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Synopsis

Medical management and intervention (using neurosurgical resection or stereotactic radiosurgery) versus medical management alone for symptomatic brain cavernoma: the CARE pilot RCT

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Abstract

Background: The top priority for research into symptomatic cerebral cavernous malformation (also known as brain cavernoma) is whether to have medical management and intervention (using neurosurgical resection or stereotactic radiosurgery) or medical management alone.

Objectives: The primary objective was to assess the feasibility of performing a definitive randomised trial addressing this top priority. The secondary objectives were to set up a collaboration involving patient advocacy organisations and clinicians in the United Kingdom and Ireland; perform a QuinteT Recruitment Intervention to identify facilitators and address barriers to recruitment; and conduct a pilot randomised trial with ≈60 participants.

Design: Prospective, randomised, open-label, assessor-blinded, parallel-group trial. A mixed-methods QuinteT Recruitment Intervention analysed sites' screening logs and qualitative data from audio-recorded recruitment discussions, interviews with healthcare professionals and patients, investigator workshops and observation of meetings.

Setting: Neuroscience hospitals in the United Kingdom and Ireland.

Participants: We aimed to recruit ≈60 people of any age, gender and ethnicity who had mental capacity, resided in the United Kingdom/Ireland, and had a brain cavernoma that had caused symptoms due to intracranial haemorrhage, non-haemorrhagic progressive/persistent focal neurological deficit or epileptic seizure(s).

Interventions: We identified and addressed barriers and facilitators to optimise informed consent and recruitment. Computerised, web-based randomisation assigned participants (1 : 1) to treatment of their symptomatic brain cavernoma with medical management and intervention (using neurosurgical resection or stereotactic radiosurgery) or medical management alone. Assignment was open to investigators, participants and carers but not clinical outcome event adjudicators.

Main outcome measures: Feasibility outcomes included site engagement, recruitment, choice of surgical management, retention, adherence, data quality, clinical outcome event rate and protocol implementation. The primary

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clinical outcome was symptomatic intracranial haemorrhage or new persistent/progressive non-haemorrhagic focal neurological deficit due to brain cavernoma or intervention during ≥ 6 months of follow-up.
Results: Investigators screened 511 patients at 28/40 (70%) sites in the United Kingdom: 322 (63%) eligible, 202 (63%) approached, 96 (48%) uncertain about whether to have intervention and 72 participants [median age was 51 years (interquartile range 39–59), 41 (57%) female, 66 (92%) white, 56 (78%) with prior intracranial haemorrhage and 28 (39%) with prior epileptic seizure] were randomly assigned to medical management and intervention (*n* = 36; 12 to neurosurgical resection and 24 to stereotactic radiosurgery) or medical management alone (*n* = 36) after a recruitment extension. Sixty-seven participants completed follow-up (retention 93%), and adherence was 91%. Barriers to recruitment included usual-care practices and logistical issues with stereotactic radiosurgery, whereas facilitators were neurosurgeons' preparedness to offer intervention to more people than in usual care, multidisciplinary team equipoise and presenting the study as a solution to equipoise. The primary clinical outcome occurred in 2/33 assigned to medical management and intervention and 2/34 assigned to medical management alone. There were no deaths or serious adverse events.
Limitations: We could not activate sites in Ireland. The generalisability of our findings outside the United Kingdom is unknown.
Conclusions: This pilot randomised trial identified facilitators and barriers to recruitment, exceeded its recruitment target and met some feasibility metrics.
Future work: A definitive randomised trial will need extensive engagement from international funders and networks of clinicians, researchers and patient groups to recruit 590–1900 participants.
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Introduction

What are brain cavernomas?

Cerebral cavernous malformations (CCMs), also known as brain cavernomas, are intracranial vascular malformations that are diagnosed using histopathological examination or magnetic resonance imaging (MRI). 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 (ICH) or new non-haemorrhagic progressive or persistent focal neurological deficits (FNDs) anatomically related to the brain cavernoma that do not appear to be due to haemorrhage.[3] The incidence of symptomatic brain cavernoma in the UK was 0.24 per 100,000 per year at the turn of the millennium,[4] so ≈160 people are newly diagnosed with symptomatic brain cavernoma in the UK annually. The impact of brain 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 brain cavernoma face a considerable risk of recurrent stroke, which is reliably known over 5 years after diagnosis,[5] but is likely to continue for their lifetime. The 5-year risk of ICH 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 ICH or FND. People with brain cavernoma who present with an epileptic seizure almost inevitably develop epilepsy within 1 year, and only half of the people with brain cavernoma-related epilepsy achieve 2-year seizure freedom.[6] These persistent symptoms also cause economic consequences for people with brain cavernoma, carers, the NHS, social services and lost productivity in the UK workforce.[7] Although most brain cavernomas are solitary and sporadic, around one-fifth are multiple with autosomal dominant inheritance due to mutations in three genes,[8] so there are implications for relatives as well.

Why is this research important?

Recurrent epileptic seizures and persistent symptoms of stroke due to ICH or FND result in disability, handicap and psychological consequences for people with brain cavernoma.[9] Therefore, 'intervention' as active treatment of cavernoma in usual clinical practice is done with neurosurgical resection for some patients (to try to prevent ICH or epileptic seizures) or stereotactic radiosurgery (which is preferred for different patients because

neurosurgery is too risky or patients want a non-invasive treatment).[10] However, intervention has complications that can be fatal or disabling,[11,12] and there are few reliable data about the benefits and risks of medical management with intervention versus medical management alone.[13–15] Consequently, guidelines have been unable to make strong recommendations for clinical practice,[14–16] and 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 brain or spine cavernoma?'[17]

How does the existing literature support this proposal?

Randomised controlled trials

A search of ClinicalTrials.gov trial register on 19 January 2024 for interventional studies using the terms 'cavernoma OR cavernous angioma OR cavernous malformation' revealed five randomised controlled trials (RCTs) of drug therapies for brain cavernoma but no completed, ongoing or planned RCTs of intervention.

Observational cohort studies

In several systematic reviews of observational cohort studies comparing intervention to medical management of brain cavernoma, or one form of intervention to another, we have not found any studies at low risk of bias that demonstrated sufficiently 'dramatic' associations between intervention versus medical management of brain cavernoma and clinical outcomes that would make a RCT unnecessary,[13,18] based on systematic reviews and meta-analyses, including (1) observational cohort studies that compared active treatment with stereotactic radiosurgery or neurosurgery against conservative management in a concurrent or historical control group and reported clinical outcome;[11–13] (2) observational cohort studies without comparison groups reporting clinical outcomes after either conservative management,[5] neurosurgery[12,19] or stereotactic radiosurgery;[11,19] and (3) decision analysis comparing all management strategies using a Markov model with a time horizon of 5 years.[20]

There are seven observational cohort studies (n = 394 participants) that compared neurosurgical resection and medical management, from which estimates of the relative risk of neurosurgery can be calculated (see *Table 1* overleaf).[10,21–26] The best available comparative data on an entire incident brain cavernoma population found neurosurgery to be associated with harm over 5 years [hazard ratios (HRs) 2.2–3.6],[10] although other comparative studies restricted to brainstem/deep brain cavernomas have suggested both harm [risk ratios (RRs) 1.9–7.8] and benefit (RRs 0.5–0.6) on the risk of ICH over 4–6 years,[22–25] but the long-term difference in risk is unknown and might favour neurosurgery.

