consideration. Deidentified data collected during the QRI will be made available by the QuinteT research group to the CAUK. Other individuals wishing to access deidentified QRI data may apply to an independent committee.

Publication and dissemination

We will submit manuscripts to peer reviewed journals for open access publication. We will present our findings at meetings of relevant professional associations.

Insurance and indemnity

The UoE has insurance in place for negligent harm caused by poor protocol design by researchers employed by the UoE. 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. Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.

FUNDING

The CARE pilot trial is funded by the National Institute for Health and Care Research (NIHR128694), which requires publication of the trial protocol but had no other role in manuscript preparation or the decision to publish.

ROLES AND RESPONSIBILITIES

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DECLARATION OF CONFLICTING INTERESTS

PW declares institutional unrestricted educational grant funding for stroke reperfusion course from Stryker, Penumbra and Medtronic. MR declares that he is a Senior Clinician of the National Centre for Stereotactic Radiosurgery.

ACKNOWLEDGEMENTS

We thank all members of the Patient, carer and public Advisory Group for contributing to the development of this study.

FIGURE LEGENDS

Figure 1: Participant flow diagram

SUPPLEMENTARY MATERIALS

1. Full CARE protocol v2.0 (22 March 2021)
2. Trial steering committee charter
3. Participant information leaflets and consent forms
4. Statistical analysis plan
5. Health economics analysis plan
6. Data monitoring committee charter

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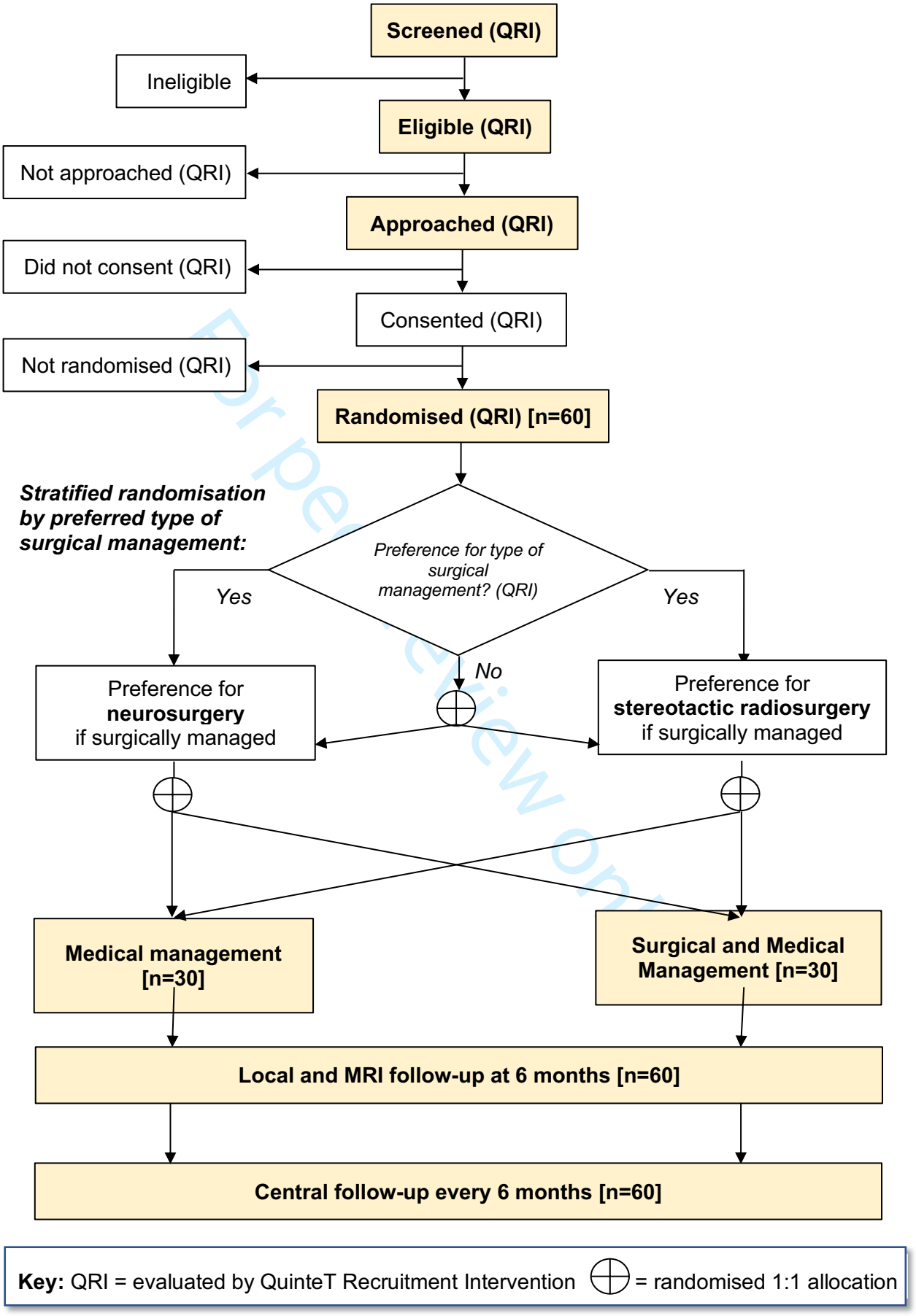

Study Protocol

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

Co-sponsors	The University of Edinburgh and/or Lothian Health Board ACCORD The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ
Trial Management Group (listed alphabetically by surname after the chief investigator)	Prof Rustam Al-Shahi Salman (chief investigator) Mr Neil Kitchen (co-chief investigator) Dr Vijeya Ganesan Dr Peter Hall Dr Kirsty Harkness Prof Peter Hutchinson Dr Elaine Kinsella Prof Steff Lewis Mr Jamie Loan Prof Conor Mallucci Mr Matthias Radatz Mr Andy Stoddart Ms Carole Turner Dr Julia Wade Mr David White Prof Phil White
Funder	National Institute for Health Research Health Technology Assessment Programme
Funding Reference Number	NIHR128694

Chief Investigator	Prof Rustam Al-Shahi Salman
Sponsor number	AC20171
REC Number	21/YH/0046
Project registration	To be confirmed
Version Number and Date	V2.0 (22Mar 2021)

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LIST OF ABBREVIATIONS

95% CI	95% confidence interval
ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
CARE	Cavernomas A Randomised Effectiveness trial
CAUK	Cavernoma Alliance UK
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
DWI	Diffusion-Weighted Imaging
eCRF	Electronic Case Report Form
ECTU	Edinburgh Clinical Trials Unit
FLAIR	Fluid Attenuated Inversion Recovery
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH GCP	International Conference on Harmonisation for Good Clinical Practice
MRI	Magnetic Resonance Imaging
PAG	Patient, carer and public involvement Advisory Group
PI	Principal Investigator
PIL	Patient Information Leaflet
QA	Quality Assurance
QRI	QuinteT Recruitment Intervention
QuinteT	Qualitative Research Integrated within Trials
RaDAR	Rare Disease Ascertainment and Recruitment
REC	Research Ethics Committee
RCT	Randomised controlled trial
SAIVMs	Scottish Audit of Intracranial Vascular Malformations
SOP	Standard Operating Procedure
TCC	Trial Coordinating Centre

TMG	Trial Management Group
TSC	Trial Steering Committee

SCIENTIFIC ABSTRACT

This is a pilot randomised controlled trial (RCT) to assess the feasibility of conducting a definitive main phase RCT to address the research question commissioned by the NIHR HTA, "How effective is active treatment (with neurosurgery or stereotactic radiosurgery) versus conservative management in people with symptomatic brain cavernoma?" The terms ‘conservative management’ and ‘active treatment were used in the commission, but throughout this protocol we will refer to ‘conservative management’ as ‘medical management’ and ‘active treatment’ as ‘medical and surgical management’. We will assess: collaborator engagement; proportions of screened patients who are eligible, approached, consented, or randomised; barriers to recruitment; RCT procedure implementation; adherence; data completeness; outcome event rates; and generalisability.

At least 160 people with brain cavernomas are newly diagnosed after symptoms due to stroke or epilepsy in the UK each year. A James Lind Alliance Priority Setting Partnership found that the top research priority for cavernoma was, “Does treatment (with neurosurgery or stereotactic radiosurgery) or no treatment improve outcome for people diagnosed with a cavernoma?”. A RCT is required to answer this question, but systematic reviews and trial register searches have not revealed any such RCTs.

The Cavernomas A Randomised Effectiveness (CARE) pilot trial aims to:

1. Engage a collaboration of specialists and patient advocacy groups in the UK and Ireland.

2. Establish a pilot RCT, with an embedded qualitative study to understand the anticipated recruitment processes and address any barriers.

3. Assess the feasibility of performing a definitive main phase of the RCT.

The CARE pilot trial will include:

I. A pilot phase parallel group RCT for patients with symptomatic brain cavernoma, comparing medical management versus medical and surgical management (with neurosurgery or stereotactic radiosurgery), with randomisation stratified by preferred type of surgical management. Collaborators will keep screening logs to capture characteristics of patients screened, eligible, approached, consented and randomised. This prospective randomised open blinded end-point RCT will recruit ~60 participants.

II. A QuinteT recruitment intervention (QRI) will evaluate screening logs and incorporate qualitative research to understand recruitment processes and barriers and identify actions to address barriers.

We will use (I) and (II) to estimate the feasibility and generalisability of a definitive main phase of the CARE RCT by extending the UK collaboration to other patient support organisations and clinical communities elsewhere in the world.

PLAIN ENGLISH SUMMARY

A cavernoma is a cluster of blood vessels that form blood-filled ‘caverns’ in the brain that look like a raspberry. Cavernomas can bleed into the brain and cause a stroke. Cavernomas can also cause a seizure or epilepsy. About 160 people in the UK each year are diagnosed with a cavernoma that has caused symptoms. Stroke and seizure may lead to disability, handicap and occasionally death. In standard practice 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. Surgical management can cause death, disability, and handicap.

The pros and cons of medical management versus medical and surgical management are finely balanced. The most reliable way of finding out which management is best is to do a randomised trial, in which suitable patients are allocated to medical management or medical and surgical management at random. This has never been done with cavernomas, and this was the top priority identified by a Priority Setting Partnership for cavernoma.

The NIHR wants research to be done 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.

In three years, we will:

(1) Create a network of specialists to do this study. We will include the UK and Ireland patient support organisations for people with cavernoma (Cavernoma Alliance UK - CAUK) and doctors representing the relevant specialties at all the major hospitals specialising in decisions about cavernoma treatment in the UK and Ireland.

(2) Invite newly diagnosed patients to join a pilot phase of a randomised controlled trial. Of 190 people diagnosed with brain cavernoma in 18 months, we estimate that 60 of them will enrol in the randomised trial. We will study why some patients take part in the randomised trial and others don't. We will use this information to change the methods of the trial if recruitment to the randomised trial goes slowly.

(3) Estimate whether enough patients can be found for a full-scale randomised trial to be done to find out whether medical management or medical and surgical management of symptomatic brain cavernomas is best.

We involved people with cavernoma, carers, and representatives of CAUK with patients and carers on 6 July 2019: all approved the design of the project and the extent of patient and public involvement. The focus group wanted the trials to be as inclusive of patients as possible. The focus group recognised how the project would benefit from them contributing their 'lived experience' of brain cavernoma.

People with cavernoma, carers, and representatives of CAUK will also keep an eye on the research by forming an advisory group and meeting regularly to discuss the research. Two representatives of this group will join and advise the steering committee.

We will publish our findings in medical journals. We will work with CAUK to produce a plain English summary and circulate it to patients via newsletters, email, the web, and social media.

1 INTRODUCTION

1.1 BACKGROUND

1.1.1 What are brain cavernomas?

Cerebral cavernous malformations or 'cavernomas' are intracranial vascular malformations that are diagnosed using histopathological examination or magnetic resonance imaging (MRI). Although most cavernomas are solitary and sporadic, around one-fifth are multiple with autosomal dominant inheritance due to mutations in three genes (1), so there are implications for relatives as well.

Large brain MRI cohorts have shown that the asymptomatic prevalence of brain cavernomas is 0.16%, currently affecting ~106,000 people in the UK (2). Some of these people present to medical attention with symptoms such as epileptic seizures or stroke due to either intracranial haemorrhage or 'focal neurological deficits' anatomically related to the cavernoma that do not appear to be due to haemorrhage (3). The incidence of symptomatic cavernoma in the UK was 0.24 per 100,000 per year at the turn of the millennium (4), so approximately 160 people are newly-diagnosed with symptomatic cavernoma in the UK annually. The impact of cavernoma is disproportionately high in comparison to their frequency, because they are usually diagnosed in children and young adults of working age (4).

People with cavernoma face a considerable risk of recurrent stroke due to intracranial haemorrhage, which is reliably known over five years after diagnosis (5), but is likely to continue for their lifetime. The 5-year risk of intracranial haemorrhage ranges from ~3.8% for people with non-brainstem cavernoma who have presented without a stroke to ~30.8% for people with brainstem cavernoma who have presented with stroke due to intracranial haemorrhage or focal neurological deficit.

People with cavernoma who present with an epileptic seizure almost inevitably develop epilepsy within one year, and only half of people with cavernoma-related epilepsy achieve two-year seizure-freedom (6).

These persistent symptoms also cause economic consequences for people with cavernoma, carers, the NHS, social services, and lost productivity in the UK workforce (7).

1.1.2 What treatments are available in standard clinical practice for brain cavernoma?

'Medical management' constitutes standard medical care alone (e.g. prevention of epileptic seizures with anti-epileptic drugs, and rehabilitation of neurological deficits, according to UK guidelines (8)). This is the most frequently used management plan for people with brain cavernoma in the UK (9).

Surgical management of brain cavernoma with neurosurgical excision or stereotactic radiosurgery is used in standard clinical practice for some patients to try to prevent recurrent epileptic seizures and stroke due to intracranial haemorrhage or non-haemorrhagic focal neurological deficit, which can result in death, disability,

handicap, and psychological consequences for patients and carers (10). Surgical management is given in addition to medical management in standard clinical practice, as described above, so throughout this protocol we will refer to this as 'medical and surgical management' for clarity.

Medical and surgical management in the CARE pilot trial involves health technologies that are available in standard clinical practice in the UK and Republic of Ireland; these are either neurosurgical excision (performed by neurosurgeons at 37 regional adult or paediatric neuroscience centres) or stereotactic radiosurgery (using Gamma Knife performed at the National Centre for Stereotactic Radiosurgery in Sheffield or the Queen Square Radiosurgery Centre). Neurosurgical excision is the most frequently-used form of surgical treatment for brain cavernoma in the UK, but it involves a craniotomy and the risk of complications is much higher for some cavernomas deep within the brain or brainstem that cannot be accessed without traversing brain tissue with important functions. 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. There are some emerging technologies for the surgical treatment of brain cavernomas, including minimally invasive therapeutic approaches for brain cavernoma such as magnetic resonance thermography-guided laser interstitial thermal therapy, or stereotactic laser ablation (11). Although medical and surgical management in the CARE pilot trial will continue to be neurosurgical excision or Gamma Knife stereotactic radiosurgery plus medical management, we will collect details of each type of surgical treatment used after randomisation to allow us to quantify the use of emerging technologies.

Medical and surgical management can have complications that can be fatal or disabling (9; 12; 13), and there are few reliable data about the benefits and risks of medical management versus medical and surgical management (8; 14; 15), so most patients have medical management (9).

Although drugs like propranolol, antiplatelet agents, anticoagulant agents and statins are not licensed for the treatment of brain cavernoma, some clinicians may use them off-label for patients who are unsuitable for medical and surgical management because these drugs may have disease-modifying effects (16).

1.1.3 What evidence supports medical management vs. medical and surgical management of brain cavernoma?

A search of ClinicalTrials.gov trial register on 17 November 2020 using the terms, "cavernoma OR cavernous angioma OR cavernous malformation" revealed five RCTs of drug therapies for brain cavernoma, but no completed, ongoing, or planned RCTs comparing medical management with medical and surgical management.

In several systematic reviews of observational cohort studies comparing medical management to medical and surgical management of brain cavernoma, or one form of surgical management to another, there were no studies at low risk of bias that demonstrated sufficiently "dramatic" associations between medical management versus medical and surgical management of brain cavernoma and clinical outcomes that would make a RCT unnecessary (14; 17).

We performed or updated (to 2018-2019) several systematic reviews and meta-analyses including:

i. observational cohort studies that compared medical and surgical management involving stereotactic radiosurgery or neurosurgery against medical management in a concurrent or historical control group and reported clinical outcome (14; 18)

ii. observational cohort studies without comparison groups reporting clinical outcomes after either medical management (5), neurosurgery (9; 19), or stereotactic radiosurgery (18; 19); and
iii. decision analysis comparing all management strategies using a Markov model with a time horizon of five years (20)

The best available evidence from observational studies comparing medical management with medical and surgical management is summarised in a table (see 1.1.4 below) and in more detail in the following paragraphs.

1.1.3.1 Neurosurgery versus medical management

There are seven observational cohort studies that compare neurosurgery and medical management (9; 21; 22; 23; 24; 25; 26). The best available comparative data on an entire incident brain cavernoma population found neurosurgery to be associated with harm over five years (hazard ratios 2.2-3.6) (9)), although other comparative studies restricted to brainstem/deep cavernomas have suggested both harm (risk ratios 1.9-7.8) and benefit (risk ratios 0.5-0.6) on the risk of intracranial haemorrhage over 4-6 years (21; 22; 23; 24), but the long-term difference in risk is unknown and might favour neurosurgery.

1.1.3.2 Stereotactic radiosurgery versus medical management

In the only observational cohort study comparing stereotactic radiosurgery with medical management at one hospital in Korea (27) (see table below), stereotactic radiosurgery might have been harmful, but the risk ratio was incalculable because of the paucity of outcomes. Indirect comparisons imply that stereotactic radiosurgery might be superior to medical management over five years. In a systematic review and meta-analysis of 30 cohort studies of patients undergoing stereotactic radiosurgery for brain cavernoma (median 61% of whom had brainstem cavernoma and median 91% of whom had presented with intracranial haemorrhage), during a median follow-up of 48 (IQR 35-62) months after stereotactic radiosurgery, the annual incidence of the composite of death, intracranial haemorrhage or focal neurological deficit was 3.6% (95% CI 3.17-4.16) (18). Using these data to estimate the five-year risk (16.9%) after stereotactic radiosurgery and comparing the risk indirectly to the cumulative 5-year risks of intracranial haemorrhage with medical management that range from ~18% to ~31% for comparable patient groups (5), suggests that stereotactic radiosurgery might be superior to medical management over five years. A systematic review of stereotactic radiosurgery restricted to brainstem cavernoma suggested that treatment was beneficial by comparing intracranial haemorrhage risks before and after treatment (13), but their findings are unreliable because they may simply reflect the untreated clinical course of brain cavernoma in which intracranial haemorrhage risk declines over time (5).

Our summary of the procedures, benefits and risks for patients and carers is also summarised in a table (see1.1.5 1.1.5 below).

1.1.4 Observational studies comparing medical management with medical and surgical management for brain cavernoma.

Study	Population	Intervention	Comparator	Outcomes / Time	Medical vs. medical and surgical management absolute &/or relative risk(s) of ICH
Neurosurgery vs. medical management					
Brain cavernomas in any location					
Moultrie *et al.* 2014 (9)	134 adults (40 had caused ICH/FND)	Surgery (n=25)	Medical management (n=109)	Functional outcome (at least 2 successive ratings of >1 on the mRS), or new ICH/FND during 5y follow-up	Functional outcome: 13/25 vs. 40/109 (**aHR 2.2, 95% CI 1.1–4.3**) ICH/FND: 8/25 vs. 17/109 (**aHR 3.6, 95% CI 1.3–10.0**)
Kida *et al.* 2015 (25)	78 adults (53 had caused ICH)	Surgery (n=29)	Medical management (n=49)	ICH during 3.8-4.6y follow-up	2/29 vs. 16/49 (**RR 0.6, 95% CI 0.1–2.6**)
Brainstem/deep cavernomas					
Esposito *et al.* 2003 (20)	30 adults (26 had caused ICH/FND)	Surgery (n=13)	Medical management (n=17)	ICH/FND over average 3.9y	6/13 vs. 1/17 (**RR 7.8, 95% CI 1.1–57.4**)
Mathiesen *et al.* 2003 (21)	68 adults (48 had caused ICH/FND)	Surgery (n=29)	Medical management (n=34)	ICH over average 4.6y	4/29 vs. 8/34 (**RR 0.6, 95% CI 0.2–1.7**)
Tarnaris *et al.* 2008 (22)	21 adults (17 had caused ICH/FND)	Surgery (n=6)	Medical management (n=15)	ICH over average 6.5y	3/6 vs. 4/15 (**RR 1.9, 95% CI 0.6–6.0**)
Huang *et al.* 2010 (23)	30 adults (30 had caused ICH/FND)	Surgery (n=22)	Medical management (n=8)	"Deterioration" over average 4y	3/22 vs. 2/8 (**RR 0.5, 95% CI 0.1–2.7**)
Brain cavernomas not in brainstem/deep locations					
Kivelev *et al.* 2009 (24)	33 adults (15 had caused ICH)	Surgery (n=18)	Medical management (n=15)	ICH over average 7.7y	0/18 vs. 4/15 (RR incalculable)
Stereotactic radiosurgery vs. medical management					
Yoon *et al.* 1998 (26)	41 adults with cavernomas in any location (20 had caused ICH/FND)	Gamma Knife stereotactic radiosurgery (n=22)	Medical management (n=19)	ICH, adverse radiation effects (ARE) over 2-3.5y	ICH: 2/22 vs. 0/19 (RR incalculable) ARE 5/22 vs. 0/19 (RR incalculable)

aHR = adjusted hazard ratio; ARE = adverse radiation effects; FND = focal neurological deficit; ICH = intracranial haemorrhage; mRS = modified Rankin Scale; RR = risk ratio (estimated from aggregate data).