In the only observational cohort study involving 41 participants comparing stereotactic radiosurgery with medical management at one hospital in Republic of Korea,[27] the RR was incalculable because of the paucity of outcomes (*Table 1*). Indirect comparisons imply that stereotactic radiosurgery might be superior to medical management over 5 years. In our 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 ICH), during a median follow-up of 48 [interquartile range (IQR) 35–62] months after stereotactic radiosurgery, the annual incidence of the composite of death, ICH or FND was 3.63% [95% confidence interval (CI) 3.17 to 4.16].[11] Using these data to estimate the 5-year risk (16.9%) after stereotactic radiosurgery and comparing the risk indirectly to the cumulative 5-year risks of ICH 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 5 years. A systematic review of stereotactic radiosurgery restricted to brainstem cavernoma suggested that treatment was beneficial by comparing ICH risks before and after treatment,[28] but their findings are unreliable because they may simply reflect the untreated clinical course of brain cavernoma in which ICH risk declines over time.[5]

Clinical guidelines

These major gaps in the evidence base informing the management of patients with brain cavernomas have prevented clinical guidelines in the UK and USA from making strong recommendations about whether to use treatment with intervention or medical management alone for brain cavernomas.[14,15] These uncertainties were confirmed by patients and carers in a James Lind Alliance Priority Setting Partnership in the UK.[17]

The need for a pilot phase randomised controlled trial

Resolving this therapeutic dilemma was likely to be challenging for several reasons: the incidence of symptomatic brain cavernoma is low despite a high prevalence, interventions are available in everyday clinical practice[14,15] and accumulated experience in specialist centres has determined usual clinical practice hitherto despite the lack of high-quality evidence.[29] Recruitment was likely to be challenging given the history of RCTs comparing active treatment of intracranial vascular malformations

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TABLE 1 Observational studies comparing intervention (with neurosurgical resection or stereotactic radiosurgery) with medical management

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

aHR, adjusted hazard ratio; mRS, modified Rankin Scale.

with invasive procedures versus medical management.[30,31] A similar RCT comparing active treatment versus medical management for arteriovenous malformations of the brain (ARUBA) revealed strong and polarised views held by different clinical specialties about different therapeutic approaches (neurosurgery, stereotactic radiosurgery and endovascular embolisation), which were barriers to RCT recruitment.[31] Slow recruitment to ARUBA seemed to be due to the disengagement of some specialty groups that did not accept the lumping of these different types of active treatment in one intervention arm, that disputed whether the findings were clinically applicable because there was insufficient funding for long-term follow-up to determine whether the early hazards of treatment were offset by gains in the longer term[31,32] and that questioned external validity because of the lack of information about patients who were not randomised. Identical problems beset a similar RCT of intracranial aneurysm management.[30] However, the reasons for poor recruitment to previous RCTs have not been formally studied. Many RCTs experience recruitment challenges due to difficulties that recruiters have in explaining concepts like uncertainty, equipoise and randomisation.[33] Also, patients may have treatment preferences (e.g. for less invasive procedures), and patient/family preferences may affect RCTs involving children in particular.[34]

Therefore, in late 2018, the NIHR issued a commissioned call for a pilot phase RCT addressing this dilemma (see *Report Supplementary Material 1* and *Report Supplementary Material 2*), and we were awarded a contract for the study.

We aimed to conduct a pilot phase RCT with embedded research to investigate the potential barriers to recruitment and optimise recruitment processes with a Qualitative research integrated within Trials (QuinteT) Recruitment Intervention (QRI),[35] which has been integrated into over 50 RCTs, including RCTs comparing surgery and medical management.[36] A QRI would allow the identification and understanding of generic and trial-specific recruitment challenges,[33,37,38] and the development of tailored plans to address these issues. There is observational evidence of the benefits associated with a QRI in at least five RCTs.[39] In our proposed Cavernomas A Randomised Effectiveness (CARE) pilot RCT, knowledge about proportions of patients screened, eligible, approached, consented and randomised, as well as what affects these stages of recruitment and could be influenced, will inform the feasibility of a definitive RCT.

Objectives

1. Engage the UK and Ireland patient advocacy organisations for cavernoma and representatives of clinical neurology, neurosurgery and stereotactic radiosurgery at all neuroscience centres throughout the UK and Ireland in a collaboration.
2. Conduct the following studies:
    a. A pilot phase of the CARE parallel-group RCT for patients with symptomatic brain cavernoma, comparing medical management and intervention (using neurosurgical resection or stereotactic radiosurgery) with medical management alone.
    b. An integrated QRI incorporating mixed-methods research to triangulate data from screening logs and a range of qualitative sources, to understand recruitment processes and barriers, and identify actions to optimise informed consent and recruitment.
3. Estimate the feasibility of performing a definitive CARE RCT by extending the UK collaboration to other patient support organisations, clinical communities and funders elsewhere in the world.

Methods for data collection and analysis

Protocol, charters and analysis plans

We published a protocol describing the CARE pilot trial collaboration, the methods of the pilot RCT and the QRI.[1] We registered the CARE pilot trial with International Standard Randomised Controlled Trial Number (ISRCTN) prospectively (number ISRCTN41647111) before recruitment started. We created charters for the Trial Steering Committee (TSC) (see *Report Supplementary Material 3*) and Data Monitoring Committee (see *Report Supplementary Material 4*) and the Patient, carer and public involvement and engagement Advisory Group (PAG) terms of reference (see *Report Supplementary Material 5*). We wrote date-stamped documents describing the statistical analysis plan (see *Report Supplementary Material 6*) and health economic analysis plan (see *Report Supplementary Material 7*).

The CARE pilot trial was a prospective, randomised, open-label, assessor-blinded, parallel-group trial at neuroscience centres in the UK and Ireland. Comprehensive information about trial design is available in the published protocol and trial report.[1,40] We aimed to recruit ≈60 people of any age, gender and ethnicity who had mental capacity, were resident in the UK or Ireland and had a symptomatic brain cavernoma. Computerised, web-based randomisation assigned participants (1 : 1) to treatment of their symptomatic brain cavernoma with medical management and intervention (using neurosurgery or stereotactic radiosurgery) or medical management alone, stratified by the neurosurgeon's and participant's consensus about intended type of intervention before randomisation. We chose a single, two-arm, 1 : 1 parallel-group trial, apparently 'lumping' the two types of intervention in one arm, but with randomisation stratified by preferred type of intervention, in order to provide information about the frequency of preferences and uncertainties about the type of intervention and separate assessments of the effects of types of intervention in two as-randomised subgroups (thereby addressing some of the criticisms of ARUBA). Assignment was open to investigators, participants and carers but not clinical outcome event adjudicators.

The embedded QRI within this trial[35] was a mixed-methods study that involved collection of screening log data (numbers and proportions screened, eligible, approached and randomised for each site and in total), 79 audio-recorded recruitment consultations between patients and healthcare professionals, 19 interviews with healthcare professionals, 11 interviews with patients who declined or withdrew from participation, discussions at 5 investigator

meetings and observation of Trial Management Group (TMG) meetings.[41] The QRI researchers identified and addressed barriers and facilitators with corresponding actions to optimise informed consent and recruitment in collaboration with the chief investigators and CARE trial team before recruitment began (e.g. co-design of patient-facing information, recruiter training at the time of site initiation visits) and throughout the recruitment period (e.g. tips and guidance documents for recruiters, CARE chief investigator narrated videos, described further below, investigator meetings and individual recruiter feedback).

Websites

We created a website (www.ed.ac.uk/care-study) that hosted information for patients and investigators and linked to the web-based trial database. The patient advocacy organisation, Cavernoma Alliance UK (CAUK), also created a website using plain English for patients, parents/guardians and carers describing the purpose and design of the study, as well as the support that CAUK provided for patients who were contemplating participation (https://cavernoma.org.uk/care-study/).