1.1.5 Summary of procedures, benefits and risks with medical management or medical and surgical management for brain cavernoma

	Medical management	Medical and surgical management	
		Neurosurgery	Stereotactic radiosurgery
What may be involved?	• Treat symptoms • Prevent seizures • Rehabilitation • Brain scan	• Treat symptoms • Prevent seizures • Rehabilitation • Brain scan	• Treat symptoms • Prevent seizures • Rehabilitation • Brain scan
		• Hospital admission for days • General anaesthetic • Opening in the skull • Operation to remove cavernoma • Follow-up brain scan • Must not drive for 6 months	• Hospital attendance for a day • Anaesthetic not needed • Head fixed in a temporary frame • Focussed radiation given once • Follow-up brain scans
What are the possible benefits?	• Bleed/stroke risk reduces as time passes • Avoids risks of neurosurgery or radiosurgery	• Risk of bleed/stroke lower if cavernoma removed • Less worry about symptoms returning	• Risk of bleed/stroke may be lower if cavernoma stabilised, but these benefits are uncertain • Less worry about symptoms returning

What are the possible risks?	• Future bleed/stroke due to cavernoma
	  ○ Can be mild
	  ○ May be disabling
	  ○ Rarely be fatal
	  ○ Risk higher for cavernoma in brainstem
	• Epileptic seizures, which may be difficult to control
	• Cavernoma remains in the brain, so the risks of stroke and seizure may never go away
	• Worry about symptoms returning
		• Bleed/stroke due to neurosurgery
		  ○ Can be mild
		  ○ May be disabling
		  ○ Rarely be fatal
		  ○ Risk higher for cavernoma in brainstem
		• Epileptic seizures may not go away
		• Complications of treatment (e.g. infection or damage to brain around the cavernoma)
		• Cavernoma may come back
			• Bleed/stroke despite radiosurgery
			  ○ Can be mild
			  ○ May be disabling
			  ○ Rarely be fatal
			  ○ Risk higher for cavernoma in brainstem
			• Epileptic seizures may not go away
			• Complications of treatment (e.g. damage to brain around the cavernoma)
			• Cavernoma not removed

1.2 RATIONALE FOR STUDY

1.2.1 The therapeutic dilemma

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 medical management or medical and surgical management for brain cavernomas (8; 15). These uncertainties were confirmed by patients and carers in a James Lind Alliance Priority Setting Partnership in the UK, which found that the top research priority for cavernoma was, “Does treatment (with neurosurgery or stereotactic radiosurgery) or no treatment improve outcome for people diagnosed with brain or spine cavernoma?” (28).

Therefore, in 2018 the NIHR HTA commissioned research to address the question, “How effective is treatment (with neurosurgery or stereotactic radiosurgery) versus conservative management in people with symptomatic brain cavernoma?” The NIHR’s commissioning brief reported that feedback from experts suggested that a randomised controlled trial (RCT) with at least 10 years of follow-up would be needed to better guide clinical care and that it would be necessary to conduct a multinational trial in countries with similar healthcare settings to the UK to ensure sufficient numbers for a robust trial.

1.2.2 Understanding recruitment barriers with a QuinteT recruitment intervention (QRI)

Resolving this therapeutic dilemma is likely to be challenging because of the low incidence of symptomatic brain cavernoma despite a high prevalence, because the availability of surgical management varies in everyday clinical practice (8; 15), and because accumulated expertise in specialist centres has guided clinical practice hitherto despite the lack of high quality evidence (29). Recruitment to the CARE pilot trial is likely to remain challenging given the history of RCTs comparing medical management versus medical and surgical management of intracranial vascular malformations with invasive procedures (30; 31). The reasons for poor recruitment to such trials have not been studied, so qualitative research is needed to investigate the potential barriers to recruitment and optimise recruitment processes in the CARE pilot trial. Many RCTs experience recruitment challenges due to difficulties that recruiters have in explaining concepts like uncertainty, equipoise and randomisation (32). Discussions with members of our collaboration during the development of this proposal have raised concerns about clinical equipoise amongst neurosurgeons, partly due to treatment preferences according to the anatomical location of the brain cavernoma, concerns about exposing children to radiation, scepticism about the effects of stereotactic radiosurgery, and the availability of stereotactic radiosurgery in the NHS for brain cavernoma at only two sites in the UK (although patients may be referred from any hospital) (29). Also, patients may have treatment preferences (e.g. for less invasive procedures), and patient/family preferences may affect RCTs involving children in particular (33).

An integrated QRI 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 CARE pilot trial (32; 33; 34). Embedding a QRI allows the identification and understanding of generic and trial-specific recruitment challenges (35; 36; 37), and enables the development of tailored plans to address these issues. A QRI (38) has been integrated into over 30

RCTs, including trials comparing surgery and medical management (39) and there is observational evidence of the benefits associated with a QRI in at least five RCTs (40).

1.2.3 This feasibility study and pilot trial will inform the feasibility of a definitive main phase trial

The NIHR HTA commissioned a UK feasibility study and pilot phase RCT to demonstrate the ability to recruit enough patients to answer the research questions and sufficient numbers in the UK such that the trial results would be applicable to the NHS. The CARE pilot trial was funded by this NIHR HTA commissioned call. A decision about whether to proceed a definitive main phase trial will be made in light of the results of the CARE pilot trial.

1.2.4 Patient, carer and public involvement (PCPI)

Between August 2014 and November 2015 we worked with people with cavernoma, carers, and representatives of the patient support organisation Cavernoma Alliance UK (CAUK) on the Steering Group of the James Lind Alliance Priority Setting Partnership that identified and prioritised the topic of this application as the top priority for further research into cavernoma. Since November 2015, individuals in the Steering Group of the James Lind Alliance Priority Setting Partnership – including patients and carers – were involved in reviewing the commissioning brief for the NIHR HTA commissioned call for research. In May-June 2016, we worked with CAUK to gather the views of patients and carers who are members of the organisation, about research to address this top priority for further research into cavernoma. We consulted 731 CAUK members affected by cavernoma or parents/guardians of affected children, by emailing them a link to a web-based survey describing the CARE trial. 70% of respondents had not received surgical management for a cavernoma and a minority (28%) of these respondents indicated that they would not participate in the RCTs proposed. Between December 2018 and June 2019, we consulted representatives and members of CAUK, including patients with the condition, who have reviewed and shaped the design of the CARE pilot trial. In July 2019, all members of CAUK were invited by the Chief Executive of the organisation to participate in a focus group on 6th July. Four carers, six patients, the Chief Executive Officer of CAUK and the Chief Investigator (CI) attended the meeting. This focus group of patients, carers, and family members considered the overall design of this project. The main themes of the discussion were: (1) The group recognised that, "many people have had to make difficult decisions without the information they need" and that in addressing this "difficult dilemma", their involvement could improve participation by contributing their 'lived experience' of brain cavernoma to the clinical experience of the co-applicants and the planned qualitative research; (2) The group approved the extent of the patient and public involvement that is planned; (3) The group wanted the CARE pilot trial to be as inclusive of patients as possible. In particular, they wanted the CARE pilot trial to include patients who have: (a) first presented with symptoms or been diagnosed some time ago, (b) multiple cavernomas (one of which might have been treated), and (c) partially treated cavernoma (for whom there is uncertainty about further treatment); (4) All participants approved the project's design. In particular, they approved a choice of the safest treatment according to cavernoma location, using the "wealth of experience" of the clinical community in the UK, permitting patient preferences, and allowing treatment if needed during follow-up; (5) The group accepted that participants would receive standard care; (6) The group asked not only that the project should include a diverse sample of patients with brain cavernoma, but

also that the analyses should account for this diversity (e.g. age, time since symptoms, single vs. multiple cavernoma, and genetic mutations).

2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary objective

Assess the feasibility of performing a definitive main phase of a RCT comparing medical management to medical and surgical management (with neurosurgery or stereotactic radiosurgery) for improving outcome for people with symptomatic brain cavernoma.

2.1.2 Secondary objectives

- Set up a collaboration of the patient advocacy organisations for cavernoma in the UK and Ireland and representatives of clinical neurology, neurosurgery, and stereotactic radiosurgery at neuroscience centres throughout the UK and Ireland.
- Evaluate screening logs and conduct qualitative research with patients and clinicians to understand recruitment processes and barriers, as well as actions to address any barriers, as part of a QuinteT recruitment intervention (QRI) to optimise informed consent and recruitment.
- Conduct the CARE pilot trial for approximately 60 patients with symptomatic brain cavernoma, comparing medical management of the brain cavernoma versus medical and surgical management (neurosurgery or Gamma Knife stereotactic radiosurgery) for improving outcome.

2.2 OUTCOMES

2.2.1 Primary outcome

We will estimate these measures of feasibility to inform the extent to which international cooperation would be needed to recruit an adequate sample size in a CARE definitive main phase RCT, and what proportion of participants might be recruited from the UK during the study:

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?

2.2.2 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.

2.2.2.1 Intracranial haemorrhage

The definition of an intracranial haemorrhage attributable to brain cavernoma is, “a clinical event involving both acute or subacute onset symptoms (any of headache, epileptic seizure, impaired consciousness, new/worsened focal neurological deficit referable to the anatomic location of the cavernous malformation as well as radiological, pathological, surgical, or rarely only cerebrospinal fluid evidence of recent extra- or intra-lesional haemorrhage. The mere existence of a haemosiderin halo, or solely an increase in cavernoma diameter without other evidence of recent haemorrhage, are not considered to constitute haemorrhage” (3).

2.2.2.2 New persistent/progressive focal neurological deficit

The definition of a non-haemorrhagic focal neurological deficit attributable to brain cavernoma is, “a new or worsened focal neurological deficit referable to the anatomic location of the brain cavernoma, which may present with other clinical features of intracranial haemorrhage, but without evidence of recent blood on timely brain imaging or pathological examination, or examination of the cerebrospinal fluid. These cases may be accompanied by an increase in cavernoma diameter alone or oedema on brain MRI (3).

The definition of a focal neurological deficit (not otherwise specified) attributable to brain cavernoma is identical to non-haemorrhagic focal neurological deficit, with the exception that pathological investigation, cerebrospinal fluid examination, or timely brain imaging have not been performed at all or at the correct time to establish whether haemorrhage, oedema, or cavernoma growth underlie the clinical deterioration (3). These focal neurological deficits may be persistent (lasting >24 hours, and staying static or improving), or progressive (lasting >24 hours with further deterioration) (3).

New persistent/progressive focal neurological deficits attributable to brain cavernoma treatment may be referrable to the anatomic location of the brain cavernoma (e.g. haemorrhage after neurosurgical treatment, or radionecrosis from stereotactic radiosurgery) or referrable to other regions of the brain (e.g. intracranial abscess following neurosurgical excision).

2.2.3 Secondary clinical outcomes

During the CARE pilot trial, investigators will collect data on the risk of several clinical primary and secondary outcomes to inform the design of a main phase RCT. The following secondary clinical outcomes will be measured at each 6-month follow-up review:

1. Death not due to a primary clinical outcome
2. Liverpool Seizure Severity Scale plus epileptic seizure frequency (number of seizures in the preceding four weeks, and attainment of one-year seizure freedom)
3. Modified Rankin Scale (mRS) score
4. National Institute of Health Stroke Scale Score (adult or paediatric)
5. EQ-5D-5L in adults and EQ-5D-Y in children
6. Karnofsky Performance Status (KPS) scale in adults and Lanksy Play-Performance Scale (LPPS) in children

We will also collect data to estimate health service use and healthcare and socioeconomic costs during the entire duration of follow-up.

2.2.4 Feasibility metrics proposed to the funder

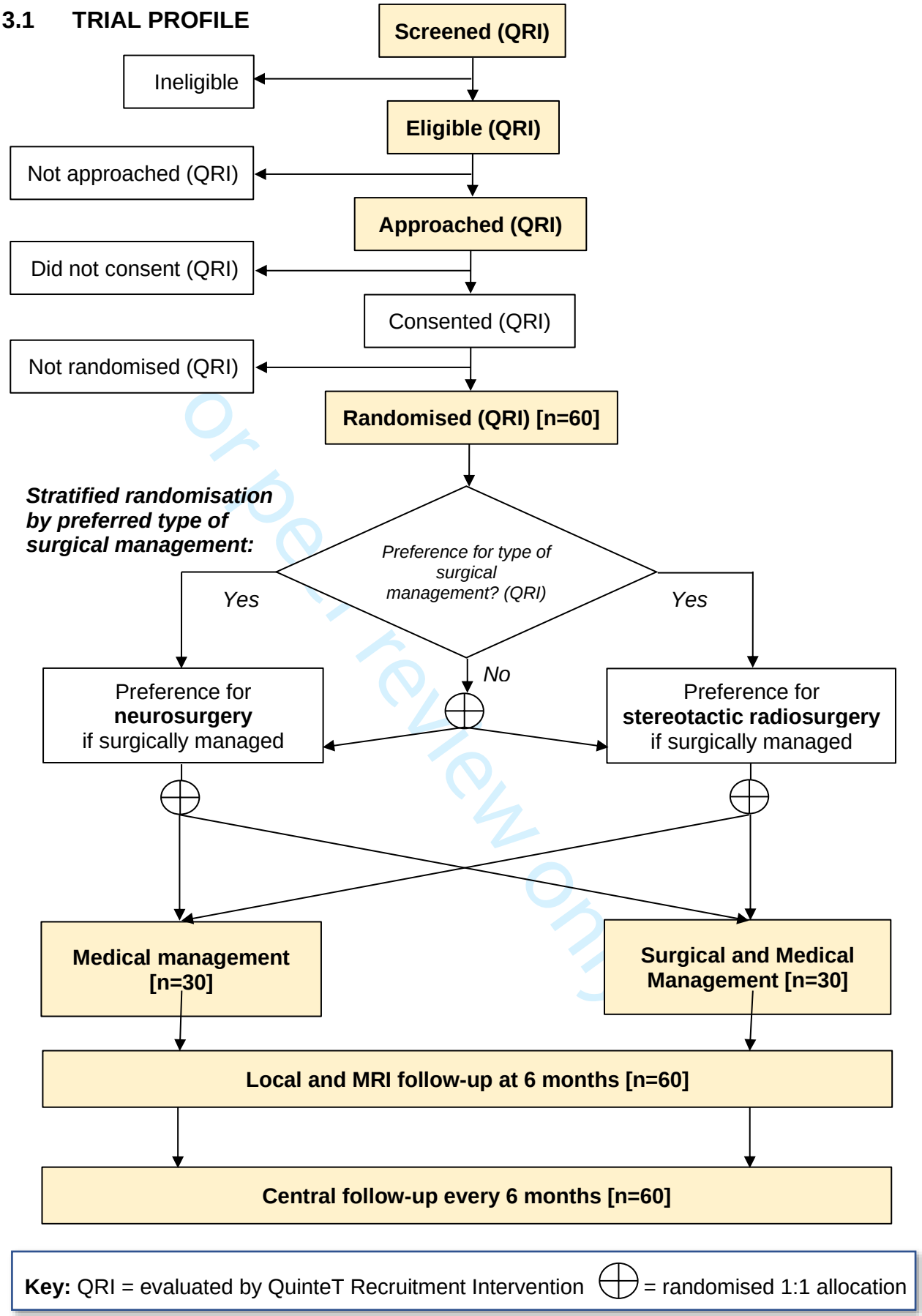
The NIHR HTA has been provided with the following criteria for success, although these are not specific secondary outcomes of the CARE pilot trial:

- At least 30 sites in the UK and Ireland collaborate
- Project delivered according to the major milestones identified in the NIHR HTA project management plan
- Recruitment to within 10% of target
- Brain cavernoma radiographic diagnosis confirmed by expert neuroradiologist review in >95% of participants recruited
- Retention of >95% of participants at six months
- <10% treatment group switches or loss to follow-up
- QuinteT recruitment intervention is associated with an improvement in recruitment
- CARE definitive main phase trial appears feasible and affordable

3 STUDY DESIGN

The CARE pilot trial is a two-arm, parallel group randomised feasibility trial which 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 outcomes for people with symptomatic brain cavernoma. An integrated QRI aims us 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 CARE pilot trial (32; 33; 34). Participants will be recruited in secondary care settings in the UK and Ireland, from a collaborative network of research sites, with input from the patient advocacy organisation CAUK. Randomisation will allocate participants to groups in a 1:1 ratio, stratified by preferred type of surgical management, but if there is no clear preference for the type of surgical management, and both are available, the patient will be allocated to either neurosurgery or stereotactic radiosurgery (see section 3.1).

3.1 TRIAL PROFILE



3.1.1 QuinteT recruitment intervention

The QuinteT recruitment intervention (QRI) has been presented as two distinct stages for clarity (data collection followed by feedback and training). In reality these are likely to overlap or run in tandem. For instance, new avenues of enquiry may emerge through feedback meetings, which can be a route to investigating recruitment difficulties in their own right. Insights into recruitment can emerge at any point during the RCT and instigate further investigations or intervention.

3.1.1.1 Phase 1

3.1.1.1.1 Before the CARE pilot trial begins recruitment

The QuinteT researcher will conduct a qualitative evaluation of what may influence recruitment during study set-up, combining evidence from previous QuinteT recruitment interventions (35; 36; 37; 38; 39; 40) and training programmes (41; 42), with data collected from patient and professional groups involved in CARE.

Qualitative work will include focus groups with healthcare professionals to explore views on eligibility and equipoise. Healthcare professionals' views will be explored in online workshops, to which we will invite relevant clinical members of the Trial Management Group (TMG), 'Consultant Cavernoma Contacts' and investigators at collaborating sites. These workshops will explore differences in views between individuals and clinical specialties regarding equipoise and identify criteria to determine patient suitability for neurosurgery or stereotactic radiosurgery, previously identified by the study team as difficult to operationalise. Discussions will also cover patient pathways into the trial, processes and management options for those declining participation, what each intervention arm involves, including potential risks and benefits, plans for follow up within the CARE pilot trial and possible advantages and disadvantages of taking part. We will organise these workshops with clinicians to maximise attendance, convenience, and efficiency by holding them virtually. The work described in this paragraph is for information only and is covered by a separate Research Ethics Committee (REC) approval (University of Bristol, Faculty of Health Sciences Research Ethics Committee Reference 111186). Qualitative work involving focus groups with healthcare professionals is therefore not covered under this protocol.

Insights into patient views to inform development of patient-facing materials, inform the design of the pathway into the trial and provide insight into the acceptability of participation in the CARE pilot trial will be obtained through the QuinteT researcher observing all CARE pilot trial Patient, carer and public involvement Advisory Group (PAG) meetings at which such issues are discussed.

A QuinteT researcher will observe all TMG and TSC meetings during which the study protocol is developed and finalised, with a focus on discussions and final presentation of equipoise and eligibility criteria.

Insights from focus groups with professionals and observation of the TMG, TSC and PAG discussions will inform the content of patient-facing information for the CARE pilot trial and site initiation visits for recruiters. The QuinteT team will provide guidance for recruiters to present CARE pilot trial information to eligible patients, carers and families during site training and initiation (see section 16.2.5.1). Guidance will raise recruiter awareness of key 'hidden' challenges when trying to recruit patients to trials comparing medical management with medical and surgical management and how these can be addressed (35; 42), as well as including insights into particular issues identified as relevant to the CARE pilot trial in how to deal with

preferences and convey equipoise between medical management and medical and surgical management.

3.1.1.1.2 During CARE pilot trial recruitment

As recruitment to the CARE pilot trial begins, recruitment processes will be investigated in-depth at study sites as they open. A QuinteT researcher will use a multi-faceted, flexible approach using triangulation of the following data to investigate site-specific or more general recruitment obstacles (34): screening logs (section 5.3); recording of recruitment consultations between recruiters and patients (section **Error! Reference source not found.**); in-depth interviews with members of the TMG, recruiters, and participants (section 9.4.3); review of study documents (section 9.4.5) and observation of monthly TMG meetings (section 9.4.4).

3.1.1.2 Phase 2

Findings from phase 1 will be presented to the CI and TMG. If recruitment difficulties are evident across the trial or at particular sites, the CI/TMG and QuinteT team will formulate a 'plan of action' to improve recruitment and information provision. The specific plan implemented will be grounded in the findings from analysis of the data above, with its format dependent on the nature of the recruitment barriers identified (see section 16.2.5.1).

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

We aim to enrol approximately 60 participants over an estimated 18 months at approximately 45 sites in the UK and Ireland. Patient follow-up will end approximately 6 months after recruitment finishes.

4.2 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 (15; 43)
3. Clinical history attributable to a brain cavernoma of:
    a. Symptomatic stroke due to intracranial haemorrhage (3), or
    b. Symptomatic stroke due to a persistent or progressive non-haemorrhagic, or not otherwise specified, focal neurological deficit (3), or
    c. Epileptic seizure(s) meeting the definition of definite or probable cavernoma-related epilepsy (44)
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).

There is no upper time limit on when a patient may be recruited following the symptomatic presentation and diagnosis of a brain cavernoma.

Patients with multiple brain cavernomas, at least one of which has been symptomatic and not undergone removal/obliteration by surgical management, may be included.

In the case of prior surgical management (with neurosurgery or stereotactic radiosurgery), patients with a symptomatic brain cavernoma that has not been completely removed/obliterated by prior surgical management may be included.