Investigator self-training materials

We developed self-training materials for investigators as narrated videos with PowerPoint® (Microsoft Corporation, Redmond, WA, USA) presentations (https://media.ed.ac.uk/channel/CARE±pilot±trial/205181893). Investigators had to watch these videos and then score 100% in an online quiz (https://forms.gle/HQ1nhyGy5ahCshAE7) in order to conduct study-related procedures. As a minimum, the principal investigator (PI) and site co-ordinator had to provide a certificate of completion of the quiz before a site initiation visit could take place. The training videos covered the following topics:

- CARE Study Training with the Chief Investigator.
- CARE Study Protocol Training for the QRI (Part 1 – Introduction). This training module provides a brief introduction to the Information Study.
- CARE Study Protocol Training for the QRI (Part 2 – Putting it into practice). This training module provides an overview of what site teams need to do for the Information Study.
- CARE Study Protocol Training for the QRI (Part 3 – Processes and SIV prep). This training module covers the QRI processes and tasks the site teams should complete before the site initiation visit.
- CARE Study Training with the Trial Manager. This training module focuses on the study assessments and time points covered in the protocol.
- Sponsor standard operating procedure (SOP) training for CARE. This training module covers the sponsor's SOPs that are applicable to this study.

Sites

We provided a public list of participating sites, including the contact details of the PI and co-ordinator at each site (www.ed.ac.uk/usher/edinburgh-clinical-trials/our-studies/all-current-studies/care/care-study/sites) in order to facilitate the patient advocacy organisations in the UK and Ireland signposting the trial to potentially eligible patients (see *Patient and public involvement*), so that they could determine whether their local neuroscience hospital was participating in the trial. We engaged all investigators and project partners with weekly e-mail newsflashes (containing a recruitment update, any good news and signposts to the latest learning from the QRI or other important issues of trial conduct) and a monthly newsletter with lengthier updates and recruitment league tables (see www.ed.ac.uk/usher/edinburgh-clinical-trials/our-studies/all-current-studies/care/care-study/newsletters for the newsletter archive).

Participant information leaflets

We developed short and supplementary information leaflets in collaboration with the PAG and QRI researchers, including separate versions customised for adults, or for parents and guardians of children, three leaflets for children (ages 0–5, 6–10 and 11–15 years) and separate information leaflets for Ireland (www.ed.ac.uk/usher/edinburgh-clinical-trials/our-studies/all-current-studies/care/care-study/get-involved).

Frequently asked questions

After recruitment began, we had foreseen that some procedural and logistical issues would arise. We also encountered barriers and facilitators to screening and recruitment as part of the QRI. In order to address these issues and frequently asked questions, we created short, narrated PowerPoint presentations as videos – involving discussions between the chief investigator (Rustam Al-Shahi Salman), co-chief investigator (Neil Kitchen), the QRI researcher (Julia Wade) and key TMG members, known as 'CARE Chats' – which were disseminated via the weekly newsflashes and posted on the trial website for investigators (www.ed.ac.uk/usher/edinburgh-clinical-trials/our-studies/all-current-studies/care/care-study/faq). These pre-recorded videoed discussions have not been used in previous QRIs. The topics included:

- screening logs
- putting the QRI into practice
- approaching patients diagnosed long ago and treated without intervention
- logistics of recruitment
- recruiter tips and guidance
- tips for conversations about the CARE study
- patients' frequently asked questions

- tips for recruitment conversations
- QRI audio-recordings
- tips for describing randomisation
- tips about timing of randomisation
- logistics of using stereotactic radiosurgery.

Outcomes

In the protocol, we pre-specified a primary feasibility outcome involving 13 measures of the feasibility of a definitive RCT; a primary clinical outcome of ICH or new persistent/progressive FND due to brain cavernoma or intervention; several secondary clinical outcomes [death, modified Rankin Scale score, National Institute of Health Stroke Scale (NIHSS) score, EuroQol-5 Dimensions, five-level version in adults and EuroQol-5 Dimensions, three-level version in young people (EQ-5D-Y), Karnofsky Performance Status scale in adults and Lanksy Play-Performance Scale in children, and Liverpool Seizure Severity Scale]; and collection of data to estimate health service use and healthcare and socioeconomic costs.[1]

In addition, the contract with NIHR pre-specified the following success criteria:

- At least 30 sites in the UK and Ireland collaborate.
- Project delivered according to the major milestones identified in the timetable.
- Recruitment to within 10% of target in the CARE pilot RCT.
- Brain cavernoma radiographic diagnosis confirmed by expert neuroradiologist review in > 95% of patients recruited.
- Retention of > 95% of participants at 6 months in the CARE pilot RCT.
- < 10% treatment group switches or lost to follow-up in the CARE pilot RCT.
- QRI is associated with an improvement in recruitment.
- Definitive RCT appears feasible and affordable.

Results summary

The main outputs that we included in the publication plan are:

1. this synopsis
2. the protocol[1]
3. the CARE pilot trial report[40]
4. the QRI substudy report.[41]

Cavernomas A Randomised Effectiveness (CARE) pilot trial

Full details about all outcomes are reported in the trial report,[40] but we report a short synopsis of the main findings here and in *Table 2*. Between 27 September 2021 and 28 April 2023, we obtained Research Ethics Committee (REC) approval for 30 (75%) of 40 sites that were invited to take part, of which 28 (70%) completed site initiation visits and became active. We obtained an extension to the recruitment period in time due to slower-than-expected overall recruitment at a smaller number of sites than expected, where investigators screened 511 patients, of whom 322 (63%) were eligible. About 202 (63%) of eligible patients were approached for recruitment, of whom 96 had collective uncertainty with their neurosurgeon about whether to have intervention for a symptomatic brain cavernoma. A surge in recruitment during the last month of screening led to 72 (22%) of the eligible patients giving consent, who were randomly assigned at a median of 287 days (IQR 67–591) since most recent symptomatic presentation. Participants' median age was 50.6 years (IQR 38.6–59.2), 68 (94%) were adults, 41 (57%) were female, 66 (92%) were White, 56 (78%) had prior ICH and 28 (39%) had prior epileptic seizure. The intended type of intervention before randomisation was neurosurgical resection for 19 (26%), stereotactic radiosurgery for 44 (61%) and no preference for 9 (13%). Baseline clinical and imaging data were complete for all participants. Randomisation assigned 36 participants to medical management and intervention (12 to neurosurgical resection and 24 to stereotactic radiosurgery) and 36 to medical management alone. Three (4%) participants withdrew, one was lost to follow-up and one declined face-to-face follow-up, leaving 67 (93%) retained at 6-month clinical follow-up. Sixty-one (91%) of participants with follow-up adhered to the assigned management strategy. The primary clinical outcome occurred in 2 of 33 participants assigned medical management and intervention [8.0% (95% CI 2.0 to 32.1) per year] and in 2 of 34 participants assigned medical management alone [7.5% (1.9–30.1) per year]. Investigators reported no deaths, no serious adverse events (SAEs), 1 protocol violation and 61 protocol deviations [deoxyribonucleic acid (DNA) sample not provided (n = 11); consent form errors (n = 10); delegation log errors (n = 10); baseline NIHSS score not

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TABLE 2 Feasibility outcomes in the CARE pilot RCT