4.3 EXCLUSION CRITERIA

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

4.4 CO-ENROLMENT

Inclusion in another RCT or observational study does not preclude participation in the CARE pilot trial as long as: participants are not overburdened; their inclusion would be unlikely to confound the CARE pilot trial's results or complicate attribution of serious adverse events and outcomes; the protocol of the other study does not preclude co-enrolment in the CARE pilot trial; and co-enrolment has been agreed with the Chief Investigators of all studies involved in co-enrolment. Research staff should obtain permission to enrol patients who are participants in other trials from the CI. A record of participants who are known to have been co-enrolled in other studies will be maintained by the TCC.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING AND SCREENING PARTICIPANTS

For a patient to be eligible for the trial, the patient and doctor must be uncertain about medical management or medical and surgical management of the symptomatic brain cavernoma. In standard clinical practice, decisions about medical management or medical and surgical management of symptomatic brain cavernomas are usually made with patients and neurologists or neurosurgeons, following discussions at multi-disciplinary meetings that may involve any or all of neurologists, neurosurgeons, stroke physicians, and radiologists. We expect uncertainty about medical management or medical and surgical management to be established during discussion between a patient and their doctor. In clinical practice, multidisciplinary meetings involving neurologists and neurosurgeons may confirm this uncertainty as well as suitability for either type of surgical management; sometimes, these multidisciplinary meetings manage this uncertainty by arriving at a consensus opinion, but investigators should note that this may make recruitment to the CARE pilot trial less likely.

The principal investigator (PI), or another clinician with delegated responsibility, is responsible for confirming eligibility for the trial, however delegated research team members can identify eligible patients. Research team members delegated this role should be members of, or affiliated to, the clinical care team. These people may identify potentially eligible patients using several sources at their site, including but not limited to data on admissions, outpatient appointments, referrals, and brain imaging that record:

- New diagnoses of symptomatic brain cavernoma made in everyday clinical practice during the recruitment period.
- Diagnoses of symptomatic brain cavernoma made at any time before the recruitment period, identified by searches of clinical or imaging databases, or clinicians' own records.
- Referrals from colleagues at other hospitals in the UK and Ireland.

Verification of eligibility will require delegated research staff to access patient medical notes.

The TMG will apply to use the Association of British Neurologists' Rare Diseases Ascertainment and Recruitment platform (RaDAR; https://www.theabn.org/general/custom.asp?page=radar), which is used by neurologists to indicate that they have seen a patient with a specified rare neurological disease (such as brain cavernoma). Once a neurologist notifies RaDAR that they have seen a patient, the neurologist will be sent the patient information leaflet about the trial to send to the patient, who can be referred to their local trial site if they are interested in discussing participation.

CAUK (and affiliated groups such as Cavernoma Ireland and Cavernoma Scotland) will share information about the trial through their website, social media platforms and any other communications channels used by them. Patients who contact, or are members of, one of the patient support organisations will be made aware of the CARE pilot trial and informed about what the CARE pilot trial involves by a CAUK member of staff. If these patients are interested in finding out more and being screened for their eligibility, CAUK may direct them to information about a Consultant Cavernoma Contact at an appropriate CARE pilot trial site. The role of CAUK will be provision of information to patients; patients will be advised to speak with their clinician about decisions related to their medical care. CAUK will record the number of patients who they identify as potentially suitable for the CARE pilot trial and suggest referral to a Consultant Cavernoma Contact.

The CI and other members of the TMG will raise awareness of the trial amongst the clinical community through presentations at conferences and meetings. This could result in referral of patients to CARE pilot trial recruitment sites from other hospitals in the UK and Ireland.

5.2 APPROACHING AND CONSENTING PARTICIPANTS

Patients in the UK and Ireland will be approached and invited to take part in adult and paediatric neurology, neurosurgery, and stroke services in secondary care, or one of the stereotactic radiosurgery services that are commissioned to provide stereotactic radiosurgery for cavernoma (29). Eligibility may have been determined by a multidisciplinary discussion, but eligible patients should be approached for recruitment to the CARE pilot trial during or after consultation with a specialist in the type of treatment that is thought to be most effective for the surgical management of the brain cavernoma. Delegated research staff involved in approaching eligible patients should be members of, or affiliated to, the clinical care team.

Potential adult participants or the parent/guardians of potential paediatric participants may approached in person or by telephone (or another technology that supports remote consultations e.g. NHS Near Me). An invite letter may be sent in advance of approaching the patient. The short and supplementary PIL will be used to introduce and discuss the trial.

There is no specific time window for approaching eligible patients for their consent (see section 4.2 above), but they should be approached whenever uncertainty arises about whether to pursue medical management or medical and surgical management of a symptomatic brain cavernoma. The oral explanation given should be performed by the PI or another member of the research team delegated to perform this task and must cover all the elements specified in the relevant PIL and ICF. The patient or the parent/guardian will be given as much time as they require to consider the study information and given every opportunity to ask questions.

The PI or another clinician with delegated responsibility, is responsible for confirming eligibility for the trial, ensuring informed consent is obtained and that the informed consent form (ICF) is signed and dated by all parties before randomisation and any protocol-specific procedures are carried out. Local research staff should follow the laws that govern consent procedures in their jurisdiction. Members of the research team will have undergone standardised training on trial-related procedures. Health Research Authority guidance on applying a proportionate approach to seeking consent has been followed (45). Adult patients lacking mental capacity to consent for themselves will not be included in this trial (see section 4.2). If an adult patient loses mental capacity during the course of the research and subsequently regains mental capacity, their consent to continue taking part in the trial will be confirmed.

Face to face informed consent discussions with potential participants may not be feasible (e.g. due to the COVID-19 pandemic). In order to avoid patients making additional trips to hospital, written informed consent may be recorded in the following ways (in addition to being done in person):

1. Remotely

When completed remotely, the patient should return the signed form, or a scan or legible photograph of all sections of it, to a research team member at the recruiting site by email, by post or in person..

2. Electronically (using an online form)

The following options may be employed to complete consent electronically:

- The consent form may be completed and signed electronically where an approved mechanism is available such as DocuSign.
- An electronic consent form, generated via the trial database. Participants providing consent using the online form will be required to enter a typewritten signature.

In both cases, the form should be countersigned by the research team member taking consent. There is no requirement that the counter-signature date match the date of the participant signature but the counter-signatory must be satisfied that the consent is genuine.

Regardless of the method of consent, patients or parent/guardians will be provided with information in-person, by post or by email to consider before providing consent.

The information will be discussed with the patient or parent/guardian as outlined above.

Confirmation of eligibility, consent, and the version of the PILs used should be recorded in the participant's paper and/or electronic medical records for any future source data verification, including the date of consent (and child's assent if relevant), that the participant received the PILs, who obtained consent, and signed and dated confirmation that the patient was eligible for enrolment.
Patients will be given the opportunity to consent to any or all of the following:

- Consent to recording their recruitment consultation(s) to inform the QuinteT recruitment intervention
- Consent to taking part in an interview to inform the QuinteT recruitment intervention
- Consent to participate in the CARE pilot trial

5.2.1 Consent to the QRI

All eligible patients who are approached to take part will be invited to take part in an interview with the qualitative researcher about their experiences of being invited to join the CARE pilot trial.

Some study centres will also be involved in audio-recording conversations where the CARE pilot trial is discussed (including conversations held in person and by remote methods). In study centres selected to participate in collecting audio-recordings, eligible patients will be invited to consent to these conversations being audio-recorded, before discussion of the CARE pilot trial begins. Information on the rationale and process for recording recruitment discussions is covered in the relevant CARE PIL. Missed recordings of recruitment conversations are not required to be recorded as protocol deviations.

Participants will be given sufficient time to consider whether they wish to take part in the QRI. Participants will only be consented if they and the local research team feel they have had enough time to consider and ask questions about the QRI. Consent to take part will be documented on the relevant verbal and/or written consent forms. Written consent to audio-recordings will cover all future recruitment discussions. Patient participation in both interviews and audio-recordings is optional. If written consent to record conversations is given, the recordings will be transferred to the University of Bristol for analysis (see section 10.3.1). If no written consent form is received, all recordings for that participant will be deleted, no further recordings will be made and no invitation to interview extended.

5.2.2 Consent to participate in the CARE pilot trial

5.2.2.1 Adults

The participant will be asked to complete a consent form. The research team member and the participant should each sign and date the ICF to confirm that consent has been obtained. Written informed consent should always be sought from the participant where possible. If this is not possible because the participant cannot write, the member of the research team can gain witnessed verbal consent. The participant should receive a copy of the completed ICF, a copy should be filed in the patient's medical records and the original ICF should be filed in the investigator site file (ISF) along with the randomisation form. The participant should also receive a copy of the current PIL.

5.2.2.2 Children

Childrens' PILs are available for children 0-5 years old, 6-10 years old and 11-16 years old. Children aged 6-10 and 11-15 who are capable of understanding it will be given the option of providing assent.

The parent/guardian should receive a copy of the current parent/guardian short and supplementary PIL and appropriate children's PIL. If the parent/guardian wishes for the child to participate in the CARE pilot trial, then they will be asked to sign the ICF. Both the parent/guardian and the person delegated to take consent will each sign and date the ICF. The parent/guardian should receive a copy of the fully completed ICF, a copy should be filed in the patient's medical records and the original ICF should be filed in the investigator site file (ISF) along with the randomisation form. The same would apply in the case of assent being given.

5.2.2.2.1 Children and young people in England, Wales and Northern Ireland

Health Research Authority (HRA) guidance states (46):

- "There is no statute in England, Wales or Northern Ireland governing a child's right to consent to take part in research other than a Clinical Trial of an Investigational Medicinal Product (CTIMP), i.e. consent for non-CTIMPs. However common law presumes that young people aged between 16 and 18 are usually competent to give consent to treatment."
- "Case law suggests that if a young person has sufficient understanding and intelligence to understand fully what is proposed, and can use and weigh this information in reaching a decision (i.e. they are 'Gillick competent'), he or she can give consent to treatment."
- ''In the absence of law relating specifically to research, it is commonly assumed that the principle of 'Gillick competence' can be applied not only to consent for treatment, but also to consent for research."
- ''When a young person is believed to be competent, consent from those with parental responsibility is not legally necessary. However, the involvement of parents in decision-making is encouraged in most circumstances."
- "When a child or young person is not competent, the Children Act and the Children Act (Northern Ireland) Order permits parents (and those with parental responsibility) to consent to medical treatment on their behalf. Consent of only one parent is required."

5.2.2.2.2 Children and young people in Scotland

Health Research Authority (HRA) guidance states (47):

- "There is no specific provision in Scots law governing a child's right to consent to take part in research, other than a Clinical Trial of an Investigational Medicinal Product (CTIMP), i.e. consent for non-CTIMPs."
- In the case of medical treatment, "young people aged 16 and over are deemed to be competent to give consent for medical treatment unless proven otherwise. Children and young people under 16 have a statutory right to give consent to surgical, medical or dental procedures or treatments if they are deemed, by a medical practitioner, to be competent to do so."
- "It is commonly accepted that we can extrapolate a child / young person's right to give consent for treatment, to give them the right to give consent to

take part in non-CTIMP research. It is commonly assumed that they also have a legal right to object to participation."

- "The Children (Scotland) Act permits parents (or those with parental responsibility) to give consent on behalf of a young person under 16 who is not competent. Consent of only one parent is required."

The above guidance will be followed for this trial in relation to participants in Scotland under the age of 16.

5.2.2.2.3 Children and young people in the Republic of Ireland

Consent will be obtained in line with ICH-GCP and all applicable laws and regulations. In line with the HSE National Consent Policy, consent to a child's participation in a study must be obtained from a parent/legal guardian for all paediatric participants under 18 years old (48). Whenever the child has sufficient competence to provide it, a child's assent must be sought in a child-appropriate manner.

5.2.2.2.4 Re-consenting paediatric patients

When a child recruited into the trial reaches the age of 16 years (or 18 years old in the Republic of Ireland) and is therefore deemed competent to provide consent, they should be re-consented if still willing to participate at their next 6-month follow up review. No further data will be collected until a signed consent form has been received.

5.2.3 Consent to be contacted for an interview exploring reasons for declining participation

Patients or their parents/carers who decline participation in the CARE pilot trial will be invited to consent to take part in an interview with the QRI researcher, exploring their experiences of being approached and invited to take part in the study. Where parents/carers consent to take part in an interview, it will be acceptable for the child/young person to attend and contribute if they choose.

5.3 SCREENING AND ENROLMENT LOGS

Research teams at each site will use screening logs to record non-identifying demographic and clinical details of patients who are screened, including: initials, age (years), sex, brain cavernoma diagnosis (yes vs. no), brain cavernoma location (brainstem vs. other), type of brain cavernoma presentation (symptomatic [type] vs. not symptomatic), prior treatment of brain cavernoma, patient certainty about brain cavernoma treatment (yes vs. no, with preferences), clinician certainty about cavernoma treatment (yes vs. no, with preferences), eligibility for the CARE pilot trial (yes vs. no, with reasons for ineligibility), whether approached to take part (yes vs. no, with reasons for not approaching), whether consent was given to the CARE pilot trial (yes vs. no, with reasons for declining), and whether the patient was randomised in the CARE pilot trial (yes vs. no, with reasons for not being randomised and preferred management outside of CARE).

Collection of this information is essential to fulfilling the objectives of the feasibility study that will determine whether a CARE definitive main phase trial could proceed

(see section 2.2.1 above). The proportions of screened patients who are eligible, approached, agree to take part, and randomised (see trial profile, section 3.1) will be quantified to identify points in the recruitment pathway at which patients are being 'lost' to recruitment. Screening logs will be analysed according to the SEAR (Screened, Eligible, Approached, Randomised) framework (49).

5.4 RANDOMISATION

5.4.1 Randomisation procedures

If consent to randomisation in the CARE pilot trial is provided, complete baseline data must be collected by the research team at the baseline visit before randomisation. These data include demographic, clinical, and radiographic information, as well as the consensus preference agreed between each patient and their clinician for neurosurgery or Gamma Knife stereotactic radiosurgery should randomisation allocate them to medical and surgical management (if there is no clear preference for the type of surgical treatment, and both are available in clinical practice, the patient will be randomly allocated to neurosurgery or Gamma Knife stereotactic radiosurgery; see section 3.1). Participants in these two strata will be assigned 1:1 to medical management or medical and surgical management using permuted blocks. Allocation will be concealed until participants are enrolled and assigned by using central web-based randomisation.

A detailed description of the randomisation system including details on block size is held in the statistics master file by Edinburgh Clinical Trials Unit (ECTU).

5.4.2 Treatment allocation

The participant, or the parent/guardian of paediatric participants, and research team at the recruiting site will be notified of the assigned treatment allocation after randomisation.

5.4.3 Blinding (masking)

Treatment allocation in the CARE pilot trial is not blinded (masked), and is therefore open to participants, the clinicians caring for them and local research staff.

We will aim to keep outcome event assessors blind to treatment allocation. We will aim to measure how often assessors are unblinded to treatment allocation during the process of event adjudication.

5.5 WITHDRAWAL OF PARTICIPANTS

Participants are free to completely withdraw, or discontinue any individual component of the study, at any point or a participant can be withdrawn by the PI. In the case of loss of mental capacity in adult participants during the trial, researchers will follow the appropriate local regulations and guidance regarding loss of mental capacity in research (noting that these differ between nations, see below). The participant will remain in the trial unless withdrawn by their representative. Data collected until the time of withdrawal will be retained. If withdrawal occurs, the primary reason for

withdrawal must be documented in the participant's case report form (CRF). The participant will have the option of withdrawal from any or all of:

- consent to be contacted about other research studies
- consent to recording of recruitment conversation(s)
- consent to complete a recorded interview with the QuinteT researcher
- DNA sample provision
- allocated treatment policy
- in-person follow-up
- brain MRI at 6-months
- participant postal follow-up questionnaires
- participant follow-up questionnaire conducted by telephone
- long-term follow-up using record linkage
- use of de-identified data or brain imaging by other research studies

5.5.1 Loss of mental capacity in adult participants in England and Wales

In England and Wales, regulations advise that advice should be sought from the participant's representative on whether the research should be carried out in relation to the participant and what they think the wishes and feelings of the participant would be if they had mental capacity (50).

Where the participant representative (consultee) requests that the participant who has lost mental capacity be withdrawn, a delegated member of the research team will discuss with this person to determine if they think the participant should be withdrawn taking into consideration what the wishes and feelings of the participant would be thought to be if they still had the mental capacity to decide for themselves. If it is agreed that the participant should be withdrawn from the trial, the appropriate trial form will be completed.

5.5.2 Loss of mental capacity in adult participants in Scotland

In Scotland, there is no specific legal provision for adults who lose capacity while taking part in non-CTIMPs. We will respect the participant's original consent to take part however will also consider the participant's representative's views.

Where the participant representative (nearest relative, welfare attorney or welfare guardian) requests that the participant who has lost mental capacity be withdrawn, a delegated member of the research team will discuss with this person to determine if they think the participant should be withdrawn taking into consideration what the wishes and feelings of the participant would be thought to be if they still had the mental capacity to decide for themselves. If it is agreed that the participant should be withdrawn from the trial, the appropriate trial form will be completed (51).

5.5.3 Loss of mental capacity in adult participants in Northern Ireland

In Northern Ireland, section 138 of Part 8 of the Mental Capacity Act (Northern Ireland) 2016 applies which states that consent can be considered to endure provided that the study has not changed significantly since consent was given. We will respect the participant's original consent to take part however will also consider the participant's representative's views.

Where the participant representative (consultee) requests that the patient who has lost mental capacity be withdrawn, a delegated member of the research team will

discuss with this person to determine if they think the participant should be withdrawn taking into consideration what the wishes and feelings of the participant would be thought to be if they still had the mental capacity to decide for themselves. If it is agreed that the participant should be withdrawn from the trial, the appropriate trial form will be completed (52).

5.5.4 Loss of mental capacity in adult participants in the Republic of Ireland

Health Service Executive Policy (48) states that:

"Outside of clinical trials, there is currently no legal framework for a person who lacks decision-making capacity to participate in research. In the absence of any such legal regulations, it is recommended that as a matter of best practice the same principles should apply to both clinical trials and other forms of research. This means that consent for participation in any form of research on behalf of an adult lacking decision-making capacity must be obtained from the person's legal representative".

The same policy defines 'legal representative' as:

"…a person not connected with the conduct of the trial who by virtue of his/her family relationship with an adult lacking decision-making capacity, is suitable to act as the legal representative and is willing and able to do so or (if there is no such individual) a person who is not connected with the conduct of the trial, who is a solicitor nominated by the relevant health care provider.".

6 COMPARATOR

Medical management constitutes standard medical care alone for brain cavernoma, according to UK guidelines (8). This may include anti-epileptic drug therapy to prevent epileptic seizures (e.g. following the recommendations of the Surgical Task Force of the ILAE Commission on Therapeutic Strategies (44)), 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. Provision of these interventions varies because of the extent of the evidence to support their use, and their availability in everyday clinical practice around the UK and Ireland according to the nature of regional and national healthcare systems.

Some clinicians arrange repeat brain MRI for patients with brain cavernoma. This may be done with good reason in order to confirm the diagnosis following intracranial haemorrhage, in case of diagnostic doubt, to guide treatment decisions, or to investigate new symptoms as recommended by recent guidelines (15). But in other cases repeat brain MRI is done to 'monitor' brain cavernomas to reassure patients, although the evidence that this strategy is beneficial is lacking.

7 INTERVENTION

Medical and surgical management in the CARE pilot trial is defined as neurosurgical excision or Gamma Knife stereotactic radiosurgery for brain cavernoma, in addition to all components of medical management described in section 6 above. These interventions will be accessed and delivered according tco what is available in standard clinical practice in the participant's health service.

It is expected (but not mandated by the trial protocol) that surgical management will be delivered within 3 months of randomisation to the trial.

7.1 Neurosurgical excision

Surgery 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.

It is recommended (but not mandated by this protocol) that a post-operative MRI scan is performed within 72 hours of surgery and used along with the surgeon's assessment to confirm complete resection or incomplete resection. A copy of this scan will be taken by the research team and uploaded to the scan database for the trial.

7.2 Stereotactic radiosurgery

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 (29).

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.

If ICH has occurred from the cavernoma, Gamma Knife stereotactic radiosurgery will be carried out once the haematoma is judged to have been reabsorbed to minimise radiation exposure and reduce volume of treatment as much as possible.

8 STUDY ASSESSMENTS

8.1 STUDY ASSESSMENTS

This section outlines the study assessments to be completed by the research team. The schedule of study assessments is provided on the following page.

8.1.1 Table of assessments

Assessment	Identification and Screening	Baseline visit	Within 3 months of baseline	6-month local in-person follow-up	6-monthly central follow-up
Assessment of eligibility	X				
Screening end enrolment logs	X				
Consent to recruitment conversation recordings	X [1]				
Consent to qualitative interview	X				
Recording of patient recruitment conversations	X [2]	X [2]			
Consent to randomisation	X [3]	X [3]			
Demographic, clinical, socio-economic, medication, and radiographic data		X			
DNA sample		X			
Provision of diagnostic brain imaging		X			
Randomisation		X			
Questionnaires		X		X	X
Cavernoma surgical management			X		X
Repeat brain MRI				X	
Outcomes and adverse events				X	X
Qualitative interview			X [4]		

1 – Research teams will be asked to capture verbal consent to audio-recordings of recruitment conversations when the approach is made to the participant. If this is not possible at this time, consent may be captured during subsequent recruitment conversations.

2 – Recordings of recruitment conversations with patients should be captured (as requested) wherever the CARE pilot trial is discussed (illustrated here but not restricted to Screening and Baseline Visit).

3 – Consent to participation in CARE may be collected at the Baseline Visit or in advance, during the Screening stage.

4 – Interviews with patients will take place within 3 months of being invited to take part in the trial.

8.1.2 Screening

Potential participant identification and screening should be carried out as per sections 5.1 and 5.2.

Approached patients who decline to take part will be given the opportunity to take part in an interview to discuss why they decided not to participate as per section 5.2.3.

Research teams should complete screening and enrolment logs as per section 5.3.

8.1.3 Informed consent

It is likely that consent to participate in the CARE pilot trial will be captured during a clinical consultation between the patient and a clinician who is also a member of the CARE pilot trial research team. The consenting procedures outlined in section 5.2. will be followed.

8.1.4 Baseline visit

Baseline visits may be conducted remotely or in person, depending on patient, carer or parent/guardian preference, and restrictions on working practices. These visits will be conducted by research team staff who are members of, or affiliated to, the clinical care team.

Research team staff will collect the following data at the baseline visit from all study participants: demographics, socioeconomic characteristics (e.g. employment, education, and carer needs), medical history (including details of the type of presentation of the symptomatic brain cavernoma and family history) and medications (including drug therapy).

The patient reported questionnaires that should be completed are EQ5D-5L for adults or EQ5D-3Y for children and Liverpool Seizure Severity Scale (LSSS).

The patient should be assessed by the research team member (assisted by parent/guardian where required) using the following scales:

1. Modified Rankin Scale (mRS) score
2. National Institute of Health Stroke Scale Score (adult or paediatric) (if examined in person)
3. Karnofsky Performance Status (KPS) scale in adults and Lanksy Play-Performance Scale in children (LPS)

If the visit is done face to face, research team staff will collect a venous blood sample of up to 10mL from patients who consent into an EDTA tube for genetic analysis. Samples will be shipped immediately by first class post and in adherence with UN3373 guidelines to the central laboratory at the Edinburgh Clinical Research Facility.

The research team at each site is responsible for entering these data onto the study Electronic Case Report Form (eCRF). Once baseline data are complete, randomisation may proceed. After randomisation is performed, the PI and other research staff on the delegation log at the participant's site will be sent email

confirmation or randomisation and treatment allocation, with a reminder about the subsequent scheduled activities in the trial.

Research teams will upload the relevant pseudo-anonymised DICOM images of the brain imaging (including diagnostic brain MRI) that confirmed the mode of presentation and diagnosis of the symptomatic cavernoma to the trial imaging database. Images may also be copied to CD and posted to the brain imaging management team for upload. These scans will be stored for subsequent validation by a senior neuroradiologist to confirm or refute eligibility.

8.1.5 Three-month adherence check

The PI and research staff at a site where a participant was randomised will be sent an email prompt around three months after baseline to report whether surgical management was undertaken after randomisation, regardless of whether the participant was allocated to surgical management by randomisation. This will allow detection of cross-overs between the two arms of the trial.

Adherence to the randomised allocation will be assessed by comparing treatment allocation with the completion of the surgical management case report form. Lack of adherence to the randomised treatment allocation will not be recorded as a protocol deviation or violation.

8.1.6 Six-month local follow-up visit

Participants will be asked to attend for their first six-month follow-up visit in person in order to perform brain MRI (which will be permitted between 5-7 months after randomisation) to assess cavernoma presence and size as a measure of the efficacy of surgical management. These images should be uploaded to the trial imaging database or research teams may post CDs to the MRI management team for upload. The radiology department at each site will issue the clinical report of any brain MRI performed for the CARE pilot trial. A copy of MRI brain scans performed before or after surgical management (if performed) will be taken by the research team and uploaded to the scan database for the trial. A copy of the MRI performed on the day of treatment for patients undergoing stereotactic radiosurgery will be taken by the research team and uploaded to the database for the trial (or copied to CD and posted to the MRI management team for upload).

Research teams will record details of any clinical outcome events that have occurred since randomisation, whether surgical management was used, including specific operative techniques or methods of stereotactic radiosurgery. Although surgical management in the CARE pilot trial will continue to be neurosurgical excision or stereotactic radiosurgery, we will collect details of each type of surgical management used after randomisation to allow us to quantify the use of emerging technologies, such as minimally invasive therapeutic approaches for brain cavernoma such as magnetic resonance thermography-guided laser interstitial thermal therapy, or stereotactic laser ablation (41).

Imaging studies performed because of the occurrence of an outcome event will be collected by the research team and uploaded to the scan database for the trial.

The patient reported questionnaires that should be completed are EQ5D-5L for adults or EQ5D-3Y for children and Liverpool Seizure Severity Scale (LSSS).

The patient should be assessed by the research team member (assisted by parent/guardian where required) using the following scales:

1. Modified Rankin Scale (mRS) score
2. National Institute of Health Stroke Scale Score (adult or paediatric) (if examined in person)
3. Karnofsky Performance Status (KPS) scale in adults and Lanksy Play-Performance Scale in children (LPS)

If a blood sample for genetic analysis was not collected as the Baseline Visit, research team staff will collect a venous blood sample of up to 10mL from patients who consent into an EDTA tube. The sample will be shipped immediately by first class post and in adherence with UN3373 guidelines to the central laboratory at the Edinburgh Clinical Research Facility.

8.1.7 Six-monthly central follow-up visit

Thereafter, staff at the TCC, will perform six-monthly follow-up (+/- one month) by post in all patients who do not withdraw from follow-up in the CARE pilot trial, after checking the participant's vital status with their general practitioner. If a response is not received by the TCC within a fortnight, a research team member (based within ECTU) will contact non-responders and follow-up data by telephone or email.

Follow-up questionnaires will confirm participants' current domicile and general practitioner, and ask about disability, health-related quality of life, the occurrence of primary or secondary clinical outcomes, serious adverse events, and the occurrence of surgical management of the brain cavernoma (as described above). These questionnaires will also ask for information about relevant concomitant medications, such as anti-epileptic drugs. We will also record the use of drugs like propranolol, antiplatelet agents, anticoagulant agents and statins, which may have disease-modifying effects (49).

The patient reported questionnaires that should be completed are EQ5D-5L for adults or EQ5D-3Y for children and Liverpool Seizure Severity Scale (LSSS).

The patient should be assessed by the research team member (assisted by parent/guardian where required) using the following scales:

1. Modified Rankin Scale (mRS) score
2. Karnofsky Performance Status (KPS) scale in adults and Lanksy Play-Performance Scale in children

8.1.8 Patient Interviews

In-depth interviews will be conducted by the qualitative researcher with a sample of eligible patients who have been approached to take part in the trial (including those accepting or declining participation) (see section 9.4). Purposive sampling will be used to identify patients who have declined participation from a variety of study sites, to gain insight into study-wide and site-specific reasons patients may have for declining. Purposive sampling of patients accepting participation in the CARE pilot trial will also be considered if findings from analysis of recorded recruitment conversations indicates this will be helpful. Interviews will take place within three months of the decision about trial participation (see 8.1.1).

8.2 LONG TERM FOLLOW UP

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.

8.3 BRAIN MAGNETIC RESONANCE IMAGING

Participants who consent to be randomised should undergo repeat brain MRI once at six months (± one month) after randomisation.

Brain MRI is usually undertaken after surgical management in clinical practice, but not always during medical management. If a participant undergoes brain MRI with the required sequences as part of their routine clinical care before the 6-month local follow up visit, the research team will request the brain MRI and upload the scan to the trial imaging database. Otherwise, repeat brain MRI should be performed six months after randomisation (± one month), regardless of treatment allocation, treatment received, and timing of treatment, for research purposes.

As a minimum standard, T1-weighted, T2-weighted, and haem-sensitive sequences (gradient recalled echo or susceptibility weighted imaging) will be required within standard sequence parameters and with an acceptable slice thickness and voxel size. We will collect any other sequences performed (e.g. Fluid Attenuated Inversion Recovery (FLAIR) post-contrast, T1 or FLAIR, and Diffusion-Weighted Imaging [DWI] sequences) to ascertain the frequency of their use for follow-up of brain cavernoma in everyday clinical practice.

8.4 OUTCOME EVENT ADJUDICATION

Clinical outcomes including death and stroke-like events will be adjudicated by a member of the TMG using all available source data (with patient identifiers and any information about cavernoma treatment redacted by the research team before upload to trial database) including clinical correspondence, brain imaging reports, and death certificate. Brain imaging performed during follow-up will be reviewed by a consultant neuroradiologist. Outcome assessors will aim to remain blinded to the brain cavernoma treatment policy that was allocated at randomisation, and if possible any medical and surgical management of the brain cavernoma received. If blinding could not be maintained, this will be documented.

8.5 DNA SAMPLE STORAGE AND ANALYSIS

A venous blood sample of up to 10mL will be collected into an EDTA tube for genetic analysis. Samples will be shipped immediately by first class post and in adherence with UN3373 guidelines to the central laboratory at the Edinburgh Clinical Research Facility for DNA extraction and future analysis. This sample will be stored for subsequent investigation of genetic modifiers of treatment effect, which are currently unknown (1). The relevant approvals will be sought for future research involving these samples.

9 DATA COLLECTION

Data items to be collected are described in section 8. This section describes the methods of data collection.

9.1 SOURCE DATA DOCUMENTATION

Source documents are those in which information is recorded and documented for the first time. The location of source data collected from the CARE pilot trial participants is detailed in the CARE pilot trial Source Data Plan. Investigators will be required to retain paper copies of completed ICFs. Otherwise, clinical data will be entered directly into the eCRF by the research team and TCC staff based on information in the medical records, which will be regarded as source data.

9.2 CASE REPORT FORMS

Documents reflecting the data required at each study assessment will be made available to research teams, to support entry into the study database of: Screening Log, Consent to Contact form, Consent and Status Log, Baseline Visit CRF, 6-Month Follow-up CRF, Serious Adverse Events Log and Change of Status form. Site research teams will be responsible for transcribing these data into the database. Data will be transcribed by those staff delegated to do so on the delegation log held at site.

9.3 STUDY DATABASE

The study database will be created and maintained by ECTU. This database will be compliant with the relevant regulations and Sponsor Standard Operating Procedures (SOPs). Trained and delegated members of the research team will be given password-protected logins to the database. The data will be stored in a secure server in the University of Edinburgh.

9.4 QRI DATA COLLECTION

9.4.1 Screening log data

Screening logs will collect de-identified data on patients screened, identified as eligible, approached and accepting randomisation into the CARE pilot trial (see section 5.4) and identify points in the pathway where patients may be ‘lost’ to recruitment. Findings will guide data collection using the qualitative methods outlined below.

9.4.2 Recordings of recruitment conversations

Patients will be invited to consent to the recording of all conversations during which participation in the CARE pilot trial is discussed. These conversations provide insight into both how the study is presented to patients and how patients interpret that

information. Analysis of these conversations can reveal misunderstandings about that trial that can then be addressed in recruiter training.

9.4.3 Patient and staff interviews

A sample of eligible patients who have been approached to take part in the trial (including those accepting and declining participation) will be invited to take part in an in-depth interview with the qualitative researcher based at the University of Bristol. This interview will take place within three months of being invited to take part in the trial.

Interviews with patients will explore views on the presentation of trial information, understanding of study processes (e.g. randomisation), and reasons underlying decisions to consent or decline to participate in the CARE pilot trial. Numbers of interviews will be guided by the concept of 'data saturation' with final sample size (up to a maximum of 20 interviews) determined by the point at which three new interviews fail to shed insights.

Staff involved in the trial will also be invited to take part in an in-depth interview. Interviews with health professionals will use purposeful sampling. Interviews with staff will include members of the trial TMG, including the CI, and those closely involved in the design, management leadership and coordination of the trial (approximately n=4-8); clinicians or researchers involved in trial recruitment (approximately n=12-20).

Interviews with TMG members and investigators at sites will investigate their perspectives on the CARE pilot trial and experiences of recruitment (where relevant). Key topics explored will include views about the study design and protocol; understandings of the evidence on which the study is based; perceptions of uncertainty/equipoise in relation to the intervention arms; views about how the arms/protocol are delivered in clinical centres; methods for identifying eligible patients; views on eligibility, and examples of actual recruitment successes and difficulties.

Interviews will take place at a mutually convenient time by telephone or video-conferencing and will be recorded using University of Bristol approved methods for data capture and storage (this may include MS Teams and Zoom, depending on current policies).

9.4.4 Meetings

A QuinteT researcher will observe all TMG and TSC meetings during which the study protocol is developed and finalised, with a focus on discussions and final presentation of equipoise and eligibility criteria.

9.4.5 Trial documentation

The QRI team will continue to review the wording of patient information leaflets (PIL) and consent forms in line with any feedback from the above that indicates content that is unclear or potentially open to misinterpretation.

10 DATA MANAGEMENT AND TRANSFER

10.1 PERSONAL DATA

The following personal data will be collected as part of this research: contact details (including home address, telephone numbers, email address,date of birth and contact information for relatives/carers), demographic information (including age and sex), socioeconomic information, medical history (including prior symptoms from brain cavernoma, major co-morbidities, medication history, family history), and unique healthcare identifier (such as the Community Health Index [CHI] in Scotland, NHS Number, or equivalent in other nations). Unique healthcare identifiers will be collected to enable long term patient follow-up and ensure correct identification of patients when contacting GPs or sites for follow-up.

Personal data will be processed by site research teams, the TCC at the University of Edinburgh and qualitative research staff at the University of Bristol:

- Personal data will be stored at site by research teams on NHS computers (desktop and laptop). Computers will be password protected and kept in locked offices. All paper files containing personal data will be held in filing cabinets in NHS offices that will be locked when unattended. Study documentation will be accessed by the study team only.
- Personal data will also be entered into the secure trial database which will be hosted on a University of Edinburgh server and will be accessed by the TCC to perform 6-monthly follow-up with patients and long term follow up via record linkage.
- Contact information will be accessed by/passed to the qualitative researcher based at University of Bristol to contact patients for interview.
- Screening log data will be accessed by the qualitative researcher based at University of Bristol as part of the research.

Additional information on personal data in relation to the qualitative aspect of the trial is included in section 10.3.

10.2 BRAIN MRI SCANS

Diagnostic brain imaging will be managed by the Systematic Management, Archiving & Reviewing of Trial Images Service (SMARTIS) at the University of Edinburgh. We will establish a scan database (housekeeping system) using established models, to track all scan episodes, completeness and assessments; this will interface with the trial database. De-identified brain MRI scans will be uploaded to this database by research teams or by SMARTIS staff if CDs are posted to them. Scan collection, quality assurance, curation, and backup will be conducted by SMARTIS staff at the Brain Research Imaging Centre (BRIC), University of Edinburgh. Prof Phil White, or another neuroradiologist involved in the trial, will review the diagnostic and follow-up brain MR imaging using standardised review proforma derived from pre-existing validated work (Scottish Audit of Intracranial Vascular Malformations - SAIVMs).

10.3 QUINTET RECRUITMENT INTERVENTION

10.3.1 Recordings of recruitment conversations

Recruitment conversations will be recorded by a research team member using a method of secure data capture and storage in line with University of Bristol procedures (as outlined on the University of Bristol website). Audio-recordings will be transferred by secure data transfer by the approved qualitative research team members onto a secure drive at the University of Bristol for long-term storage and analysis. Audio-recordings will be labelled with the participant identification number; identifiable patient details will not be used.

Audio-recordings will be subject to targeted transcription and edited to protect the anonymity of respondent. Transcription will be undertaken by an approved transcription service/transcriber that has signed the necessary confidentiality agreements with the University of Bristol. Data will be managed using NVivo software and stored on encrypted drives at the University of Bristol, in line with the university's data storage policies and in line with GDPR legislation.

At the end of the study, audio-recordings will be kept for at least 10 years before they will be destroyed. Transcripts will be stored indefinitely in secure research data storage designated 'controlled access', so can only be accessed by approved individuals who are interested in conducting their own analyses of the data. These individuals will have to submit an application to do this, which will be assessed by an independent committee. However, all data will have identifiable information removed before they are made available, and there will be no way to identify any individuals mentioned in interviews/appointments.

10.3.2 Interviews

Approved qualitative research team members from University of Bristol will access participants' contact details via the trial database or be securely passed them by the research team for the purposes of contacting patients who have consented to interviews as part of the QRI. Team members will be provided with an individual user account for the database with restricted, password-controlled access.

Interviews with patients and staff will be recorded directly by the qualitative researcher using processes for secure data capture and storage in line with University of Bristol procedures (as outlined on the University of Bristol website). Recordings will be held on a secure drive with restricted access at the University of Bristol for long-term storage and analysis. Recordings will be labelled with the participant identification number; identifiable patient details will not be used. At the end of the trial, recordings will be held for a minimum of 10 years after which they will be destroyed.

Data from the QRI will be shared at the end of the trial as outlined in section 17.3.

10.3.3 QRI documentation

Paper or electronic documentation which is generated through the process of performing the QRI will be stored securely at the University of Bristol with access restricted only to approved personnel.

10.4 DATA CONTROLLER

The University of Edinburgh and NHS Lothian are joint data controllers.

10.5 DATA BREACHES

Any data breaches will be reported to the University of Edinburgh and NHS Lothian Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

11 STATISTICS AND DATA ANALYSIS

11.1 SAMPLE SIZE CALCULATION

Symptomatic brain cavernoma incidence data indicate that ~240 people would be newly-diagnosed during 18 months of recruitment (4). We aim for all of these patients to be screened, but if 10% are missed and 10% decline to participate, we expect research teams to identify ~190 patients. In the ARUBA trial, 226/726 (31%) of the eligible patients approached were randomised (30), so we expect ~60 patients with symptomatic brain cavernoma to be randomised in the CARE pilot trial.

11.2 PROPOSED STATISTICAL ANALYSES

In this pilot phase, analyses are descriptive only, and there will be no formal statistical tests.

We will quantify the number and proportions (with 95% confidence intervals to reflect their precision) of patients who are screened, eligible, approached, consent and are randomised. We will construct a CONSORT diagram to summarise the distribution and progress of participants in the trial including the numbers of withdrawals (50).

We will report descriptively the following: the number and the proportion of the collaborating sites that take part and recruit participants to the CARE pilot trial; research teams' implementation of trial procedures measured by number and type of protocol deviation; the numbers of participants allocated to neurosurgery and stereotactic radiosurgery; adherence to the allocated intervention; completeness of follow-up that would be due at each 6-month interval; completeness of baseline, imaging and outcome data; the frequency of outcome events overall and in an intention-to-treat analysis keeping patients in the treatment group to which they were allocated during all available follow-up.

We will also compare descriptively the characteristics of eligible patients who are screened and do not participate in the CARE pilot trial to eligible patients who are randomised using the characteristics recorded on the screening logs to assess generalisability (external validity) and any recruitment bias.

We will assess measures of functional outcome, to assess which has suitable statistical properties for use in a main phase trial (such as lack of floor/ceiling effects). We will assess whether such a measure (like the method we have used before (9)) would be more suitable as a primary outcome in place of intracranial haemorrhage.

11.3 QUINTET RECRUITMENT INTERVENTION DATA ANALYSIS

11.3.1 Screening and enrolment logs

The QuinteT researcher will analyse data using the SEAR framework to observe differences between sites in recruitment patterns as new sites open (51). Simple descriptive analyses will identify points in the recruitment pathway at which patients are lost to recruitment to the cohort or trials and the reasons why. Detailed eligibility and recruitment pathways will be compiled for sites, noting the point at which patients receive information about the study, which members of the clinical team they meet, and the timing and frequency of appointments. Recruitment pathways will be compared with details specified in the trial protocol and pathways from other sites to identify practices that are potentially more/less efficient. Numbers of eligible and recruited patients will be compared across sites and considered in relation to estimates specified in the grant application/study protocol. These data will be triangulated with qualitative findings (see below) to identify barriers and potential solutions to recruitment.

11.3.2 Recordings of recruitment conversations and interviews

Audio recordings of recruitment conversations will be sought from a purposefully sampled range of recruiting sites (showing higher and lower recruitment) to ensure maximum variation and recordings will be analysed by the QuinteT researcher. The audio recordings will be used to explore information provision, management of patient treatment preferences, and randomisation decisions to identify recruitment difficulties and improve information provision. Audio-recorded recruitment consultations will be subjected to targeted transcription with relevant sections first identified then transcribed and identifying data removed before fuller analysis. Analysis will employ content, thematic, and novel analytical approaches, including targeted conversation analysis (52) and quanti-qual appointment timing (the ‘Q-Qat method’) (53), as described in the QuinteT recruitment intervention protocol [24]. Interview data will be analysed thematically using constant comparative approaches derived from Grounded Theory methodology (54).

Findings from the investigation of recruitment to the CARE trials will be fed back to the CI, TMG, and collaborator Bauld, where appropriate, to determine a plan of actions to optimise recruitment to the pilot trials. Actions may include feedback to individuals or in groups as appropriate and will include template patient pathways, individualised or generic ‘tips’ sheets for recruiters and delivery of recruiter training. Group feedback and training will be timed to coincide with the meetings of professional associations mentioned above.

12 HEALTH ECONOMICS AND DATA ANALYSIS

We will collect self-reported health service use and social/economic outcomes using bespoke question sets that will inform future economic analyses (9; 10). If data collection is confirmed as feasible, then a previously developed decision model (20) will be updated and further developed to incorporate data collected within this study to provide a putative estimate of cost-effectiveness and its drivers. In the context of the CARE pilot trial, the health economics objectives are to: (i) design and test an optimal mechanism for the capture of resource use and cost data in community NHS

settings, NHS secondary care, participants' out of pocket expenses and carer costs, (ii) estimate expected effect size and variance of relevant outcomes including health-related utility and quality-adjusted life years, and (iii) identify and measure the potential cost implications of surgical management of cavernomas. We will measure health-related utility (55), healthcare-related resource use and costs using participant questionnaires before randomisation and at each follow-up timepoint (56). These costs will be ratified by the study team through scrutiny of the patient pathway in both arms of the trials using available medical records to populate CRFs. We will assign unit costs using standard national costing sources where available, or through consultation with relevant service business managers. Costs will be summarised from the perspectives of (a) the NHS and personal social services, and (b) wider society (including participants' and their carers' out-of-pocket costs and lost productivity).