Feasibility outcome	Metric(s)
What proportion of the collaborating sites take part and recruit participants to the CARE pilot trial?	30/40 (75%) sites obtained REC approval. 28/40 (70%) sites were activated. 22/40 (55%) sites recruited ≥ 1 participant[40]
Do investigators implement trial procedures correctly?	61 protocol deviations. One protocol violation. Independent review confirmed definite certainty of brain cavernoma diagnosis in 70 (97%)[40]
What proportion of screened patients is eligible?	322 (63%) eligible of 511 screened[40]
What proportions of eligible patients are approached and randomised (and why are eligible patients not approached or not randomised)?	202 (63%) of 322 eligible patients were approached, and 72 (22%) were randomised following an extension to recruitment.[40] Certainty about whether to have intervention was the main reason that patients were not approached or not randomised[40,41]
What is the distribution of participants between neurosurgery and stereotactic radiosurgery?	The intended type of intervention that was pre-specified before randomisation for the 72 participants was neurosurgical resection for 19 (26%), stereotactic radiosurgery for 44 (61%) and no preference for 9 (13%)[40]
Do participants adhere to the assigned management and follow-up?	Completeness of 6-month follow-up was 67/72 (93%).[40] Adherence to assigned management was 61/67 (91%).[40] Adherence to pre-specified type of intervention in participants assigned to intervention and medical management was 29/29 (100%)[40]
How complete are baseline, imaging and outcome data?	Baseline clinical case report form complete 72/72 (100%).[40] Baseline brain imaging received 72/72 (100%);[40] 6-month clinical follow-up complete 67/72 (93%);[40] 6-month brain imaging received 69/72 (96%)[40]
What are the outcome event rates? (Rate of first outcome event during follow-up, quantified per participant per year)	First ICH/FND 7.8% (95% CI 2.9 to 20.7%). First ICH 3.8% (1.0%–15.1%). First FND 3.8% (1.0%–15.1%). Death not due to a primary outcome 0%[40]
How do the baseline characteristics, outcome event rates and differences between treatment groups compare to observational data about outcomes during medical management alone or after intervention and medical management?	*Baseline characteristics:* demographics, clinical and imaging characteristics similar to systematic reviews/meta-analyses of untreated clinical course[5] and after intervention.[11,12] *Outcome event rates:* similar to rates described in the untreated clinical course[4] and after intervention.[11,12] *Association between medical management and intervention vs. medical management alone with subsequent* ICH ± FND *in cohort studies:* RR 0.6 (95% CI 0.2 to 1.7) over ≈5 years,[23] RR 0.6 (0.1–2.6) over ≈4 years,[26] HR 0.76 (0.4–1.4),[40] RR 1.9 (0.6–6.0) over ≈6 years,[24] aHR 3.6 (1.3–10.0) over 5 years[10] and RR 7.8 (1.1–57.4) over ≈4 years[22]
What estimates of effect size/variability should be used in the design of the CARE definitive randomised trial?	The observed unadjusted HR for the effect of medical management and intervention vs. medical management alone on the primary clinical outcome was 0.99 (95% CI 0.14 to 7.03)[40]
What is the sample size required for a definitive trial to address the overall question over a 10-year follow-up?	Sample size estimates are provided in the research recommendations section
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 randomised trial?	Data about care pathways and outcomes were sufficient to estimate mean resource use and costs per participant as well as quality-of-life measurement for QALY estimation[40] and to be used by a published Markov model[20]

Note

recorded (*n* = 9); study visit done outside the time window specified in the protocol (*n* = 8); investigator training not completed (*n* = 5); 6-month visit not done face-to-face (*n* = 4); late DNA sample (*n* = 4); surgery done > 3 months after randomisation (*n* = 1)].

QuinteT Recruitment Intervention

Full details about all findings, including quotes from investigators and patients, are to be found in the report of the QRI,[41] but we provide a short synopsis of the findings here. The QRI substudy found several

barriers: reluctance to offer randomisation to people recommended medical management alone within usual practice, reluctance to offer stereotactic radiosurgery (particularly for children or people with epilepsy), logistical challenges to review and recruit participants, especially during the COVID-19 pandemic, concerns about short follow-up in the trial and challenges of organising stereotactic radiosurgery. The substudy also identified several facilitators: investigators who were comfortable offering randomisation to people for whom medical management alone was usual practice, crucially with local multidisciplinary team support to do so and justifying the offer of stereotactic radiosurgery with reference to low risk of morbidity. The QuinteT and trial teams implemented multiple actions promoting recruitment at various stages in the pilot trial both before and during recruitment, including: balanced portrayal of the two trial arms in the participant information leaflet; emphasis on an inclusive approach to screening and training in optimising information provision about the trial at site initiation visits; videos to coach investigators in screening and recruitment discussions; tips and guidance documents for investigators; and investigator meetings.[41]

Success metrics proposed to the National Institute for Health and Care Research

Table 3 shows our findings in relation to the metrics we proposed to the NIHR in the contract; we fulfilled the majority of these metrics, and the one metric that we failed (retention > 95%) came close (93%) and would have been achieved had two more of the 72 participants been followed up at 6 months.

Discussion and interpretation

TABLE 3 Fulfilment of the success metrics that were proposed to NIHR

Success metric	Findings	Achieved?
At least 30 sites in the UK and Ireland collaborate	30 sites (28 in England, Wales and Scotland; 2 in Ireland) obtained REC approval. 28 sites (in England, Wales and Scotland) were activated[40]	Yes
Project delivered according to the major milestones identified in the timetable	We delivered the project according to the project milestones with a 5-month extension (awarded due to delays attributable to the impact of COVID-19 pandemic)[40]	Yes
Recruitment to within 10% of target	The trial recruited 72 participants at 28 sites over 23 months (mean recruitment rate 0.2 ± 0.25 participants per site per month), which exceeded the recruitment target of 60 participants at 40 sites over 18 months (recruitment rate 0.11 participants per site per month)[40]	Yes
Brain cavernoma radiographic diagnosis confirmed by expert neuroradiologist review in > 95% of patients recruited	Expert review of diagnostic brain imaging confirmed definite certainty of brain cavernoma diagnosis in 70 (97%) and probable certainty in two (3%) participants[40]	Yes
Retention of > 95% of participants at 6 months	67 (93%) participants were retained at 6-month clinical follow-up[40]	No
< 10% treatment group switches or lost to follow-up	61 (91%) of 67 retained participants adhered to the assigned management strategy[40]	Yes
QRI is associated with an improvement in recruitment	Visual interpretation of the recruitment graph indicates that the recruitment rate increased over time in association with the conduct of the QRI,[40,41] but other potential confounders (e.g. the number of sites) changed at the same time[40]	Maybe
Definitive RCT appears feasible and affordable	We have estimated a range of potential sample sizes for a definitive RCT, which would require a multicentre, international network to recruit sufficient participants over 5 years. We have had expressions of interest from a range of potential international partners	Maybe

The text below includes minor additions and formatting changes to the original text.

Principal findings and achievements per project outcome

The CARE pilot trial is, to the best of our knowledge, the first RCT to address the top uncertainty for brain cavernoma, with an embedded QRI to understand recruitment barriers and facilitators and develop corresponding actions to optimise informed consent and recruitment.

In the QRI, we found that the main barriers related to equipoise and patient eligibility, with conventions of usual care making a position of equipoise challenging for some, multidisciplinary teams preventing approach of some patients with symptomatic brain cavernoma, and logistical issues surrounding diagnosis and assessment for stereotactic radiosurgery adding further barriers.[41] The main facilitators included the high level of commitment of the chief investigators, TMG and the PIs who were prepared to change practice within the research context to offer intervention to people who would have been offered medical management alone outside the trial. Multidisciplinary team equipoise and skilful information provision to facilitate patient understanding (so that the trial could be viewed as a solution to uncertainty about management) were key in optimising recruitment.