13 ADVERSE EVENTS

The PI is responsible for the detection and documentation of events meeting the criteria and definitions detailed below. This task may also be carried out by another suitably qualified clinician in the research team at that site who has been delegated this role. Only clinical outcomes and relevant serious adverse events (SAE) related to medical and surgical management that occur after randomisation until the final 6-month follow-up review must be recorded in the eCRF. Participants will be instructed to contact their local research team if any symptoms develop at any time after being randomised.

13.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

An **adverse reaction** (AR) is any untoward and unintended response to an IMP which is related to any dose administered to that participant.

A **serious adverse event** (SAE), **serious adverse reaction** (SAR). Any AE or AR that at any dose:

- results in death of the clinical trial participant;
- is life threatening*;
- requires in-patient hospitalisation^ or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect;
- results in any other significant medical event not meeting the criteria above.

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

^Any hospitalisation that was planned prior to enrolment will not meet SAE criteria. Any hospitalisation that is planned post enrolment will meet the SAE criteria.

13.2 IDENTIFYING SAEs

Participants will be asked about the occurrence of SAEs wherever contact is made with them between randomisation and the final central six monthly follow up review. Open-ended and non-leading verbal questioning of the participant will be used to enquire about SAE occurrence. Only events which are clinical outcomes on the trial or are related to medical and surgical management will be recorded as AEs and SAEs. Participants will also be asked if they have been admitted to hospital, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an SAE, the event will be recorded. SAEs might also be identified via information from support departments e.g. laboratories.

13.3 RECORDING SAEs

When an SAE occurs, it is the responsibility of the PI, or another suitably qualified clinician in the study team who is delegated to record and report SAEs, to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. It is the PIs responsibility, or another suitably qualified clinician that has been delegated this role, to assess whether an AE is an outcome in the trial. The PI or delegated research team member will then record all relevant information in the CRF/AE log and on the SAE form (if the AE meets the criteria of serious). If the AE is detected by central means of follow-up, the TCC will initiate the collection of this information but enlist the help of local site research staff to acquire the relevant clinical and imaging information. Information to be collected includes type of event, onset date, clinical assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

13.3.1 Pre-existing medical conditions

Pre-existing medical conditions (i.e. existed prior to informed consent) should be recorded as medical history and only recorded as SAEs if medically judged to have worsened during the trial and meet the definition of an SAE.

13.3.2 Worsening of the underlying condition during the trial

Medical occurrences or symptoms of deterioration that are expected to be due to the participant's underlying condition should be recorded in the participant's medical notes and only be recorded as SAEs if medically judged to have unexpectedly worsened during the trial. Events that are consistent with the expected progression of the underlying disease should not be recorded as SAEs.

13.4 ASSESSMENT OF AEs AND SAEs

Each AE which may be a clinical outcome for the trial or may be related to surgical management must be assessed for seriousness, causality, severity and ARs must be assessed for expectedness by the PI or another suitably qualified clinician in the study team who has been delegated this role.

The CI may not downgrade an event that has been assessed by an Investigator as an SAE or a related and unexpected SAE, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate.

13.4.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 13.1.

13.4.2 Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the study intervention according to the definitions below.

Unrelated: where an event is not considered to be related to the treatment allocated at randomisation.

Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the treatment allocated at randomisation.

13.4.3 Assessment of Expectedness

If the AE is judged to be related to the study interventions, the Investigator will make an assessment of expectedness.

Expected: The type of event is expected in line with the treatment allocated at randomisation.

Unexpected: The type of event was not listed in the protocol or is not an expected clinical occurrence.

13.4.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE and record this on the CRF or SAE form according to one of the following categories:

Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.

Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: an event that prevents normal everyday activities.

Note: the term ‘severe’, used to describe the intensity, should not be confused with ‘serious’ which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

13.5 REPORTING OF SAEs

Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the ACCORD (Academic and Clinical Central office for Research and Development) Research Governance & Quality Assurance (QA) Office **immediately or within 24 hours**. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received.

The SAE form will be emailed to ACCORD via Safety@accord.scot. Only forms in a PDF format will be accepted by ACCORD via email.

The Investigator will follow up each event until resolution. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the investigator and request the missing information.

All reports faxed to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).

The sponsor is responsible for reporting SAEs that are considered to be "possibly related" to the treatment allocation and "unexpected", to the REC within 15 days of becoming aware of the event.

The TCC will provide SAE line listings from ACCORD for circulation prior to DMC meetings.

14 PREGNANCY

Although pregnancy is not considered an AE or SAE; as a matter of safety, the Investigator will be required to record any female participant's pregnancy which occurs while participating in the study. The Investigator will need to record the information on a Pregnancy Notification Form and submit this to the ACCORD office within 14 days of being made aware of the pregnancy. All pregnant female participants will be followed up until the outcome of the pregnancy.

15 OVERSIGHT ARRANGEMENTS

15.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a TMG, consisting of the CI, grant holders, Trial Manager and PAG members. The roles and responsibilities of the TMG and the names of committee members are detailed in the TMG charter.

The Trial Manager will coordinate and oversee the trial and will be accountable to the CI. The Data Manager will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the site team.

15.2 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. The terms of reference of the TSC, reporting arrangements and the names of committee members are detailed in the TSC charter.

15.3 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the trial. The terms of reference of the Data Monitoring Committee and the names of committee members are detailed in the DMC charter. The DMC Charter will be signed by the appropriate individuals before recruitment to the trial starts.

15.4 PATIENT ADVISORY GROUP

The patient advocacy organisation CAUK will organise input from a diverse Patient Advisory Group which will aim to meet bi-monthly. Two representatives of this PAG will join the TSC. The terms of reference of the Patient Advisory Group and the names of committee members are detailed in the PAG Terms of Reference.

15.5 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial 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.

15.6 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.

16 GOOD CLINICAL PRACTICE

16.1 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). Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

16.2 INVESTIGATOR RESPONSIBILITIES

The PI 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 PI. Responsibilities may be delegated to an appropriate member of study site staff. A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

16.2.1 Informed Consent

The PI 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 PILs and ICFs will be provided. The oral explanation to the participant will be performed by the PI or qualified delegated person, and must cover all the elements specified in the PIL 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).
The PI or delegated member of the research team and the participant will sign and date the ICF(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes (if applicable).

16.2.2 Study Site Staff

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

16.2.3 Data Recording

The PI is responsible for the quality of the data recorded in the CRF at each Investigator Site.

16.2.4 Investigator Documentation

The PI will ensure that the required documentation is available in local Investigator Site files.

16.2.5 Training

16.2.5.1 Recruitment site training

Research teams will be trained on the trial protocol, sponsor SOPs and QRI processes by the trial team and qualitative researcher (in person or remotely). This will be completed before the site is permitted to open to recruitment.

QRI training of PIs and recruiters will take place as needed and as indicated by QRI findings as described in 3.1.1.2 above. Findings from data collected during the QRI will be presented to the CI and TMG and a plan of action formulated to improve recruitment and information provision. Generic challenges such as how to explain study processes (e.g. randomisation) may be addressed through dissemination of 'tips and guidance' documents. Supportive feedback will be a core component of the plan of action, with the exact nature and timing dependent on the issues that arise. Site-specific feedback may cover institutional barriers, while multi-centre group feedback sessions may address widespread challenges, that would benefit from discussion. All group feedback sessions will be aided by de-identified data extracts from interviews and recorded recruitment conversations. Individual confidential feedback will also be offered, particularly where recruiters experience specific difficulties or where there is a need to discuss potentially sensitive issues. Investigator meetings and site visits may also be employed to discuss technical or clinical challenges (e.g. discomfort surrounding eligibility criteria).

16.2.5.2 GCP training

For non-CTIMP (i.e. non-drug) studies all researchers are encouraged to undertake Good Clinical Practice (GCP) training in order to understand the principles of GCP. However, this is not a mandatory requirement unless deemed so by the sponsor. GCP training status for all research team members should be indicated in their respective CVs or a GCP certificate may be provided.

16.2.6 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. The PI and research 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 information, which is confidential or identifiable, and has been 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 parties not involved in the trial.

16.2.7 Data Protection

All PIs and research team staff (including central research team staff and qualitative research staff) involved with this study must comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act) with regard to the collection, storage, processing and disclosure of personal information.

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

Published results will not contain any personal data and be of a form where individuals are not identified and re-identification is not likely to take place.

STUDY CONDUCT RESPONSIBILITIES

16.3 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 will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

16.4 MANAGEMENT OF PROTOCOL NON-COMPLIANCE

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. All protocol deviation logs and violation forms should be emailed to QA@accord.scot

Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies. An alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

The following will not be recorded as protocol deviations:

- Missed audio-recordings of conversations by research teams.
- Lack of adherence to the randomised treatment allocation.

16.5 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree: (a) the safety or physical or mental integrity of the participants of the trial; or(b) the scientific value of the trial.

If a potential serious breach is identified by the CI, a site PI or delegates, the co-sponsors must be notified via seriousbreach@accord.scot within 24 hours. It is the

responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to REC as necessary.

16.6 STUDY RECORD RETENTION

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

QRI audio-recordings will be kept for at least 10 years before they will be destroyed and electronic transcripts will be stored indefinitely in secure research data storage.

16.7 END OF TRIAL

The end of study is defined as the last participant's last visit. This will be a 6-month follow up review.

The PIs 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, and Research and Development Offices and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The PIs will inform participants if the study is closed prematurely and ensure that the appropriate follow up is arranged for all participants involved.

End of study notification will be reported to the co-sponsors via email to resgov@accord.scot.

16.8 CONTINUATION OF TREATMENT FOLLOWING THE END OF STUDY

There are no provisions for ancillary or care for participants after the trial ends, because the interventions in the CARE pilot trial are provided in standard clinical practice and aftercare will occur as normal in standard practice.

16.9 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, researchers employed by the University and the TMG. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the CI 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 National Health Service will have the benefit of NHS Indemnity.

- Sites outside the United Kingdom may be responsible for arranging their own indemnity or insurance for their participation in the study, and will be responsible for compliance with local law applicable to their participation in the study.

17 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

17.1 AUTHORSHIP POLICY AND REPORTING

On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with the International Conference on Harmonisation guidelines.

A final research report will be prepared as required by the funder. A summary report of the study will be provided to the REC within one year of the end of the study.

The success of the CARE pilot trial will be determined by the collaboration of a large number of doctors, nurses, other health professionals, patients, relatives, and the patient support organisation CAUK. For this reason, the credit for the main results will be given, not exclusively to the TMG, but to all collaborators with the trial. The primary trial publication will be drafted by a writing committee drawn from the TMG, whose membership has been approved by the TSC. Authorship will be under a group name for the CARE pilot trial collaboration and include the writing committee. People included on active sites' delegation logs will be included in any listing of collaborators in trial publications. The manuscript will be approved by the TSC before submission for publication.

17.2 PUBLICATION AND DISSEMINATION

Publications will be managed in line with funder requirements. We will submit manuscripts to peer reviewed journals, describing the findings of the QuinteT recruitment intervention and the CARE pilot trial (in addition to the final report for publication in the HTA journal). We will pay for these papers to be published open access. We will also present our findings at meetings of the Association of British Neurologists, the Society of British Neurological Surgeons, the British Paediatric Neurosurgery Society, and the British Paediatric Neurology Association.

We will disseminate a plain English summary of the findings of the CARE pilot trial to participants and public audiences with input from, and acknowledgement of, the Patient Advisory Group. We will offer to present our project and its findings to the annual meetings of CAUK, which is a national event that gives people affected by cavernoma a voice to talk about the issues that matter to them. We will produce an easy access report of our findings to share with the public and patients, and we will post it in the public domain on the CAUK website. We will keep the public, patients, and carers informed about study progress and results via social media channels (Facebook and Twitter).

17.3 DATA SHARING

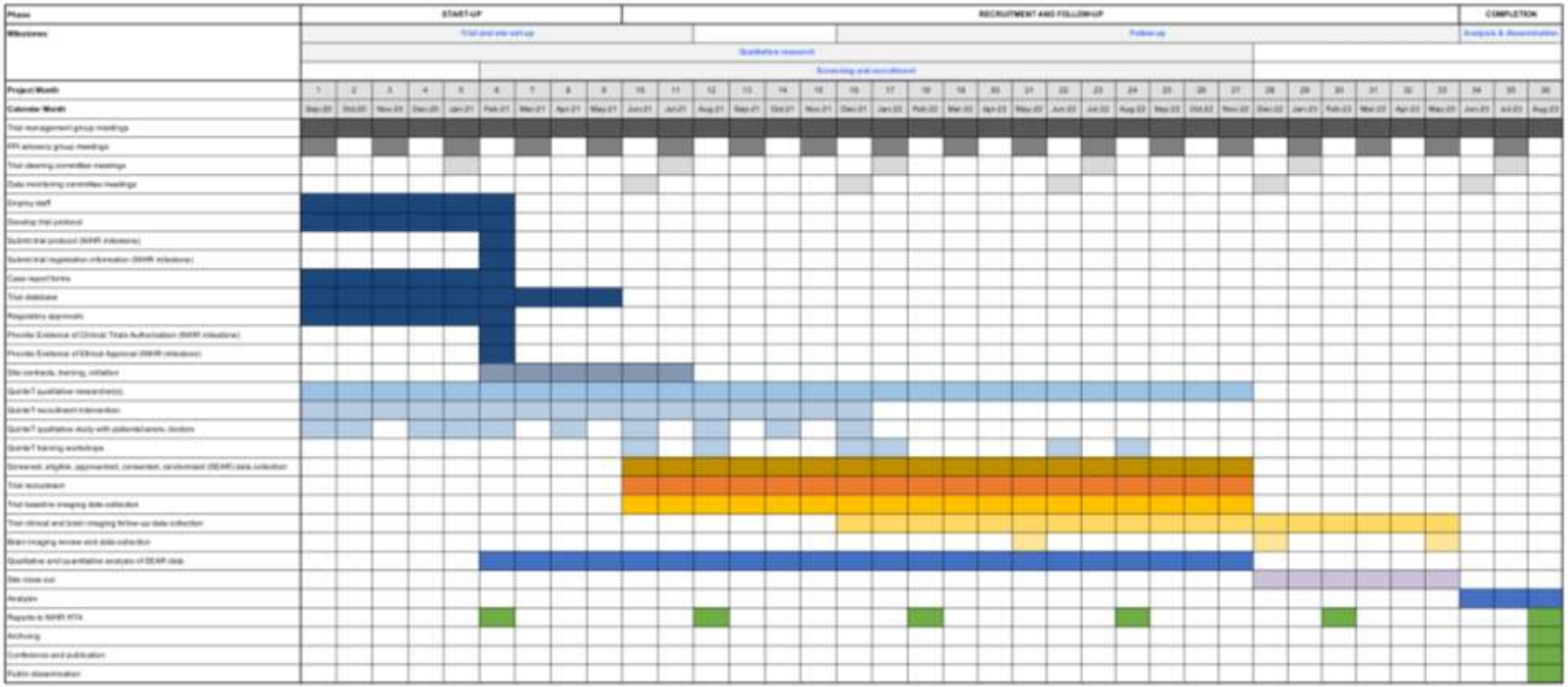
Ownership of the data arising from this study resides with the study team.

Following publication of the primary paper, a de-identified individual participant data set will be prepared for sharing purposes. All data requests should be submitted to the CI for consideration. Access to de-identified data may be granted following review by CI and TMG.

Data collected during PAG discussions or in QuinteT recruitment intervention data collection with patients may include quotes that will be useful to CAUK in producing or optimising existing patient or carer information; where participant consent has been given, these data (after removing or disguising identifiers) will be made available by the QuinteT research group in Bristol to CAUK in order to maximise their impact.

At the end of the study, QRI audio-recordings will be kept for at least 10 years before they will be destroyed. Transcripts will be stored indefinitely in secure research data storage, which can be accessed by approved individuals who are interested in conducting their own analyses of the data. These individuals will have to submit an application to do this, which will be assessed by an independent committee. However, all data will have identifiable information removed before they are made available, and there will be no way to identify individuals mentioned in interviews/appointments.

18 TRIAL TIMELINE



Footnote: Trial delivery timings are targets, variations will not be recorded as a protocol deviation/violation.

19 PROTOCOL VERSION CONTROL HISTORY

19.1 Version 1.0 (29Jan2021)

Original sponsor-approved version, submitted as part of application for REC review.

19.2 Version 2.0 (22Mar2021)

Protocol updated following REC meeting comments. Summary of changes:

- REC reference added to cover page table (page 1).
- Specific reference to Gamma Knife stereotactic radiosurgery added throughout and clarification added that neurosurgery and Gamma Knife stereotactic radiosurgery will be used according to their availability in clinical practice (section 3, 7 and throughout).
- Clarification added that imaging studies performed because of the occurrence of an outcome event will be collected by the research team and uploaded to the scan database for the trial (section 8.1.6)
- Trial timeline added (section 18).
- Version history table added (section 19).

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Academic and Clinical Central Office for Research and Development

CARE Trial Steering Committee Charter

CAVERNOMAS: A RANDOMISED EFFECTIVENESS TRIAL

Study Title:	Cavernomas A Randomised Effectiveness (CARE) pilot trial, to address the effectiveness of active treatment (with neurosurgery or stereotactic radiosurgery) versus conservative management in people with symptomatic brain cavernoma
Funder and funder reference:	National Institute for Health Research Health Technology Assessment Programme - NIHR128694
Chief Investigator:	Prof Rustam Al-Shahi Salman
Co-Sponsors:	University of Edinburgh & NHS Lothian
Sponsor reference:	AC20171
Trial Registration Reference(s):	ISRCTN41647111
REC reference:	21/YH/0046
Charter Version Number and Date:	V3.0 (08 Mar 2023) *Based on Sponsor Template CR015-T02 v2.0*

Approval Signatures:

The following individuals, by providing their signatures, indicate their understanding of and willingness to comply with the roles and responsibilities assigned to them in this Charter.

1. TSC Independent Chair:

   Prof Garth Cruickshank

   _____ _____ _ _ / _ _ /_ _ _ _

   PRINT NAME SIGNATURE DATE

2. Prepared by Trial Manager:

   Dr Laura Forsyth

   _____ _____ _ _ / _ _ /_ _ _ _

   PRINT NAME SIGNATURE DATE

3. Chief Investigator:

   Prof Rustam Al-Shahi Salman

   _____ _____ _ _ / _ _ /_ _ _ _

   PRINT NAME SIGNATURE DATE

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1 Introduction

This Charter is for the Trial Steering Committee (TSC) for the Cavernomas A Randomised Effectiveness (CARE) pilot trial, a pilot randomised controlled trial (RCT) which aims to assess the feasibility of conducting a definitive main phase RCT to address the research question "How effective is active treatment (with neurosurgery or stereotactic radiosurgery) versus conservative management in people with symptomatic brain cavernoma?". The trial objectives are to:

1. Engage a collaboration of specialists and patient advocacy groups in the UK and Ireland.
2. Establish a pilot RCT, with an embedded qualitative study to understand the anticipated recruitment processes and address any barriers.
3. Assess the feasibility of performing a definitive main phase of the RCT.

This charter will define the primary responsibilities of the TSC, its membership, and the purpose and timing of its meetings. It will also provide the procedures for ensuring confidentiality and proper communication, decision making, reporting and after trial publications. The trial will be conducted in accordance with sponsor SOPs (https://www.accord.scot/research-access/resources-researchers/sop). The contents of the Charter are based on the NIHR Research Governance Guidelines for Trial Steering Committees (https://www.nihr.ac.uk/documents/research-governance-guidelines/12154).

2 Roles and Responsibilities

The role of the TSC is to provide overall supervision for this project on behalf of the Project Sponsor (ACCORD) and Project Funder (NIHR HTA) and to ensure that the project is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice.

The specific roles of the TSC include:

- Provide oversight of the trial and monitor the overall conduct of the trial. The TSC should provide advice through its independent Chair to the Chief Investigator (CI) and Trial Management Group (TMG) on all appropriate aspects of the trial.
- Concentrate on progress of the trial, QuinteT Recruitment Intervention (QRI) progress and recommendations, adherence to the protocol, patient safety and the consideration of new information of relevance to the research question
- Ensure appropriate ethical and other approvals are obtained in line with the project plan
- Review regular trial progress reports
- Monitor recruitment rates and advise the TMG about strategies to deal with recruitment issues

- Monitor follow-up completeness and advise the TMG about strategies to deal with retention issues
- Review serious adverse events blind to treatment allocation
- Assess the impact and relevance of any accumulating external evidence (any relevant external evidence identified by the CI will be passed onto the TSC Chair for review by the committee)
- Review and accept/reject recommendations from the DMC to amend the protocol or conduct of the study
- Contribute to enhancing the integrity of the trial. The TSC may also formulate recommendations relating to:
    - The selection, recruitment, or retention of participants, or their management
    - Extending recruitment or follow up
    - Improving participant adherence to protocol-specified regimens
    - Procedures for data management and quality control
- Promptly review DMC recommendations which include deciding to continue or terminate the trial
- Oversee the timely reporting of the trial results
- Maintain confidentiality of all trial information that is not already in the public domain
- Comment on the main trial manuscript before publication (if desired)

3 Before or early in the trial

All potential TSC members will have sight of the protocol before the first TSC meeting. Before recruitment begins, the trial will have undergone review by the sponsor and a research ethics committee. Therefore, if a potential TSC member has major reservations about the trial (e.g. the protocol or the logistics) they should report these to the CI and may decide to decline the invitation to join. TSC members should be constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.

The TSC will meet before the start of recruitment to the trial, to discuss the protocol, methods of providing information to and from the TSC, frequency and format of meetings, relationships with other committees and have the opportunity to clarify any aspects with the CI and Co-Chief Investigator. TSC input into the protocol will be discussed with the CI before deciding what protocol updates need to be implemented.