The pilot RCT met its targets for participation by neuroscience hospitals, investigators and people with symptomatic brain cavernoma.[40] Estimates of recruitment rate, retention, surgical preference, adherence, outcome event rates, healthcare utilisation and intervention effects are informative for determining the feasibility of a definitive RCT. Although the generalisability of the findings outside the UK is unknown, a definitive RCT will require an extensive international multicentre network of sites and prolonged follow-up in view of the rarity of symptomatic brain cavernoma, the willingness of one-fifth of approached eligible patients to take part and the frequency of outcome events. The data collected were adequate to allow the conduct of both a within-trial and a model-based economic evaluation alongside a definitive RCT.

Contribution to existing knowledge

The non-randomised cohort studies comparing outcome after intervention for brain cavernoma with concurrent or historical control groups of people with brain cavernoma who underwent medical management alone have found a wide range of associations between intervention and poor outcome (see *Table 1*). These associations have ranged from a non-significant association with better outcome (RR 0.6, 95% CI 0.2 to 1.7) over ≈5 years[23] to a significant association with worse outcome (RR 7.8, 95% CI 1.1 to 57.4) over ≈4 years (see *Table 1*).[22] The similarity in outcome between medical management and intervention versus medical management alone in the CARE pilot RCT justifies the uncertainty about the benefits of management of symptomatic brain cavernoma with intervention and includes the possibility of harm or benefit.

Considering the challenges of conducting research during the COVID-19 pandemic and during the recovery of the research infrastructure afterwards, we had exceptional engagement from sites, investigators and participants.[42] They demonstrated that this RCT could be done and that one-fifth of eligible patients who were approached were recruited, which is close to the finding of a similar RCT.[31] The QRI added to the body of work on facilitators and barriers to recruitment to RCTs in general,[33] RCTs involving children[34] and RCTs comparing surgical with medical management.[35,36]

Strengths and weakness of the study in relation to other studies

The main strengths are that this project was a methodologically rigorous RCT with an embedded QRI and the first to address brain cavernoma. This was endorsed by the opening comments from two peer reviewers of the main trial report submitted to *The Lancet Neurology*;[40] the first stated, 'As a general comment, I much appreciated this study and do believe that methodologically sound feasibility studies like this should be performed more than is currently done', and the second stated, 'The authors have thoroughly investigated the importance of the research question. The methods are sound, the trial is very well conducted, and the paper is very well written. The authors are to be commended for involving patients and carers involved from the development of the research idea and question to the conduct of the trial. I think this manuscript should serve as an example of how to develop and conduct a trial and report on it'.

There was good engagement from the neurosurgical community, including neurosurgical trainees via the NIHR associate PI scheme. We had exceptional involvement from our Patient, Carer and Public Involvement (PCPI) collaborators, who supported many patients with their individual decisions about participation. The RCT exceeded its recruitment target. We did not find evidence of selection bias based on the similarities between eligible patients who declined and those who participated. Characteristics of participants by intended type of intervention reflected their appropriate selection for each type of intervention. Characteristics of intervention reflected usual practice in

the UK. The trial achieved good retention and adherence, and provided estimates of preference for type of intervention (we found that stereotactic radiosurgery was chosen as the type of intervention twice as often as neurosurgical resection, contrary to prior expectations), and outcome event rates to inform the planning of a definitive trial. No participants died, clinical outcome event rates were similar to observational studies and no SAEs were reported. A definitive trial would benefit from repeating the collaboration with patient support organisations and implementing the actions from the QRI.

However, there were some limitations. Participants in qualitative data collection were largely supportive of the RCT; this may be representative, although negative perceptions may be less well documented, and this meant that within the qualitative data collection, we were unable to reach saturation on the influences of some demographic and clinical features on recruitment. The QRI was not a randomised study, and other factors may have contributed to the RCT exceeding its recruitment target (e.g. COVID-19 recovery, chief investigator engagement, trial marketing that signalled a time-bound recruitment target and our highly engaged PCPI partners). It was difficult to evaluate the numerical impact of PCPI support for patients from the patient advocacy organisations, because we had not arranged and sought regulatory approval for the identities of patients on the CAUK call log to be compared with the identities of participants in the RCT. The RCT sample size was small given the frequency of brain cavernoma, recruitment at 28 sites and 2-year duration of recruitment. Only 4 of the 72 participants were aged < 18 years. Participants' ethnicities (92% White, 1% Asian, 1% mixed and 6% other) were less diverse than the UK. In a recent project assessing readiness for RCTs of drugs for brain cavernoma at five neuroscience centres in the USA, restricted to people aged > 18 years with symptomatic ICH from a brain cavernoma over the preceding year, participants seemed younger, more ethnically diverse, more likely to have a brainstem cavernoma and more likely to have a family history than in the CARE pilot RCT, but other characteristics and the outcome event rate were similar.[43] Generalisability of our findings outside the UK is unknown. Finally, correspondence following the publication of the CARE pilot trial illustrated anecdotal misunderstanding or concern among neurosurgeons about 'lumping' both types of intervention in one arm of the trial,[44,45] even though randomisation was stratified by type of intervention, and outcomes for these two subgroups were reported separately, which we clarified;[46] reassuringly, the correspondents agreed that a definitive main phase RCT is needed.

Take-home message(s)

Fundamentally, it was possible to conduct a RCT of intervention for symptomatic brain cavernoma. This pilot phase RCT met its targets for participation by neuroscience hospitals, investigators and people with symptomatic brain cavernoma. Recruitment to a definitive RCT would benefit from training and support to encourage more clinicians to be comfortable approaching patients for whom medical management alone would conventionally be offered in usual care in the UK and broadening the pool of surgeons and multidisciplinary team members prepared to offer surgical interventions, particularly stereotactic radiosurgery, within a trial context. A definitive RCT would need to address the lack of consensus from the outset and use some key supporters of recruitment to the RCT within the neurosurgical community to address the issues head-on before and throughout recruitment, via repeated discussion of issues that challenge equipoise, as well as materials to encourage investigators to shift their usual practice towards recruitment to a RCT. Estimates of recruitment rate, retention, surgical preference, adherence, outcome event rates and intervention effects inform the feasibility of a definitive randomised trial. Although the generalisability of the findings outside the UK is unknown, a definitive trial will require an extensive international multicentre network of sites and prolonged follow-up in view of the rarity of symptomatic brain cavernoma, the willingness of one-fifth of eligible patients to take part and the frequency of outcome events.

Reflections on the project and what could have been done differently

It was worthwhile to begin to address the top uncertainty from brain cavernoma with a pilot phase RCT, which benefited from being conducted with PCPI and qualitative researchers. The QRI worked particularly well by involving qualitative researchers with discussions about equipoise at site initiation visits, contribution of general and disease-specific insights to the creation of participant information materials, engagement with the PAG and communications with investigators. In retrospect, the requirement to have a PI at each site who was a neurosurgeon helped recruitment, but neurologists (who see many patients with brain cavernoma) could have been more explicitly engaged with referring, assessing and approaching potential participants for the RCT; neurologists' greater involvement with a definitive RCT would be desirable. In retrospect, we created materials successfully to support investigators who were already comfortable with enrolling participants in the RCT, but there were fewer materials orientated to encourage neurosurgeons to rethink their usual practice and introduce the RCT into it.

This synopsis should be referenced as follows:
Al-Shahi Salman R, Kitchen N, Forsyth L, Ganesan V, Hall PS, Harkness K, *et al*. Medical management and intervention (using neurosurgical resection or stereotactic radiosurgery) versus medical management alone for symptomatic brain cavernoma: the CARE pilot RCT. *Health Technol Assess* 2025;**29**(38). https://doi.org/10.3310/GJRS5321

Challenges faced and limitations

The main logistical challenges we encountered were because of the effects of the COVID-19 pandemic on the research infrastructure and recruitment to research. Investigators navigated some of these challenges by using remote consultations and e-consent, for which we had sought regulatory approval from the outset.