Members and observers of the TSC will not be asked to formally sign a contract but should formally register their assent by confirming (1) that they agree to be a member of the TSC and (2) that they agree with the contents of this Charter by signing and dating the required form (Appendices 1-3).

4 Composition

TSC members were selected and approved by the funder in accordance with NIHR Research Governance Guidelines (V1.0 February 2019).

The Chairperson

The Chair of the TSC will be independent of the trial and have experience of serving on previous TSC(s). The Chair is directly answerable to the relevant NIHR programme, as funder and the primary TSC reporting line is via the Chair to the relevant NIHR Programme Director; however communication is likely to be between the Chair, the trial manager and the NIHR Research Manager who has day to day responsibility for the project.

The Chair's specific responsibilities include:

- Liaising with the CI to arrange a meeting to finalise the protocol and to set up a schedule of meetings to align with the project plan
- Establishing clear reporting lines to the Funder, Sponsor, etc.
- Being familiar with relevant guidance documents and with the role of the DMC, if appropriate
- Providing an independent*, experienced opinion if conflicts arise between the needs of the research team, the funder, the sponsor, the participating organisations and/or any other agencies
- Leading the TSC to provide regular, impartial oversight of the study, especially to identify and pre-empt problems
- Ensuring that changes to the protocol are debated and endorsed by the TSC. Letters of endorsement should be made available to the project team when requesting approval from the funder and sponsor for matters such as changes to protocol
- Being available to provide independent* advice as required, not just when TSC meetings are scheduled
- Commenting on any extension requests and, where appropriate, providing a letter to the funder commenting on whether the extension request is supported or otherwise by the independent* members of the TSC
- Commenting in detail (when appropriate) regarding the continuation, extension or termination of the project. NB: The TSC Chair does not need to be a content expert him/herself but needs to ensure that sufficient content expertise is available for the group to perform its oversight function effectively

*** Independence**

According to the NIHR Research Governance Guidelines, independence is defined as:

- Not part of the same institution as any of the applicants or members of the project team
- Not part of the same institution that is acting as a recruitment or investigative centre, including Patient Identification Centres (PIC), identifying and referring

patients to a recruitment or investigative centre (in both cases, 'not part of the same institution' means holding neither a substantive or honorary contract with said institution)

- Not related to any of the applicants or members of the project team
- For the chair only: not an applicant on a rival proposal

TSC membership and voting

The TSC will consist of a minimum of 75% independent members. Only appointed TSC members will be entitled to a vote and the chair will have a casting vote. To minimise the risk that fewer than 75% of TSC members are independent at a TSC meeting, the CI is an observer and not formally a member of the TSC for this trial and therefore cannot vote. Attendance of non-members at meetings is at the discretion of the TSC Chair.

The **members** of the TSC are listed below.

Name of Member	Role in TSC	Responsibility	Independent
Prof Garth Cruickshank	Independent Chair	Provide independent neurosurgical and trial expertise	Y
Prof Catherine Hewitt	Independent member	Provide independent statistical expertise	Y
Mr Richard Kerr	Independent member	Provide independent vascular neurosurgery and trial expertise	Y
Prof Haleema Shakur-Still	Independent member	Provide independent clinical trial management expertise	Y
Mr Ian Stuart	Independent member	Patient/carer representative	Y
Mr David White	Independent member	Patient/carer representative	Y
Mr Neil Kitchen	Co-chief investigator	Neurosurgical lead	N

The **observers** of the TSC are listed below.

Prof Rustam Al-Shahi Salman	Chief Investigator	Inform TSC of any relevant updates	N
Prof Steff Lewis	Study Statistician	Blinded trial statistician	N
Dr Laura Forsyth	Trial Manager / Facilitator	Co-ordinate meetings and facilitate the group	N
Dr Julia Wade	Lead Qualitative Researcher	Report on the progress, conduct, and outcomes of the embedded QuniteT Recruitment Intervention	N

5 Relationships

TSC / DMC relationship

The TSC is the oversight body of the trial. All substantial issues regarding the trial must go to the TSC for consideration. The DMC is advisory to the TSC.

Payments to TSC members

If required, standard travel and accommodation costs will be paid to members of the TSC. No other payments or rewards will be given.

Competing Interests

Any competing interests, either real or potential, should be disclosed before TSC meetings (see Appendices). These are not restricted to financial matters, involvement in other trials or intellectual investment could be relevant. Although members may well be able to act objectively despite such connections, complete disclosure enhances credibility.

6 Organisation of TSC Meetings

Meeting Frequency and Format

The TSC should have a formal meeting at least yearly. At the request of the TSC, interim meetings will be organised. Meetings will be scheduled to follow shortly after DMC meetings so that any DMC recommendations can be considered, if appropriate. The responsibility for calling and organising TSC meetings lies with the CI who will be assisted by the Trial Manager/Facilitator.

Meetings will be held either in person, by video-conference (e.g. Zoom, MS Teams) or by teleconference. Major trial issues may need to be dealt with between meetings, by phone, video-conference or by email. TSC members should be prepared for such instances. There may be occasions when the Sponsor or the Funder will wish to organise and administer these meetings for particular projects. This is unlikely, but the NIHR reserves the right to attend any meeting therefore should be included in relevant invitations and also reserves the right to convene a meeting of the TSC in exceptional circumstances.

Attendance

Presence will be usually limited to the TSC members, observers and the Facilitator (and/or their delegate) however, other attendees such as representatives of the Funder and Sponsor may also be invited to all or part of every meeting by the TSC. Other observers who are not members of the TSC may be invited to provide expert input.

Effort will be made to ensure that all members can attend. The CI must try to attend all meetings, especially if major actions are expected. In the case of face to face meetings, members who cannot attend in person will be encouraged to participate by teleconference/videoconference. If TSC members cannot attend meetings by tele-/video-conference, they will be encouraged to send comments in advance via email.

Quoracy

If, at short notice, any TSC members cannot attend then the TSC may still meet if at least five members (two thirds of the appointed membership) including the Chair will be present, plus a member of the trial team. If the TSC is considering a major action after such a meeting the TSC Chair should communicate with the absent members, including the CI, as soon after the meeting as possible to check they agree. If they do not, a further meeting should be arranged with the full TSC.

Non-attendance

TSC members who will not be able to attend the meeting should pass comments to the TSC Chair in advance for consideration during the discussion. If an independent member does not attend a meeting or provide comments when requested between meetings, it will be ensured that the independent member is available for the next meeting. If an independent member does not attend the next meeting or provide comments when next requested, they will be asked if they wish to remain part of the TSC. If an independent member does not attend a third meeting, strong consideration will be given to replacing this member.

7 Trial Documentation and Procedures to Ensure Confidentiality and Proper Communication

Progress Report and Meeting Minutes

At the first meeting, the TSC will review the project plan and discuss targets for recruitment, data collection, compliance etc. Based on these targets, the TSC should agree a set of data that should be presented in a progress report at each meeting. The progress report will be written and presented by the Chief Investigator (or designee) and will include updates on trial progress, recruitment, participant drop-out, safety data (SAEs), adherence to the protocol (deviations and violations), summary of new evidence/literature review, publications and A.O.B, as appropriate. The TSC will receive the report and any associated documentation at least two weeks before the meeting.

Minutes will be prepared by the facilitator on behalf of the CI, and uploaded to the NIHR MIS. Copies of minutes will be sent to all members, the sponsor and the funder, and a copy will be retained in the Trial Master File. These minutes and actions will be used as a basis for the following TSC meeting agenda.

External evidence

Identification and circulation of published external evidence (e.g. from other trials/ systematic reviews) is a responsibility of the CI. The TSC should continue to be made aware of other data that may impact on the trial.

Communication

The facilitator will be responsible for the organisation of meetings and should be copied into all communications with and between the TSC.

Confidentiality

TSC members are expected to store securely copies of the reports to and from the

TSC, agenda and minutes, as well as copies of communications between meetings. All documentation should be considered confidential.

8 Decision Making

TSC / DMC decision-making

The TSC is jointly responsible with the DMC for safeguarding the interests of participating patients and for the conduct of the trial. Recommendations to amend the protocol or conduct of the study made by the DMC will be considered and accepted or rejected by the TSC. The TSC will be responsible for deciding whether to continue or to stop the trial based on the DMC recommendations.

Possible decisions by the TSC include:

- No action needed, trial continues as planned
- Early termination of the trial (e.g. because of harm of treatment or futility or external evidence. This would generally be after a recommendation from the DMC).
- Stopping recruitment within a subgroup
- Extending recruitment or extending follow-up
- Sanctioning or proposing protocol changes

Based on other factors, other possible decisions could include:

- Approving proposed new trial sub-studies
- Approving presentation of results during the trial or soon after closure
- Approval of strategies to improve recruitment or follow-up
- Approving feasibility of proceeding to a definitive main phase trial application

Considerations on statistical methods

Formal statistical methods may have been considered by the DMC in making their recommendations to the TSC. These methods are usually used as guidelines rather than absolute rules. This is because they generally only consider one dimension of the trial. The DMC will record reasons for disregarding stopping guidelines and will review and agree any interim analysis plan and note these decisions in their meetings and may choose to also note this in their report to the TSC if necessary.

Consensus and quoracy

Every effort should be made to achieve consensus. The role of the Chair is to summarise discussions and encourage consensus; therefore, it is usually best for the Chair to give their own opinion last. If a vote is required to achieve consensus, all independent members of the TSC have the opportunity to cast a vote with the chair voting last. The CI is not able to cast a vote.

To be quorate, at least five members (two thirds of the appointed membership) including the Chair will be present, plus a member of the trial team. It is important that the implications (e.g. ethical, statistical, practical, and financial) for the trial be considered before any decision is made.

The DMC will be notified of all changes to the protocol or to study conduct. The DMC's approval will be sought on all substantive recommendations or changes to the protocol or study conduct before their implementation.

9 Reporting

TSC recommendations

Notes of key points, decisions and actions will be made by the Facilitator. This will include details of whether potential competing interests have changed for any attendees since the previous meeting. The draft minutes will be initially circulated for comment to those TSC members who were present at the meeting. The TSC Chair will approve the final version of minutes within three weeks of the meeting and a copy sent to all attendees and the NIHR. Copies will be retained in the Trial Master File and archived at the time of study closure. The TSC may also provide feedback to the DMC, and where appropriate the Sponsor. Copies of communications will pass through the Facilitator.

The TSC is the oversight body for the trial. However the TSC should have good reason before deciding not to accept requests from the TMG or DMC. If there are serious problems or concerns with the TSC decision following a DMC recommendation, a joint meeting of the TSC and DMC should be held. The information to be shown would depend upon the action proposed and each committee's concerns. Depending on the reason for the disagreement confidential data and/or data by trial and may have to be revealed to all or some of those attending such a meeting: this would be minimised where possible. The meeting would be chaired by an external expert who is not directly involved with the trial.

10 After the Trial

Publication of results

The TSC will oversee the timely analysis, writing up and publication of the main trial results. The independent members of the TSC will have the opportunity to read and comment on the proposed main publications of trial data prior to submission and abstracts and presentations during the trial. This review may be concurrent to that of the trial investigators and DMC. TSC members will be named and their affiliations listed in the main report, unless they explicitly request otherwise.

Confidentiality of results

Unless permission has been agreed with the TSC, individual members will not discuss confidential information to which they have become party as a result of their involvement in the trial until 12 months after the primary trial results have been published.

Appendix 1: Agreement and competing interests form for independent members

Trial Steering Committee: Agreement to join the CARE Trial Steering Committee as an independent member and disclosure of potential competing interests

Please complete the following document and return to the TSC Facilitator.

(please **initial** box to agree)

	I have read and understood the CARE pilot trial TSC Charter version 3.0 dated 08 March 2023 and agree with the contents of this Charter
	I agree to join the Trial Steering Committee for this trial as an **independent** member
	I agree to treat all sensitive trial data and discussions confidentially

The avoidance of any perception that independent members of a TSC may be biased in some fashion is important for the credibility of the decisions made by the TSC and for the integrity of the trial.
Potential competing interests should be disclosed via the study office. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) independent TSC member should remove the conflict or stop participating in the TSC. **Table 1** lists potential competing interests.

	No, I have no competing interests to declare
	Yes, I have competing interests to declare (please detail below)

Please provide details of any competing interests:

NAME: _____

SIGNATURE: _____

DATE: _____

Table 1: Potential competing interests for independent members

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the Sponsor/Funder
- Frequent speaking engagements on behalf of the intervention
- Career tied up in a product or technique assessed by trial
- Hands-on participation in the trial
- Involvement in the running of the trial
- Emotional involvement in the trial
- Intellectual conflict e.g. strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Involvement in the writing up of the main trial results in the form of authorship

Appendix 2: Agreement and competing interests form for non-independent members

Trial Steering Committee: Agreement to join the CARE Trial Steering Committee as a non-independent member and disclosure of potential competing interests

Please complete the following document and return to the TSC Facilitator.

(please **initial** box to agree)

	I have read and understood the CARE pilot trial TSC Charter version 3.0 dated 08 March 2023 and agree with the contents of this Charter
	I agree to join the Trial Steering Committee for this trial as a **non-independent** member
	I agree to treat all sensitive trial data and discussions confidentially

The notion that non-independent members can act objectively despite potential competing interests is important for the credibility of the decisions made by the TSC and for the integrity of the trial. Potential competing interests should be disclosed via the study office. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) non-independent TSC member should remove the conflict or stop participating in the TSC. **Table 1** lists potential competing interests.

	No, I have no competing interests to declare
	Yes, I have competing interests to declare (please detail below)

Please provide details of any competing interests:

NAME: _____

SIGNATURE: _____

DATE: _____

Table 1: Potential competing interests for non-independent members

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the Sponsor/Funder
- Frequent speaking engagements on behalf of the intervention
- Intellectual conflict e.g. strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures

Appendix 3: Agreement and confidentiality agreement for observers

<u>Trial Steering Committee</u>: Agreement to attend the CARE Trial Steering Committee and treat all information confidentially

Please complete the following document and return to the TSC Facilitator.

(please **initial** box to agree)

	I agree to attend the Trial Steering Committee meeting on ___/____/_____
	I agree to treat as confidential any sensitive information gained during this meeting and all future meetings unless explicitly permitted

NAME: _____

SIGNATURE: _____

DATE: _____

Statistical Analysis Plan	CARE
Version No	1.0
Date Finalised	8th Dec 2022

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

Statistical Analysis Plan

CONFIDENTIAL

Version No	v1.0
Date Finalised	8 Dec 2022
Author(s)	Dr Jacqueline Stephen
CI Name	Prof Rustam Al-Shahi Salman
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Signatures	
Trial Statistician:	**Date: 12 Dec 2022**
Chief Investigator: Rustam Al-Shahi Salman **RUSTAM AL-SHAHI SALMAN**	**Date:** 12 December 2022

Document Control		
Version No	**Date**	**Summary of Revisions**
1.0	8 Dec 2022	Initial Creation

Statistical Analysis Plan	CARE
Version No	1.0
Date Finalised	8th Dec 2022

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List of Abbreviations

Abbreviation	Full name
CI	Confidence interval
CRF	Case report form
ECTU	Edinburgh Clinical Trials Unit
FND	Focal neurological deficit
ICH	Intracranial haemorrhage
IQR	Inter quartile range
ITT	Intention-to-treat
mRS	Modified rankin scale
RCT	Randomised controlled trial
SAE	Serious adverse events
SD	Standard deviation
SOP	Standard operating procedure

Statistical Analysis Plan	CARE
Version No	1.0
Date Finalised	8th Dec 2022

1. Introduction

This document details the criteria to be used for the definition of the analysis populations and the statistical methodology for analysis of CARE, a two-arm, parallel group randomised feasibility trial which aims to estimate the feasibility of performing a definitive main phase randomised controlled trial (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 outcomes for people with symptomatic brain cavernoma.

The aim is to randomise approximately 60 participants to groups in a 1:1 ratio, to medical management alone, or medical and surgical management, stratified by preferred type of surgical management. If there is no clear preference for the type of surgical management, and both are available, the patient will be randomly allocated to either neurosurgery or stereotactic radiosurgery, and then randomised between medical management alone, or medical and surgical management.

This document has been compiled according to the Edinburgh Clinical Trials Unit (ECTU) standard operating procedure (SOP) "Statistical Analysis Plans v6.0" and has been written based on information contained in the study protocol version 2.0, dated 22nd March 2021.

The pilot phase of CARE will be submitted for publication and reported according to the CONSORT 2010 extension to randomised pilot and feasibility trials.[1]

2. Statistical Methods section from the protocol

In this pilot phase, analyses are descriptive only, and there will be no formal statistical tests.

We will quantify the number and proportions (with 95% confidence intervals to reflect their precision) of patients who are screened, eligible, approached, consent and are randomised. We will construct a CONSORT diagram to summarise the distribution and progress of participants in the trial including the numbers of withdrawals.[1]

We will report descriptively the following: the number and the proportion of the collaborating sites that take part and recruit participants to the CARE pilot trial; research teams' implementation of trial procedures measured by number and type of protocol deviation; the numbers of participants allocated to neurosurgery and stereotactic radiosurgery; adherence to the allocated intervention; completeness of follow-up that would be due at each 6-month interval; completeness of baseline, imaging and outcome data; the frequency of outcome events overall and in an intention-to-treat analysis keeping patients in the treatment group to which they were allocated during all available follow-up.

We will also compare descriptively the characteristics of eligible patients who are screened and do not participate in the CARE pilot trial to eligible patients who are randomised using the

characteristics recorded on the screening logs to assess generalisability (external validity) and any recruitment bias.

We will assess measures of functional outcome, to assess which has suitable statistical properties for use in a main phase trial (such as lack of floor/ceiling effects). We will assess whether such a measure (like the method we have used before[2]) would be more suitable as a primary outcome in place of intracranial haemorrhage.

3. Overall Statistical Principles

The analysis dataset for the trial will include all screened patients in addition to eligible, approached, consented, and randomised participants.

All analyses will be based on the intention to treat (ITT) principle with patients analysed according to allocated treatment, irrespective of whether they adhered to the allocated treatment, in the group to which they were allocated.

In general terms, categorical data will be presented using counts and percentages, whilst continuous variables will be presented using the mean, median, standard deviation (SD), minimum, maximum, inter quartile range (IQR) and number of patients with an observation.

All analyses and data manipulations will be carried out using SAS version 9.4 or later.

4. List of Analyses

In this pilot trial, analyses are descriptive only, and there will be no formal statistical significance tests.

The outcomes of the pilot trial follow the SEAR (screened, eligible, approached, and randomised) framework for recording the recruitment process and reasons for non-participation[3]: Screening, to identify potentially eligible trial participants; Eligibility, assessed against the trial protocol inclusion/exclusion criteria; Approach, the provision of oral and written information and invitation to participate in the trial; and Randomised.

4.1 Outcomes

Descriptive statistics of the following outcomes will be reported for the entire pilot trial population:

1. The number of active sites, and the number of sites who have randomised participants

2. Implementation of trial procedures correctly as assessed by the number and type of protocol deviations recorded. The numbers of deviations will be tabulated, and deviations will be listed.

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3. The numbers and proportions of patients (overall, and by site) who are screened, eligible, approached, uncertain, consented and randomised, which will be defined as:
    a) Screened: Number of patients screened with sufficient information to determine eligibility.
    b) Eligible: Screened patients meeting the trial's eligibility criteria (quantify any patients for whom this is uncertain separately). Proportion of screened patients who were eligible = b/a.
    c) Approached: Eligible patients who were approached for discussion (quantify any patients who were not approached and why or where this is unknown, separately). Proportion of eligible patients who were approached = c/b.
    d) Uncertain: Eligible patients who were approached about treatment with vs. without surgery and both doctor and patient were uncertain and therefore confirmed fully eligible (quantify any patients where only doctor, only patient, or neither is uncertain, or where this is unknown). Proportion of approached patients who are fully eligible = d/c.
    e) Consent: Fully eligible patients who have provided consent (quantify any not consented with reasons separately). Proportion of fully eligible patients who provide consent = e/d. Method of obtaining consent and who provided consent for the randomised study will be summarised.
    f) Randomised: Fully eligible patients consented, and randomised (quantify any patients who were not randomised and why or where this is unknown, separately). Proportion of eligible patients who were randomised = f/b.
    g) Withdrawn: Randomised patients who have withdrawn including who is withdrawing the participant, reason for and type of withdrawal (overall only, not by site).

    Proportions will be given with 95% confidence intervals (CI) (overall only, not by site).

4. Baseline characteristics will be summarised using descriptive statistics for eligible participants who were randomised versus eligible participants who were not randomised based on data collected at screening.
    - Source of screening
    - Speciality doing screening
    - Clinical history attributable to a brain cavernoma
        - Intracranial haemorrhage (ICH): one versus more than one vs none
        - Focal neurological deficit (FND): yes/no
        - Either ICH or FND
        - Epileptic seizure(s): yes versus no
    - Location of the symptomatic brain cavernoma (supratentorial lobar vs supratentorial deep grey matter vs brainstem vs cerebellum)
    - Time from most recent symptomatic event (months)

5. The number of participants randomised will be presented numerically overall and by site, and graphically overall over time.

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6. The overall recruitment rate per month with 95% CI and the recruitment rate per site per month.