The customs of usual care, even though they have been based on poor-quality observational studies, were hard to shift. We encountered entrenched views about the effects of stereotactic radiosurgery for brain cavernoma. However, there was a 2 : 1 preference for stereotactic radiosurgery over neurosurgical excision as the intended type of intervention, which the QRI found to be due to investigators' perceptions of lower morbidity after stereotactic radiosurgery and participants' greater comfort with a non-invasive procedure; this finding provides some reassurance which could help build consensus in support of a definitive RCT.

Engagement with partners and stakeholders

This pilot RCT would not have been successful without the involvement of PCPI partners, the QRI and collaboration with the Society of British Neurological Surgeons research network.

Individual training and capacity-strengthening activities

The NIHR associate PI scheme provided training in RCT conduct and oversight for many neurosurgeons in training, who obtained certificates for their involvement. We have created a web-based archive of training videos that could be reused, or adapted, for a definitive RCT. CAUK, Cavernoma Ireland and the PAG received training and first-hand experience from their involvement with trial oversight, conduct, dissemination and engagement.

Patient and public involvement

This section of the synopsis was written by David White, on behalf of the PAG.

Aim

The aim was to bring the PCPI voice into all aspects of the CARE pilot trial, to ensure that the project was accessible and appropriate for potential participants irrespective of age, pregnancy, race, ethnicity or mental capacity. This included advice on: the grant application and its plain language summary; methods of recruitment; the design, language and content of the project's documentation (including the project's patient/parents/guardian information leaflets, informed consent forms and the design, content and accessibility of progress reports and newsletters for participants); and the evolving findings of the QRI. The PCPI partner sought to promote enrolment in the CARE pilot RCT to potential participants.

Methods

The PCPI was organised and run jointly by the two patient support organisations CAUK and Cavernoma Ireland, under the responsibility of the Trustees and Chief Executive of CAUK. We created a diverse PAG of 12 members ranging in age and including patients, parent carers and unpaid carers which reported to the TMG and TSC. The PAG met via Zoom (Zoom Video Communications, San Jose, CA, USA) every other month during the recruitment phase, and then as required. The chief investigator, trial manager and Dr Julia Wade (QuinteT) and the chief executive of CAUK attended PAG meetings as observers. The work of the PCPI input varied according to the phases of the trial.

Funding application

In 2015, CAUK co-ordinated a James Lind Alliance Priority Setting Partnership of cavernoma patients and clinicians 'Priorities for research into cavernoma' that placed the subject of the CARE trial as its top priority. CAUK ran a focus group in July 2019 to consider the overall design of CARE.

Cavernomas A Randomised Effectiveness start-up

Cavernoma Alliance UK developed comprehensive resources on its website with input from the chief investigator and QRI researchers. This was constantly updated and included: Frequently Asked Questions, Recruitment & Eligibility, Information Leaflets, Importance of Randomised Controlled Trials and Contacts. The site had two explanatory videos (https://cavernoma.org.uk/care-study/).

The PAG provided feedback on the patient information leaflets. A key focus of the PAG input was in shaping the content and presentation of a table included in the participant information leaflets showing processes, risks and benefits involved with each arm within the CARE pilot RCT (*Table 4*). The PAG shaped the content and presentation of information in both the short and supplementary adult participant information leaflets. This content, in turn, fed into codevelopment with the trial team of other participant information leaflets (child with capacity, children 0–5 years, children 6–10 years, parent

TABLE 4 Process, benefits and risks portrayed in the participant information leaflet

		Medical and surgical management	
	Medical management	**Neurosurgery**	**Stereotactic radiosurgery**
What may be involved?	• 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	• Treat symptoms • Prevent seizures • Rehabilitation • Brain scan • Hospital attendance for a day • Anaesthetic not needed • Head fixed in a temporary frame • Focused 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

This synopsis should be referenced as follows: Al-Shahi Salman R, Kitchen N, Forsyth L, Ganesan V, Hall PS, Harkness K, *et al.* Medical management and intervention (using neurosurgical resection or stereotactic radiosurgery) versus medical management alone for symptomatic brain cavernoma: the CARE pilot RCT. *Health Technol Assess* 2025;**29**(38). https://doi.org/10.3310/GJRS5321

guardian) shaped by advice from parents with children. The main concern of feedback from the sponsor and REC was the retention of adults who may lose mental capacity during the trial. Other major topics discussed were outcome measures and how the helpline should address referral to study sites. The PAG expressed its gratitude for the spirit of collaboration that Professor Salman brought to the meeting, with the emphasis of reaching consensus.

All those answering the CAUK helpline during the recruitment phase received training from the QRI team (May 2021). This included tips on how to present information in a way that conveyed equipoise, to respond to people who expressed preferences and explaining the reason for randomisation.

Recruitment

The primary role during the recruitment phase was to promote CARE to potential participants:

- CAUK ran a telephone and e-mail helpline throughout the CARE recruitment phase, supporting trial candidates, enrolled participants and unpaid carers by providing objective and unbiased information, alongside emotional support.
- The helpline team attended refresher training courses delivered by the QRI and CARE trial teams in November 2021 and February 2022.
- The co-chief investigators gave an introduction to the CARE study to the annual meeting of CAUK's Annual International Forum in June 2021 with very positive feedback.
- CAUK's outreach community worker posted regular updates and recruitment promotions on Facebook [Meta Platforms, Inc. (formerly Facebook, Inc.) Menlo Park, CA, USA], Twitter [X Corp. (formerly Twitter) San Francisco, CA, USA] and Instagram (Meta Platforms, Inc Menlo Park, CA, USA).
- CAUK's monthly newsletter, circulated to all members of CAUK (2800 in 2020, 3500 in March 2023), had a CARE update.

Follow-up

There were no meetings of PAG during the follow-up phase of the trial, although a representative from each of CAUK and from Cavernoma Ireland continued to attend meetings of the TMG and the TSC.

Documentation

The PAG met twice to provide feedback on late drafts of the following documentation: QRI report, clinical trial report, NIHR synopsis and the plain language summary. The PCPI representatives led on the creation of a video abstract to disseminate results to the public, participants, patients and carers.

Study results

Helpline

The helpline responded to 253 inputs (calls 34%, e-mails 64% and 2% other) from 131 individuals, of whom 24 were seen by a study site team. Of the calls/e-mails, 40% were for general information, 36% for how to take part and 7% concerning special problems of referral to a study site with an assortment of other matters. The average time for each input was 23 minutes, that is, roughly 100 hours in total. As shown in *Tables 5* and *6*, 58% of those calling the helpline heard about CARE through CAUK sources.

Social media

Facebook, Instagram, Twitter and LinkedIn (LinkedIn, Sunnyvale, CA, USA) were used as communication channels to reach the widest possible audience, to support recruitment to the project. Engagement was strong throughout with an uptake in helpline enquiries after each post (*Figure 1*).

TABLE 5 How had helpline callers heard about CARE?

Source	*N*	%
CAUK website	96	39
Caller's neurologist	26	11
CAUK social media	24	10
Helpline chat	20	8
Caller's neurosurgeon	7	3
Trial site	4	2
Team	4	2
Other	65	25

TABLE 6 Where had helpline callers seen information about CARE?

Source	*N*	%
CAUK website	142	39
Participant information leaflet	126	34
Site study team	24	7
CARE website	9	2
None	29	8
Other	36	10

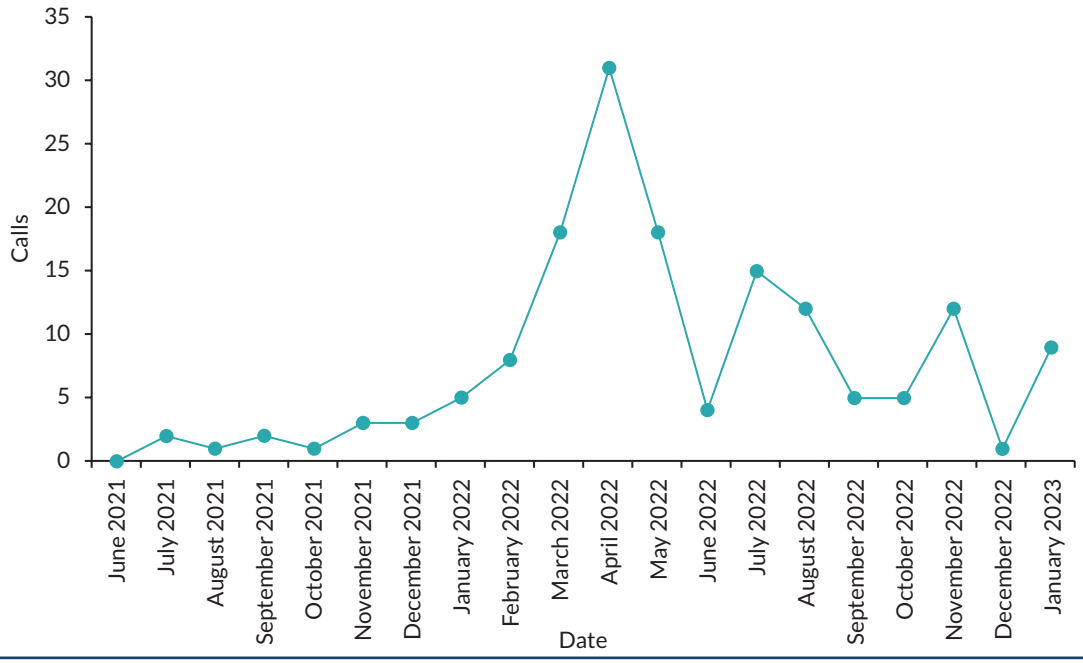

FIGURE 1 Helpline calls over time.

Website

The CAUK webmaster estimated that he spent about 8 week's work, spread over the 3 years of the project, on work maintaining the website. Most of this work was paid within the terms of his contract with CAUK (i.e. not funded from CARE study funds).

Discussion and conclusions

The attention paid by the TMG to the PAG's comments on the various documents it considered suggested to the PAG that it had a significant input into their quality for patients and carers. All the PAG input was given true consideration, and most adopted. The efforts of the PAG brought the CARE pilot trial to the attention of members of CAUK and Cavernoma Ireland on a regular basis via social media and monthly newsletter and to a wider audience via the CAUK website. Data protection and clinical confidentiality issues prevented CAUK being able to report which callers to CAUK helpline subsequently contacted a CARE pilot study site and whether CAUK input influenced the decision to take part. Qualitative data captured by the QRI team included positive comments about the support received from CAUK from people choosing to take part. Some CAUK members reported to the helpline having contacted CARE sites, and we asked those patients to comment on the contribution the PCPI/CAUK had on their decisions to take part in CARE (*Table 7*).

Reflections

What went well from a patient and public involvement perspective was the role played by CAUK and Cavernoma Ireland in supporting patient recruitment, retention and compliance through the helpline, website and other communication channels. The PAG was also gratified by the willingness of the TMG to incorporate their feedback and ensure patient information was accessible and inclusive.

What was problematic, because it was not anticipated by PCPI representatives, was the delay to CARE study sites opening, in particular the lack of study sites opened in central England in the first year and no study sites opened in Ireland. This was, in part, a consequence of the impact of COVID-19 on research in clinical establishments and is documented in the CARE pilot trial publication.[40] CAUK's promotion of CARE started in a major way in July 2021, yet the first site did not open until the end of August 2021. This meant that early on, people contacting the helpline, and people to whom CAUK was promoting CARE, had no easily accessible study site when they were most geared up to considering CARE. CAUK could have also benefited from having more consistent guidance on how to arrange for an interested patient to contact a study site in England.

Equality, diversity and inclusion

The inclusion criteria of the pilot RCT were intentionally broad, in order to prevent any selection of participants according to their protected characteristics (age, sex, disability, gender reassignment, marriage or civil partnership, pregnancy and maternity, race, religion/belief, or sexual orientation). We produced information leaflets for adults, children and parents/guardians of children in order to offer the opportunity to take part regardless of

TABLE 7 Comments on PCPI input from patients who also contacted a CARE site

Comment	Respondent
'I also went onto the Cavernoma Alliance UK website which I found very informative and which led me to other associated sites, including the Edinburgh University and Prof Salman's involvement. From the CAUK website I was made aware early on that there were many other cavernoma sufferers with much worse symptoms than mine, which made their life very difficult' 'My contact with CAUK was always helpful and supportive. My questions were always answered and I was put in touch with parents who could also support me. If I had queries as to how CARE study would proceed I was given extra information. Or if I had not heard back from the hospital I was given support in prompting the hospital to make contact with me, etc'	Took part and was randomised to intervention. Had neurosurgery Parent of child who joined the study but later opted out
'My contact with CAUK was helpful. They pointed me in the correct direction and outlined a bit about the study'	Took part and was randomised to stereotactic radiosurgery, delivered outside the target 3-month window
'Although there was plenty of information on the CAUK website, it was useful to chat it through. It was particularly relevant to me . . . that CAUK was involved in the RCT as a partner, and reassuring that I could get in touch if I needed to. I also attended the online presentation from Prof Salman in summer 2023 (by which stage I had already had surgery), organised by CAUK and was pleased this was made available'	Took part and was randomised to intervention. Had neurosurgery
'My contact with CAUK was very helpful to understand the specialists in the areas and options for surgery'	Decided not to take part in the study
'[My contact with CAUK] was extremely helpful in two main ways. Firstly, being able to speak to someone that could provide support and understanding during such a stressful time when the way ahead was very unclear made a huge difference. Especially when there was some time to wait for hospital appointments and tests to be organised. Secondly the knowledge and information provided helped to increase not just my understanding of what might be happening but also possible ways forward. It was also very helpful to me to take part in the focus group as this brought me into contact with other people who had been impacted in many different ways by cavernomas and also to hear about the plans for future studies'	Decided not to take part in the study
'[My contact with CAUK] was helpful in the fact that the team at [site] have said I do not have any cavernoma and that the lesions are likely to be amyloid deposits. I had all my original MRIs at [site]. The CARE study MRI was carried out in [site], I understand they are better MRIs. I wish I had known this at my original contact with [site], as I would have asked for my MRIs to have been carried out in [site]. This would have saved months/years of worry for myself and my family'	Asked to take part, but then found not eligible

age. We used non-sex-specific terminology when referring to people with brain cavernoma. Participant information leaflets were written in plain English with PCPI input, and translation was offered into Welsh, but not any other languages. We collected data on age, sex, disability and ethnicity for participants who were randomised, but not any other protected characteristics.

Ultimately, we included 4 children and 68 adults. Symptomatic brain cavernoma is a rare disease, and in clinical practice, it is relatively more frequent in adults, although incidence and prevalence studies have not been done on entire populations, including children.[4,47] We had hoped to include more children, but the extent to which the age distribution of participants is unrepresentative remains uncertain. The sex distribution in the RCT (41 females, 31 males) reflected the female preponderance seen in hospital- and population-based studies.[4,5,47] Epidemiological data about the ethnicity of people with brain cavernoma in the UK are not available, but participants' ethnicities were less diverse than in England (www.ons.gov.uk/peoplepopulationandcommunity/culturalidentity/ethnicity/bulletins/ethnicgroupenglandandwales/census2021), but similar to ethnicity in Scotland (www.scotlandscensus.gov.uk/census-results/at-a-glance/ethnicity/). The overall sample size was too small to disaggregate data to determine differences in findings by protected characteristics.