Descriptive statistics of the following baseline data and outcomes will be reported for (1) randomised participants overall and by randomised group, and (2) randomised participants by randomised group and stratification variable (preferred type of surgical management: neurosurgery versus stereotactic radiosurgery):

7. Baseline characteristics
    - Age
    - Gender
    - Ethnicity
    - Symptomatic brain cavernoma presentation
        - Brain cavernoma-related symptomatic ICH
        - Brain cavernoma-related symptomatic persistent or progressive FND
        - Brain cavernoma-related symptomatic epileptic seizure(s)
    - Symptomatic brain cavernoma details as reported by the investigator
        - Number of cavernomas (brain or spinal) (single versus multiple and median number in those with multiple)
        - Side of symptomatic brain cavernoma that could be managed surgically
        - Location of symptomatic brain cavernoma that could be managed surgically
        - Proximity of symptomatic brain cavernoma to surface of this location
        - Prior treatment of symptomatic brain cavernoma
    - Brain cavernoma certainty and imaging characteristics as reported by the study neuroradiologist
        - Received brain imaging required to confirm symptomatic brain cavernoma diagnosis and mode of presentation
        - Certainty about diagnosis of the symptomatic cavernoma
    - Intended type of surgical management agreed
    - Other medical history
    - Current medication
    - Current therapies
    - Modified Rankin scale score (adults only)
    - NIH stroke scale score total
    - Karnofsky Performance scale (adults only)
    - Lansky play performance scale (children only)
    - EQ-5D (Index and visual analogue scale (VAS))
    - Liverpool seizure severity scale (only patients with epileptic seizures in the preceding 4 weeks)

8. Intervention characteristics
    - Surgical management in participants undergoing neurosurgical excision
        - Type of anaesthesia
        - Craniotomy performed but cavernoma not found
        - Was neuro-navigation used
        - Was neurophysiological monitoring/stimulation used
        - Was intra-operative MRI performed
        - Was functional MRI performed

- Grade of most senior neurosurgeon performing the procedure
- Did the participant return to theatre for re-operation
- Was post-operative MRI performed during this admission

- Surgical management in participants undergoing stereotactic radiosurgery
  - Location of stereotactic radiosurgery
  - Treatment prescription dose
  - Prescription isodose
  - Maximum dose
  - Paddick Conformity Index
  - Dose Gradient Index
  - Coverage
  - Treatment volume
  - Frame or mask-based
- Were any novel therapies used
  - Magnetic resonance thermography-guided laser interstitial thermal therapy used
  - Stereotactic laser ablation used
  - Other novel technique used
- Medical management
  - Physiotherapy
  - Speech and language therapy
  - Psychology
  - Occupational therapy

9. The number and proportion of randomised patients adherent to
   a) the allocated intervention based on
      i. intervention received and
      ii. whether the pre-specified type of surgical management (neurosurgery/radiosurgery) was the same as the type of intervention received
   b) follow-up based on completion of 6-month review CRF for those participants who are alive. Completeness of individual sections of the CRF will be summarised.

10. Completeness of data presented as the number and proportion with missing data for:
    a) Baseline. Defined as completion of the baseline CRF.
    b) Imaging. Defined as “Received brain imaging required to confirm symptomatic brain cavernoma diagnosis and mode of presentation” = yes, and at 6-months defined as “6-month MRI performed” = yes from the brain imaging data (not the CRF).
    c) Outcomes. Defined as completion of the follow-up review CRF for all follow-up time points (6, 12 and 18 months) that should have been reached by the participant. Completeness of individual sections of the CRF will be summarised.

11. Outcome event rates will be quantified using the number and proportion of participants with an event, the number of events, and the average event rate per participant per year. Outcome functional scores will be summarised descriptively and graphically to explore which has suitable statistical properties for use in a main phase trial (such as lack of floor/ceiling effects) for each time point available (6, 12 and 18 months). Clinical outcomes are:

    Primary

- 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.

Secondary

- Death not due to a primary clinical outcome
- Liverpool Seizure Severity Scale plus epileptic seizure frequency (number of seizures in the preceding four weeks, and attainment of one-year seizure freedom)
- Modified Rankin Scale (mRS) score
- National Institute of Health Stroke Scale Score (adult or paediatric)
- EQ-5D-5L in adults and EQ-5D-Y in children
- Karnofsky Performance Status scale in adults and Lanksy Play-Performance Scale in children

12. Follow-up imaging

6 month follow-up MRI

- MRI acquired as required by the protocol
- Is the symptomatic cavernoma that led to the participant's enrolment still present?
- Evidence of neurosurgical excision of the symptomatic brain cavernoma
  - If yes, was excision complete
- Evidence of stereotactic radiosurgery for the symptomatic brain cavernoma
  - If yes, change in cavernoma size, new signal change in surrounding brain, probable radio necrosis

Outcome Imaging

- Evidence of acute haemorrhage and locations

Outcomes 9-13 as listed in the protocol are not within the scope of this analysis plan and will be handled separately using data provided in this report to inform decisions for the design of the definitive main phase trial.

The analyses of the QuinteT recruitment intervention and health economics are also not within the scope of this analysis plan and will be handled separately.

4.2 Serious adverse events

Serious adverse events (SAEs) are reported if they are not outcome events or expected complications related to medical and surgical management.

SAEs will be summarised by treatment received and a listing will be produced detailing each event, and what happened to the patient subsequently.

5. Validation and QC

The statistical report will be read and sense-checked by a second statistician.

6. Data sharing

A file, or set of files, containing the final data will be prepared, along with a data dictionary. These will be made available to the Chief Investigator at the end of the analysis phase.

Following publication of the primary paper, a de-identified individual participant data set will be prepared for sharing purposes.

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CARE

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

Health Economic Analysis Plan (HEAP)

Version No	1.0
Date Finalised	7 February 2023
Author(s)	Alistair Bullen, Andrew Stoddart, Aileen Neilson
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Chief Investigator: Rustam Al-Shahi Salman	Date: 7 February 2023

Document Control		
Version No	Date	Summary of Revisions
1.0	22.11.2022	Initial Creation by author Alistair Bullen

Version No	1.0
Effective Date	7 February 2023

Supporting Internal Documents	Version No
CARE Protocol	2.0
CARE Statistical Analysis Plan	1.0

Version No	1.0
Effective Date	7 February 2023

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List of Abbreviations

Abbreviation	Full Name
CCM	Cerebral Cavernous Malformations
CEAC	Cost Effectiveness Acceptability Curve
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CT	Computerized Tomography
ECTU	Edinburgh Clinical Trials Unit
EQ-5D-5L	Euroqol Quality of Life Survey [5 Dimension, adult version]
EQ-5D-Y	Euroqol Quality of Life Survey [3 Dimension, child version]
FND	Focal Neurological Deficit
GP	General Practitioner
HCRU	Healthcare Resource Utilisation
HEAP	Health Economic Analysis Plan
ICER	Incremental Cost Effectiveness Ratio
ICH	Intracerebral Haemorrhage
MRI	Magnetic Resonance Imaging
NHS	[The UK] National Health Service
NICE	[The] National Institute for [Health and] Care Excellence
ONS	Office of National Statistics
PSA	Probabilistic Sensitivity Analysis
POD	Post-Operative Day
QALY	Quality Adjusted Life Year
SAP	Statistical Analysis Plan
UK	United Kingdom

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1. Introduction

This document details the criteria to be used for the definition of the analysis populations and the health economic methods for analysis of CARE (Trial Registration: ISRCTN Number: 41647111); Trial Funding: National Institute for Health and Care Research (NIHR) Health Technology Assessment (project no. 128694), a two-arm, parallel group randomised feasibility trial which aims to estimate the feasibility of performing a definitive main phase randomised controlled trial (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 outcomes for people with symptomatic brain cavernoma.

The aim is to randomise approximately 60 participants (from sites in the UK and Ireland) to groups in a 1:1 ratio, to medical management alone, or medical and surgical management, stratified by preferred type of surgical management. If there is no clear preference for the type of surgical management, and both are available, the patient will be randomly allocated to either neurosurgery or stereotactic radiosurgery, and then randomised between medical management alone, or medical and surgical management (detailed in section 3.1 of the trial protocol).
The pilot phase of CARE will be submitted for publication and reported according to the CONSORT 2010 extension to randomised pilot and feasibility trials.

The strategy set out here to guide the CARE health economic analyses, is intended to establish the rules that will be followed as closely as possible, when analysing and reporting the CARE trial health economic analyses. The principles set out here follow current published best practice for trial based economic assessments and recommended guidance regarding the content of the HEAPs for clinical trials.[1] This HEAP document has been written based on information contained in the trial protocol version 2.0, dated 22nd March 2021, and Statistical Analysis Plan (SAP) version 1.0, 12/12/2022. The HEAP is designed to ensure that there is no conflict with the protocol and associated statistical analysis plan and it should be read in conjunction with them.

Any deviations from the health economic analysis plan (described in this document) will be detailed and justified fully in the final report of the trial.

2. Objectives and Overview of Economic Evaluation

2.1. Overview of the Economic Evaluation

We aim to pilot the data collection methods for the CARE trial, and their assess suitability for use in a future full-scale trial providing descriptive statistics only, and an assessment of the completeness of surveys.

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If suitable, we aim to adapt an existing decision analytic Markov health economic model by Rinkel et al, which presently only models QALYs, to further include costs enabling full economic evaluation to be conducted.[2] We plan to assess the appropriateness of each parameter in the model, augmenting with trial data as necessary and where possible, making recommendations for future use or development in a full-scale trial. If deemed viable, we will then undertake a dry run of the updated model using the updated parameters by way of proof of concept, to provide highly provisional cost-utility estimates based on NICE reference case recommendations and estimate plausible ranges of incremental costs and QALYs and understand the main driver parameters within the model.[3]

The broader aim is to support the case for a full scale RCT in the setting that has the potential to identify the most cost-effective solution for clinical practice that can improve resource allocation efficiency in order to maximise the benefits provided by the NHS.

2.2. Primary Health Economic Objectives

The primary health economic objectives as defined in the CARE protocol are:

1. Design and test optimal methods for capture of resource use and cost data in community NHS settings, NHS secondary care, participants' out of pocket expenses and carer costs.
2. Estimate expected effect size and variance of relevant outcomes including health-related quality of life (utility) and quality-adjusted life years (QALYs)
3. Identify and measure the potential cost implications of surgical management of cavernomas.

These relate to and comprise of the within-trial analysis component of the study, which focuses on assessment of the quality of data collected during the observed follow-up period of the trial.

2.3. Secondary Health Economic Objectives

The secondary objective of the health economics analysis are:

4. To test the effect of updated parameters informed by the results of the primary health economic analysis on a previously published decision analytical model in the same setting.[2]
5. Provide recommendations for revisions to the model to aid future definitive trial design.

These relate to and comprise of the modelled analysis component of the study, which focuses on assessment of the feasibility of simulating longer term outcomes, beyond those of the observable trial period.

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3. Economic Principles

3.1. Cost Perspective

The primary perspective for analysis is the healthcare payer (NHS) perspective. Secondary analyses include wider societal perspective which includes some personal costs borne by patients as well as community care costs.

3.2. Time Horizon

Time horizon for within-trial elements of the analysis will be 18 months, reflecting the observed time frame from baseline to last follow-up. Time horizon for economic modelling will be 5 years, to include the simulated extrapolation beyond the observed trial time horizon, match the time period used by the original model, and to facilitate meaningful comparisons between original and adapted (CARE) models.

3.3. Discount Rates

Base-case discount rates will be set to 3.5% for both costs and outcomes, following the NICE reference case recommendations.[3]

4. Data Collection & Processing

4.1. Analysis Software

The primary within trial analyses (Objectives 1 to 3) will be performed on STATA 17.[4] Secondary analysis re-purposing an existing decision analytical model (Objectives 4 and 5) is expect to be completed on R Studio.[5] Additional analysis may also be completed on Microsoft Excel and TreeAge.[6,7]

4.2. Summary of Data Collection & Follow up Timing

Table 1 presents data collection for items and corresponding time points relating specifically to the within trial health economics analysis. Patient utility values will be collected using the EQ-5D-5L measure for adults[8] and EQ-5D-Y[9,10] measure in children. Healthcare resource use and socioeconomic data will also be collected from information gathered in the form of participant self-reported questionnaires.

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Table 1: Summary of Health Economic Data Collection based on baseline and follow-up

Item	Time since baseline			
	Baseline	6-month	12 -month	18 month
Health Utility data				
EQ-5D-5L (adults only)	✓	✓	✓	✓
EQ-5D-Y (children only)	✓	✓	✓	✓
Socioeconomic data*				
Employment data	✓	✓	✓	✓
Education data	✓	✓	✓	✓
Informal Care data	✓	✓	✓	✓
Healthcare Resource Use				
In-patient stays		✓	✓	✓
Out-patient service use		✓	✓	✓
Hospital tests		✓	✓	✓
Community and primary care		✓	✓	✓

* number of days lost due ill health, days of care provided by family and friends

4.2.1. Intervention

A case report form (CRF) is completed after the intervention, with data collected depending on the intervention performed (neurosurgical excision or stereotactic radiosurgery). Date of hospital admission and discharge for surgical management are collected for both interventions, and for patients who receive neurosurgical excision the type of ward attended (e.g. Adult, Paediatric, Neurology/Neurosurgery ,Other) is recorded. This information will be used to guide the selection of appropriate unit costs (from standard UK published literature sources) to assign to each type of surgical management intervention. We will also consult with relevant NHS service business managers as an alternative information source to estimate the costs associated with the different surgical treatment options.

4.3. Resource Use and Cost Calculations

4.3.1. Base Year and Unit Cost Selection

Base year for all costs will be selected as the latest financial year for which price weight reports are available at time of analysis and at least one patient provided data. A unit cost (in GBP) for each item for this base year will be sourced prior to analysis. As additional unit cost sources may be published

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by time of analysis, unit costs will be identified close to time of analysis, prior to unblinding, and detailed in an updated HEAP signed off by PH & RASS. Table 2 below details the variables recorded in the relevant CRF, associated cost category, and anticipated sources for unit costs to be prioritised for each item. Alternatives unit costs maybe sourced for those unavailable or not deemed generalisable to the trial population/context at time of analysis.

Table 2: Summary of costs and expected correspond sources.

Item	Units	Anticipated Source*
Direct Intervention Related Costs (In-Patient Hospitalisation)		
Neurosurgical excision		NHS Reference costs[11]
Stereotactic excision		NHS Reference costs[11]
Adult ward in-patient stay (Post neurosurgical excision)	Per night	NHS Reference costs[11]
Paediatric ward in-patient stay (Post neurosurgical excision)	Per night	NHS Reference costs[11]
Neurology/Neurosurgery ward in-patient stay (Post neurosurgical excision)	Per night	NHS Reference costs[11]
Other ward in-patient stay (Post neurosurgical excision)	Per night	NHS Reference costs[11]
In-patient Hospital Services		
Hospital in-patient stay	Per night	NHS Reference costs[11]
Other unscheduled hospital or A&E attendance	Per attendance	NHS Reference costs[11]
Out-patient Hospital Service		NHS Reference costs[11]
Neurologist service	Per clinic/phone consultation	NHS Reference costs[11]
Surgeon service	Per clinic/phone consultation	NHS Reference costs[11]
Specialist nurse service	Per clinic/phone consultation	NHS Reference costs[11]
Hospital Tests		NHS Reference costs[11]
MRI Scan	Per clinic/phone consultation	NHS Reference costs[11]
CT Scan	Per clinic/phone consultation	NHS Reference costs[11]
Community and Primary Care Services		
GP surgery (doctor)	Per clinic/phone consultation	PSSRU[12]
GP surgery (nurse)	Per clinic/phone/home consultation	PSSRU[12]
NHS 24/111	Per clinic/phone/home consultation	Pope et al. [13]
Out of hours GP	Per clinic/phone/home consultation	PSSRU[12]
District nurse	Per clinic/phone/home consultation	PSSRU[12]
Nurse (other)	Per clinic/phone/home consultation	PSSRU[12]
Psychologist	Per clinic/phone/home consultation	PSSRU[12]
Physiotherapist	Per clinic/phone/home consultation	PSSRU[12]
Dietician	Per clinic/phone/home consultation	PSSRU[12]
Occupational therapist	Per clinic/phone/home consultation	PSSRU[12]
Employment and Support (Indirect Costs)		
Productivity losses (patient time off work due to health problems)	Per day	National average wage according to ONS[14]

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Productivity losses (informal carers time off work to support/help patient)	Per day	National average wage according to ONS[14]

* Where a given item has multiple consultation types (e.g. clinic/phone/home), separate unit costs will be identified for each.

4.3.2. Cost Calculations

Each item of resource use will be multiplied by its unit cost to estimate a cost per patient, plus a total cost over all follow-up time points. This will be undertaken separately for each trial arm.

The following total cost categories will be calculated:

1. Mean per patient NHS costs will be calculated as the sum of mean cost per patient pertaining to direct intervention, in-patient hospital services, out-patient hospital service, hospital tests, and utilisation of community and primary care services.
2. Mean per patient wider societal costs will be calculated as the sum of mean cost per patient pertaining to NHS costs (as per 1.) plus lost income from days taken off of work by patients and informal carers.

4.4. Health Outcomes

4.4.1. QALY Outcome Calculation

Following NICE guidance, health utilities will be calculated for each patient based on their EQ-5D-5L or EQ-5D-Y at each time point if they were issued, and derived using the recommended UK EQ-5D-5L to 3L "Crosswalking" algorithm,[15] or based on sensitivity analysis between possible alternative scoring algorithms for the UK EQ-5D-Y.

QALYs will be calculated from these health utility values using an area-under-the-curve technique.[16]

5. Within Trial Analyses & Reporting

5.1. Scope of Analyses

We only aim to assess the suitability of the data collected for use in a future trial, and/or economic model. As such, calculations of incremental cost-effectiveness Ratios (ICERs) will not be undertaken on the within trial proportion of the analysis. Some preliminary calculations may however be undertaken as part of the modelling proportion of the sub study, see section 6. The main outputs from the within trial analysis will instead be the expected effect size and variance of relevant outcomes including health related quality of utility, QALYs, and cost factors.

All analyses will be based on the intention to treat (ITT) principle with patients analysed according to allocated treatment, irrespective of whether they adhered to the allocated treatment, in the group to which they were allocated.

5.2. Reporting Standards

Results will be presented in accordance to guidance set out in the Consolidated Health Economic Evaluation Reporting Standards (CHEERS).[17]

5.3. List of Analyses

As CARE is a pilot trial, only descriptive statistics will be provided with no formal statistical significance tests.

Completeness of the following outcomes will be summarised for each time point (6, 12 and 18 months) and each trial arm, with completion defined as the number and percentage of responses from participants that should have been reached at that time point.

i. Each resource use item listed in Table 2 (see section 4.3.1)

ii. Each EQ-5D-5L or EQ-5D-Y sub-scale (Mobility, Self-Care, Usual-Activities, Pain and Discomfort, and Anxiety and Depression).

The following outcomes will be reported for each trial arm:

iii. Mean rates of utilisation per patient, and associated standard deviation of each resource use item listed in Table 2 (see section 4.3.1), at each time point (6, 12 and 18 months) and total over all time points.

iv. Mean cost (calculated as per section 4.3.2) of each resource use item listed in Table 2 (see section 4.3.1) per patient and associated standard deviation totalled over all time points.*

v. Mean total costs (calculated as per section 4.3.2) per patient for each category of cost.*

vi. Mean utility scores (calculated as per section 4.4.1) per patient and associated standard deviation at each time point (6, 12 and 18 months).

vii. Mean QALYs per patient (calculated as per section 4.4.1) and associated standard deviation.*

* Cost and QALY figures (Outcomes iv., v., and vii.) may be calculated accounting for missing data e.g. through imputation, with the selection of a specific method being informed by the quantity and pattern of missingness present and , subject to data quality assessment (see Section 5.4).

Subject to data quality (See Section 5.4), regression analyses adjusting for baseline may be explored for total costs and QALYs (Outcomes v. and vii.).

Subgroup analysis (for items i-vii above) considering age-group (adults vs children) and by intervention type (neurosurgery or stereotactic radiosurgery) will also be conducted subject to adequate numbers

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being available. Finally, costs related to the specific health states defined in the previously developed QALYs (only) model by Rinkel et al (see section 6.1 below) will be reported if identifiable from the pilot data collected.

5.4. Assessment of Data Quality

A qualitative assessment of missingness and data quality pertaining to the health economic analysis, from outcomes i. and ii. In Section 5.3., will be produced by the health economics team. Analysts will provide an expert assessment of the data quality with respect to:

- Suitability for use in future definitive trials in light of larger sample sizes.
- Adaptation for use in parameters of the economic modelling in Section 6, and any similar modelling alongside a hypothetical definitive future trial in light of larger sample sizes.

We will also make recommendations around appropriate forms of imputation that may be necessary in future trials. QALY and total cost calculations are composite variables by their nature. As such even single missing items on any resource or utility observation at any time point can render a participants QALY or total cost figures incalculable, without some form of imputation. Assessment of data quality will include consideration of what form of imputation may be necessary in a future main phase definitive trial. However as the regressions needed for more advanced imputation techniques would be underpowered, at most, simple mean imputation may be applied at the analysts discretion.

6. Modelling

Subject to data quality assessment (see Sections 5.4, and 6.2), an existing model by Rinkel et al[2] will be rebuilt, and adapted to incorporate trial data. The latter being important in order to add cost elements in particular, as the existing model simulates effectiveness in terms of QALYs only.

The purpose of the model will be to:

1. Create a model structure for potential adaptation and reuse alongside future definitive trial.
2. Undertake a proof of concept dry run analysis to identify any issues in the model and make recommendations for adaptation for use in any future definitive trial.
3. If data quality are suitable, provide highly provisional early estimates of cost-utility of medical management alone vs medical and surgical management (with neurosurgery or Gamma Knife stereotactic radiosurgery, according to their availability in clinical practice) for the treatment of symptomatic brain cavernoma.

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To maximise UK policy relevance, this adaptation will follow NICE reference case recommendations[3] where possible including: Adoption of an NHS and PSS (personal social service) costing perspective for primary analyses; cost-utility approach (results presented in terms of incremental cost per QALY derived from EQ-5D-5L); discount rate of 3.5% for both costs and QALYs; and the use of probabilistic sensitivity analysis (PSA), to generate cost effectiveness acceptability curves (CEACs).[18] Any exceptions to reference case methodology will be noted and justified. Time horizon for analysis will be 5 Years (see Section 3.2).

6.1. Existing Model

A model schematic, including diagrams, parameter estimates and sources, and modelling assumptions can be found in the technical appendix to Rinkel et al.[2] By way of overview, the model compares three treatment arms (Conservative Management, Stereotactic radiosurgery, and neurosurgical excision) using a 5 year Markov model, with 3 primary health states (Well, Disabled and Death). Well and Disabled health states are subdivided into proportions with about without seizures and/or ICH. The model simulated three cohorts: (patients with brainstem cerebral cavernous malformations(CCM), patients with non-brainstem CCM presenting with intracerebral haemorrhage (ICH)/ focal neurological deficit FND, and patients presenting with epilepsy. Model parameters are populated using systematic review of published studies of CCM from the inception of Medline and Embase to December 2016. Primary outcomes from the model are expected number of QALYs, and ICH recurrence risk.

6.2. Assessment of Model Parameters for use in Current and Future Modelling

A table of model parameters will be generated detailing:

a. The parameter name and description.

b. Desired statistical distribution for the parameter for use in a Method of Moments approach to enable PSA.[19]

c. Candidate values and sources (trial data, or existing model) where available. Where multiple sources are identified, each will be listed.

d. A qualitative expert assessment of the suitability of the available source(s), accounting for generalisability to patient population and context, and a statement of which parameter is preferred (where a choice exists), for (i) current modelling utilising pilot data, and (ii) future modelling utilising data from a hypothetical future definitive scale trial. Note that it is possible that recommendations for current modelling source prioritisation may differ due to expected larger sample sizes in a future trial.

Results for d. may be reported as body text if the discussion is too large to be included in the table.

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A qualitative expert assessment in the form of a short interim report of the model structure as a whole will then be undertaken highlighting any areas of weakness, with a focus on parameters which may not be suitable from either source (existing model or trial data) and with recommendations for future literature reviews which may be needed to populate them if necessary. Such reviews may be undertaken, subject to available time, at the analysts discretion.

6.3. Dry Run Analysis

Subject to suitability of available parameters, the model[2] will be rebuilt in R and RStudio[5] with the addition of cost parameters linked to key health states and transitions. The model will be parameterised applying the recommendations for best current available data from the interim report generated by process described in Section 6.2.

Any adaptation to the model structure from that of the original which arise as necessary during the models development will be noted and justified, with a new model schematic diagram generated.

6.3.1. Outcomes

Outcomes for the model will be:

A. Mean QALYs per patient for each trial arm, and difference in mean QALYs per patient between trial arms (intervention minus control). Note that the method for calculating QALYs will depend on data available (see Section 6.2, though preference will be given to calculation via NICE recommended[3] EQ-5D utilities where available)

B. Mean NHS cost per patient for each trial arm, and difference in mean NHS cost per patient between trial arms (intervention minus control).

C. ICER(s) in terms of incremental cost per QALY (intervention vs control, calculated as [A]/[B] above).[16,19]

D. A CEAC, generated via PSA utilising a method of moments approach[19], with point estimates of likelihood of each arm being the most cost-efficient at NICE recommended thresholds of £20k, and £30k per QALY.

Note we will not undertake value of information analysis (VoI) as this assumes all data to be generalisable to the patient population and context, and we do not anticipate this to be the case. However, we will conduct a limited range of deterministic and probabilistic (one-way) sensitivity analysis in order to help understand the influence and implications of important model input parameters.

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6.4. Results

Outcomes A – D in section 6.3.1 will be reported, however these are expected to carry strong caveats that they are provisional results only.

A short report summarising the findings from Section 6.3.1 and experiences developing and running the model will be created by the analyst, with support from senior health economists, which will provide recommendations for developments for the model for use alongside any future definitive trial such as:

- Changes to model structure.
- Alternative data sources for parameterisation (Including need for literature reviews(s)).
- Any concerns about the model, or matters arising in its development so far.

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Academic and Clinical Central Office for Research and Development

CARE Trial Data Monitoring Committee Charter

CAVERNOMAS: A RANDOMISED EFFECTIVENESS TRIAL

Study Title:	Cavernomas A Randomised Effectiveness (CARE) pilot trial, to address the effectiveness of active treatment (with neurosurgery or stereotactic radiosurgery) versus conservative management in people with symptomatic brain cavernoma
Funder and funder reference:	National Institute for Health Research Health Technology Assessment Programme - NIHR128694
Chief Investigator:	Prof Rustam Al-Shahi Salman
Co-Sponsors:	University of Edinburgh & NHS Lothian
Sponsor reference:	AC20171
Trial Registration Reference(s):	ISRCTN41647111
REC reference:	21/YH/0046
Charter Version Number and Date:	V2.0 (24Jan2023) *Based on sponsor template CR015-T01 v3.0*

Approval Signatures:

The following individuals, by providing their signatures, indicate their understanding of and willingness to comply with the roles and responsibilities assigned to them in this Charter.

1. DMC Chair:

_____	_____	__/__/____
JOHN BAMFORD	SIGNATURE	DATE

2. DMC Member:

_____	_____	__/__/____
DAVID MENDELOW	SIGNATURE	DATE

3. DMC Member:

_____	_____	__/__/____
NIGEL BAKER	SIGNATURE	DATE

4. Chief Investigator:

_____	_____	__/__/____
RUSTAM AL-SHAHI SALMAN	SIGNATURE	DATE

5. Trial Statistician:

_____	_____	__/__/____
PRINT NAME	SIGNATURE	DATE

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1 Introduction

This Charter is for the Data Monitoring Committee (DMC) for the Cavernomas A Randomised Effectiveness (CARE) pilot trial, a pilot randomised controlled trial (RCT) which aims to assess the feasibility of conducting a definitive main phase RCT to address the research question "How effective is active treatment (with neurosurgery or stereotactic radiosurgery) versus conservative management in people with symptomatic brain cavernoma?". The trial objectives are to:

1. Engage a collaboration of specialists and patient advocacy groups in the UK and Ireland.
2. Establish a pilot RCT, with an embedded qualitative study to understand the anticipated recruitment processes and address any barriers.

   Assess the feasibility of performing a definitive main phase of the RCT.

The Charter will define the primary responsibilities of the Data Monitoring Committee (DMC) for the CARE pilot trial, its membership, and the purpose and timing of its meetings. The Charter will also provide the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the DMC, and an outline of the content of the Open and Closed Reports that will be provided to the DMC.

The trial will be conducted in accordance with sponsor SOPs: (https://www.accord.scot/research-access/resources-researchers/sop).

The contents of the Charter are based on the NIHR Research Governance Guidelines for Data Monitoring Committees: (https://www.nihr.ac.uk/documents/research-governance-guidelines/12154).

2 Roles and Responsibilities

The DMC is an independent multidisciplinary group consisting of clinicians and statisticians that, collectively, have experience/expertise in the management of patients with the condition relevant to trial and in the conduct and monitoring of randomised clinical trials. University of Edinburgh insurance indemnifies DMC members for their work on the committee.

The specific roles of the DMC include:

- The DMC will be responsible for:
  - Safeguarding the interests of trial participants, potential participants, investigators and sponsor, ensuring that the safety, rights and well-being of the trial participants are paramount
  - Assessing the safety and efficacy of the interventions during the trial, with due allowance for this being a feasibility study
  - Reviewing external evidence with an impact on risk/benefit balance, with due allowance for this being a feasibility study

- Monitoring the overall conduct of the clinical trial

- The DMC will provide recommendations about stopping, modifying or continuing the trial to the Trial Steering Committee (TSC).

- The DMC will contribute to enhancing the integrity of the trial, and may also formulate recommendations relating to the selection, recruitment, or retention of participants, or their management, or to improving their adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

- The DMC will consider the need for any interim analysis advising the TSC regarding the release of data and/or information

- On rare occasions when the DMC chair might be asked, through the chair of the TSC, by the Funder to provide advice based on a confidential interim or futility analysis if serious concerns are raised about the viability of the study or if the research team are requesting significant extensions, but this in unlikely in a feasibility setting.

- The DMC will be notified of all changes to the protocol or to study conduct. The DMC concurrence will be sought on all substantive recommendations or changes to the protocol or study conduct prior to their implementation.

3 Before or early in the trial

All potential DMC members will have sight of the protocol before the first DMC meeting. Before recruitment begins, the trial will have undergone review by the sponsor and a research ethics committee. Therefore, if a potential DMC member has major reservations about the trial (e.g. the protocol or the logistics) they should report these to the CI and may decide to decline the invitation to join. DMC members should be constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.

The DMC will aim to meet before or close to the start of recruitment to the trial, to discuss the protocol, methods of providing information to and from the DMC, frequency and format of meetings, relationships with other committees and have the opportunity to clarify any aspects with the CI and Co-Chief Investigator. DMC input into the protocol will be discussed with the CI before deciding what protocol updates need to be implemented.

Members and observers of the DMC will not be asked to formally sign a contract but should formally register their assent by confirming (1) that they agree to be a member of the DMC and (2) that they agree with the contents of this Charter by signing and dating the required form (Appendix 1).

4 Composition

DMC members were selected and approved by the funder in accordance with NIHR Research Governance Guidelines (V1.0 February 2019).

The **members** of the DMC are listed below.

Name of Member	Role in DMC	Responsibility
Dr John Bamford	Independent Chair	Provide independent neurological expertise
Prof David Mendelow	Independent member	Provide independent neurosurgical expertise
Mr Nigel Baker	Independent member	Provide independent statistical expertise

In addition, the following individuals will also be involved in DMC meetings:

Name	Trial Role	Responsibility
Prof Rustam Al-Shahi Salman	Chief Investigator	Inform DMC of any relevant updates
Mr Neil Kitchen	Co-chief investigator	Neurosurgical lead
Prof Steff Lewis	Statistician	Blinded trial statistician
Ms Jacquie Stephen	Statistician	Unblinded trial statistician
Dr Laura Forsyth	Trial Manager / Facilitator	Co-ordinate meetings and facilitate the group

See section 7 for more information on the roles of the blinded and unblinded trial statisticians.

DMC membership is normally for the duration of the trial. If any member leaves the DMC during the course of the trial, the Sponsor, in consultation with the TSC and/or Investigators will promptly appoint their replacement.

5 Relationships

DMC/ TSC relationship

The primary DMC reporting line is via the Chair to the TSC. The DMC will be advisory to the TSC. The TSC will be responsible for promptly reviewing the DMC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in study conduct are required.

Payments to DMC members

If required, standard travel and accommodation costs will be paid to members of the DMC. No other payments or rewards will be given.

Competing Interests

Any competing interests, either real or potential, should be disclosed before DMC meetings (see Appendix 1). These are not restricted to financial matters, involvement in other trials or intellectual investment could be relevant. Although members may well be able to act objectively despite such connections, complete disclosure enhances credibility.

6 Organisation of DMC Meetings

Meeting Frequency

Responsibility for calling and organising DMC meetings lies with the Chief Investigator, in association with the Chair of the DMC, who will be assisted by the Trial Manager/Facilitator. The DMC should meet at least annually, or more often as appropriate, and meetings should be timed so that reports can be fed into the TSC.

Meeting Format and Attendance

Sessions involving only DMC membership (but often including the unblinded statistician as well, as a non-voting member) called Closed Sessions will be held to allow discussion of confidential data from the clinical trial, including information about the relative efficacy and safety of interventions. In order to ensure that the DMC will be fully informed in its primary mission of safeguarding the interest of participating patients, the DMC will be unblinded in its assessment of safety and efficacy data. During these sessions, the DMC will develop a consensus on its list of recommendations, including that relating to whether the trial should continue. Attendance at DMC meetings by non-members is at the discretion of the Chair

DMC members and all other participants in the closed session of DMC meetings and the production of unblinded reports are expected to maintain confidentiality, and will refrain from revealing to the Trial Steering Committee, or any other party, information that would lead to compromising the integrity of the trial unless such release is required to protect patient safety.

In order to allow the DMC to have adequate access to information provided by the trial investigators, or by members of the regulatory authorities, a joint session between these individuals and DMC members (called an Open Session) will be held before the Closed Session. The trial Chief Investigator, Trial Statistician and Trial Manager will be available in-person or by phone for an open session at the beginning of the meeting, and will be available at the end of the meeting to answer any urgent questions. If necessary, a further Open Session can be held, on request either in the middle or end of the Closed Session. Open sessions give the DMC an opportunity to query these individuals about issues that have arisen during their review in the initial Closed Session. With this format, important interactions are facilitated through which problems affecting trial integrity can be identified and resolved.

Effort will be made to ensure that all members can attend. The CI must try to attend

all meetings, especially if major actions are expected. In the case of face to face meetings, members who cannot attend in person will be encouraged to participate by teleconference/videoconference. If DMC members cannot attend meetings by tele-/video-conference, they will be encouraged to send comments in advance via email.

Meetings will be held either in person, by video-conference (e.g. Zoom, MS Teams) or by teleconference. Major trial issues may need to be dealt with between meetings, by phone, video-conference or by email. DMC members should be prepared for such instances. There may be occasions when the Sponsor or the Funder will wish to organise and administer these meetings for particular projects. This is unlikely, but the NIHR reserves the right to attend any meeting therefore should be included in relevant invitations and also reserves the right to convene a meeting of the TSC in exceptional circumstances.

Quoracy

The minimum quoracy for a meeting to conduct business is 67% (two thirds) of appointed members. If, at short notice, any DMC members cannot attend then the committee may still meet if at least 2 members including the Chair will be present. If the DMC is considering a major action after such a meeting the Chair should communicate with the absent members, including the CI, as soon after the meeting as possible to check they agree. If they do not, a further meeting should be arranged with the full DMC.

Non-attendance

DMC members who will not be able to attend the meeting should pass comments to the committee Chair in advance for consideration during the discussion. If a member does not attend a meeting or provide comments when requested between meetings, it will be ensured that the member is available for the next meeting. If a member does not attend the next meeting or provide comments when next requested, they will be asked if they wish to remain part of the DMC. If an independent member does not attend a third meeting, strong consideration will be given to replacing this member.

7 Trial Documentation and Procedures to Ensure Confidentiality and Proper Communication

To enhance the integrity and credibility of the trial, procedures will be implemented to ensure the DMC has sole access to evolving information from the clinical trial regarding comparative results of efficacy and safety data, aggregated by treatment arm. An exception will be made to permit access to an unblinded statistician who will be responsible for creating the closed report and sending it to the DMC. The Chief Investigator will provide the chair of the DMC with information on any serious unexpected adverse reactions to the study drug, and will also be responsible for satisfying the standard requirements for reporting of relevant events to the regulatory authorities.

Meeting Content and Reports

At the first DMC meeting, the committee will provide an advisory review of scientific and ethical issues relating to study design and conduct, discuss the functioning of the DMC and discuss the format and content of the Open and Closed Reports that will be used to present trial results at subsequent DMC meetings.

The following intended content may be included in the reports:

- *Intended content of material to be available in open sessions.*
  Open Reports, available to all who attend the DMC meeting, will include any major protocol changes, data on recruitment and baseline characteristics; pooled data on eligibility violations; completeness of follow-up and compliance. The unblinded statistician will prepare these Open Reports.

- *Intended content of material to be available in closed sessions.*
  Closed Reports, available only to those attending the Closed Sessions of the DMC meeting, will include analyses of primary and secondary efficacy endpoints with due allowance for this being a feasibility study; analyses of adverse events and symptom severity; and Open Report analyses that are displayed by intervention group. The unblinded statistician, who is not involved in any decisions relating to the trial, will prepare these Closed Reports for the DMC.

For each DMC meeting, Open and Closed Reports will be provided to DMC members approximately two weeks prior to the date of the meeting by the unblinded trial statistician. The Open and Closed Reports should provide information that is as accurate as possible at the time of preparation, with follow-up that is as complete as possible.

External evidence

Identification and circulation of published external evidence (e.g. from other trials/ systematic reviews) is a responsibility of the CI. The DMC should continue to be made aware of other data that may impact on the trial.

Communication

The facilitator will be responsible for the organisation of meetings and should be copied into relevant communications with and between the DMC.

Confidentiality

DMC members are expected to store securely copies of the DMC reports, agenda and minutes, as well as copies of communications between meetings. All documentation should be considered confidential.

8 Decision Making

TSC / DMC decision-making

To be quorate for decision-making, at least two members (two thirds of the appointed membership) including the Chair will be present. It is important that the implications

(e.g. ethical, statistical, practical, and financial) for the trial be considered before any decision is made.

The DMC is jointly responsible with the TSC for safeguarding the interests of participating patients and for the conduct of the trial. Recommendations to amend the protocol or conduct of the study made by the DMC will be considered and accepted or rejected by the TSC. The TSC will be responsible for deciding whether to continue or to stop the trial based on the DMC recommendations.

DMC recommendations include but are not limited to:

- Trial continues as planned
- Early termination of the trial
- Stopping recruitment within a subgroup
- Extending recruitment or extending follow-up (pending approval by the funder)
- Proposing protocol changes

There are no pre-specified stopping rules in this feasibility trial. Should the DMC decide to recommend early termination of the trial, a full vote of the DMC will be required. In the event of a split vote, the decision will go with the majority vote, but a report should be provided to the TSC, written anonymously by the DMC members who are in the minority, for the purposes of officially stating their position on the issue. This report should not include unblinded data unless deemed necessary by the DMC. This information should be forwarded to the trial chief investigator as rapidly as possible.

Consensus and quoracy

Every effort should be made to achieve consensus. The role of the Chair is to summarise discussions and encourage consensus; therefore, it is usually best for the Chair to give their own opinion last. If a vote is required to achieve consensus, all independent members of the DMC have the opportunity to cast a vote with the chair voting last. The CI is not able to cast a vote.

9 Reporting

Meeting Minutes

Two sets of minutes will be prepared: the Open Session Minutes and the Closed Session Minutes.

Minutes of the open session will be prepared by the facilitator on behalf of the CI within two weeks of the meeting, and uploaded to the NIHR MIS when approved. Copies of minutes will be sent to all members, the sponsor and the funder, and a copy will be retained in the Trial Master File. These minutes and actions will be used as a basis for the following DMC meeting agenda.

The method of recording the outcome of the Closed session of the DMC will be at the discretion of the DMC Chair, and will be the responsibility of the DMC members to ensure confidentiality. Minutes of the closed session will be prepared within two weeks of the meeting. Any minutes of record of the Closed session of the DMC

should not be circulated out with the DMC members. Copies will be kept by the DMC chair or other designated DMC member. These will be sent to the trial manager and archived at the time of study closure.

Recommendations

Within two weeks of the meeting, the DMC chair/other designated DMC member will report via email to the Trial Manager their recommendations/decisions. The trial manager will forward the DMC meeting report and recommendations to the CI, TSC and the trial management group.

Disagreements

If there is a serious disagreement between the DMC and the TSC a meeting of these groups should be held. The information to be shown would depend upon the action proposed and the DMC's concerns. Depending on the reason for the disagreement some confidential data might have to be revealed to all those attending such a meeting. The meeting could be chaired by an external expert who is not directly involved with the trial.

10 After the Trial

- Publication of results
- The information about the DMC that will be included in published trial reports
- Whether the DMC will have the opportunity to approve publications, especially with respect to reporting of any DMC recommendation regarding termination of a trial
- Any constraints on DMC members divulging information about their deliberations after the trial has been published

Publication of results

DMC members will have the opportunity to read and comment on the proposed main publications of trial data prior to submission and abstracts and presentations during the trial, especially with respect to reporting of any DMC recommendation regarding termination of a trial.

This review may be concurrent to that of the trial investigators and TSC. DMC members will be named and their affiliations listed in the main report, unless they explicitly request otherwise.

Confidentiality of results

Unless permission has been agreed with the TSC, individual members will not discuss confidential information to which they have become party as a result of their involvement in the trial until 12 months after the primary trial results have been published.

Appendix 1: Agreement and Competing interests form for DMC members

Please complete the following document and return to the DMC Facilitator.

☐	I have read and understood the CARE Trial DMC Charter V2.0
☐	I agree to join the Data Monitoring Committee for this trial
☐	I agree to treat all sensitive trial data and discussions confidentially

The avoidance of any perception that members of a DMC may be biased in some fashion is important for the credibility of the decisions made by the DMC and for the integrity of the trial. Possible competing interest should be disclosed via the trial office. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) DMC member should remove the conflict or stop participating in the DMC.

Table 1 lists potential competing interests.

☐ **No,** I have no competing interests to declare

☐ **Yes,** I have competing interests to declare (please detail below)

Please provide details of any competing interests:

Name: _____

Signature: _____ Date: _____

Table 1

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the sponsor
- Frequent speaking engagements on behalf of the intervention
- Career tied up in a product or technique assessed by trial
- Hands-on participation in the trial
- Involvement in the running of the trial
- Emotional involvement in the trial
- Intellectual conflict eg strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) in competing products
- Involvement in the publication

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	24
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	24
Roles and	#5b	Name and contact information for the trial sponsor	1

responsibilities: sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	24
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	24 and supplementary
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7-8
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	8-9

		eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9-10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9-10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-12
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13-15
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	16-17
Methods: Assignment of interventions (for controlled trials)			

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	17
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	17
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	17
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	17
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17-18
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	18
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data	18-19

		entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19-21 and supplement
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19-21 and supplement
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19-21 and supplement
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	21
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	21
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	21-22
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	22
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	22-23
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to	23

		relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	16
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18-19
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	24 and 25
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	23
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	10
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	23
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	23
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	23
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	16 and supplement
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the	NA

current trial and for future use in ancillary studies, if applicable

Notes:

- 5d: 24 and supplementary
- 20a: 19-21 and supplement
- 20b: 19-21 and supplement
- 20c: 19-21 and supplement
- 32: 16 and supplement