Ultimately, the generalisability of the evidence is uncertain for age, good for sex and uncertain for ethnicity. The generalisability of the evidence outside the UK remains to be determined. In future, we would implement recommendations from the INCLUDE ethnicity framework in the design, oversight and conduct of the research to maximise diversity and inclusiveness.

Impact and learning

The CARE pilot trial has already had an impact on patients and professionals in the clinical neuroscience

community, by showing that a wide-ranging collaboration can be formed across the UK and potentially Ireland, also including patient advocacy organisations and qualitative researchers. We obtained engagement from a large number and proportion of the neurosurgical sites in the UK, which engaged with the QRI, which was itself embedded in clinical consultations, where interventions about barriers and facilitators could be implemented.

In the longer term, the result of the CARE pilot RCT seems likely to reinforce reasons for uncertainty about symptomatic brain cavernoma management with intervention. In time, the RCT will be incorporated into updated clinical guidelines.[14–16] The pilot RCT justifies the conduct of a definitive RCT, informs its feasibility and provides suggestions for how multidisciplinary decision-making, conventions of usual care, willingness to offer intervention and the design of participant materials may increase the recruitment rate. The financial and logistical feasibility of a definitive RCT will be determined by clinical communities' reactions to the result, equipoise, willingness of sites to engage with a definitive RCT across the world, willingness of clinical researchers to apply for funding to support the RCT in their own country and funding agencies' decisions.

Implication for decision-makers

The CARE pilot RCT gave inconclusive results about the effects of medical management and intervention (using neurosurgical resection or stereotactic radiosurgery) compared with medical management alone for brain cavernoma.[40] However, the recruitment rate did confirm that there is uncertainty about the use of both types of intervention in the UK, and that stereotactic radiosurgery was twice as likely as neurosurgical resection to be selected as the type of intervention to use in a RCT, confirming ongoing equipoise in the clinical community about the use of stereotactic radiosurgery for symptomatic brain cavernoma, despite the existence of a clinical commissioning policy in NHS England.[29]

Research recommendations

The main priority for future research into symptomatic brain cavernoma is to conduct a definitive RCT comparing medical management and intervention (using neurosurgical resection or stereotactic radiosurgery) with medical management alone, to fully address the top priority for research into cavernoma.[17] This pilot RCT has shown that a RCT of intervention can be done for this indication, and it has provided metrics that help to inform the design and feasibility of a definitive RCT.

In the CARE pilot RCT, we found that the majority of patients, who were either eligible but not approached or who were approached but were not uncertain, were reported to prefer medical management alone. Patients' conversations reported by clinicians, QRI researchers and CAUK indicated that they would consider/prefer a non-invasive treatment. This confirms the need to address the fourth uncertainty identified by the James Lind Alliance Priority Setting Partnership for cavernoma, which was, 'Could drugs targeted at cavernomas improve outcome for people with brain or spine cavernomas compared to no drug treatment?'[17] Promising data exist for many drug treatments to prevent ICH from brain cavernomas,[48,49] including propranolol,[50] antithrombotic drugs[51] and statins.[52]

Given these ongoing uncertainties about intervention and drugs for brain cavernoma, the most efficient way to resolve these therapeutic uncertainties seems to be an umbrella platform study,[53] in which a definitive parallel-group RCT addressing intervention could be conducted using the same infrastructure as a multiarm, multiphase drug trial, such that a RCT would be available for all prevalent and incident patients with brain cavernoma other than people who had already undergone neurosurgical resection of a solitary symptomatic brain cavernoma.

Sample size required for a definitive randomised trial

We have used the feasibility outcomes and metrics from the CARE pilot RCT (see *Tables 2* and *3*) to estimate the sample sizes that might be required for a definitive RCT using the same primary clinical outcome as the pilot RCT. We assumed a recruitment duration of 5 years, an estimate of the recruitment rate (0.2 or 0.3 participants per site per month), a primary outcome event rate of 8% per year, annual withdrawal/dropout/death rate of 7% per year, a duration of follow-up of 10 years [as indicated in the NIHR HTA commissioning brief (*Report Supplementary Material 1* and *Report Supplementary Material 2*)], a probability of falsely rejecting a true null hypothesis of 0.05 (using a two-sided test) and a power of the statistical test of 0.9. We chose to estimate the sample size and number of sites required by a definitive RCT (*Table 8*) using two estimates of recruitment rate (as above) and two estimates of a beneficial effect of intervention in reducing the primary clinical outcome (0.60 and 0.75) that are within the 95% CI of the estimate of effect in the pilot RCT and are similar to associations between intervention and a reduction in the primary clinical outcome in non-randomised observational

TABLE 8 Estimates of the sample size and number of sites required by a definitive RCT with two different assumptions about each of effect size and recruitment rate

Total sample sizes and number of sites required for a definitive RCT with 1 : 1 assignment:					
		Estimated HR for medical management and intervention			
		0.60		0.75	
		Sample size	Sites	Sample size	Sites
Recruitment rate (per site per month)	0.2	590	56	1900	259
	0.3	590	36	1900	166

cohort studies.[23,26,54] Estimates assume that the maximum number of sites that open each month is 4, except for the HR of 0.75 and recruitment rate of 0.2 where this figure is taken to be 6 (as 4 would be insufficient).

Feasibility of a definitive randomised trial

The feasibility of a definitive main phase RCT is not only determined by the estimates above but also by the number of sites, countries and funding agencies that would be required to provide an adequate network to support recruitment over 5 years. The activation of 56–259 sites clearly mandates the involvement of additional countries, given that the UK and Ireland has 40 neurosurgical sites and only 28 (70%) of them took part in the CARE pilot trial. While we have good initial engagement and interest from professional networks (below), several additional countries may be needed for a definitive RCT. First, the number of neurosurgical sites in countries smaller than the UK will be lower. Second, the proportion of sites that can support RCTs in other countries may be lower than in the UK. Third, some large countries with good clinical research infrastructure (e.g. USA) have fee-for-service healthcare systems, which can complicate the conduct of pragmatic clinical trials of interventions already available in standard practice with levels of per-participant reimbursement that do not match the income generated for the care provider by the intervention under study. Fourth, the recruitment rate at international sites may not match the rate in a pilot phase in the lead country. Fifth, the letters of support we have received do not guarantee other countries' inclusion, because they will require funding. Sixth, the cost of a definitive RCT will be large given that this pilot study cost over £1 M and will be most likely to be met by joint, collaborative funding from different agencies committed to commissioning research on the topic (thereby avoiding the 'double jeopardy' of approaching funding agencies independently). All of these challenges are not unique to brain cavernoma, but they have been surmounted for some neurosurgical RCTs in the past:[55] in a review of 52 Cochrane reviews of neurosurgical interventions, seven focused on neurovascular surgery, among which UK-led, publicly funded international RCTs of ruptured intracranial aneurysm coiling versus clipping (ISAT) and surgical evacuation of acute intracerebral haemorrhage achieved sample sizes > 1000.

The feasibility of attaining the estimated recruitment rates will be determined by clinical communities' awareness of, and reaction to, the results of the pilot RCT. Clinicians will not be aware of the results until April 2024, after which equipoise in the community can be reassessed. However, in anticipation of re-evaluating equipoise to determine feasibility, at the time of the application for this pilot RCT we obtained letters of support for a definitive RCT from professionals and patients:

1. Professionals
    a. European Organisation for Research and Treatment of Cancer
    b. International Paediatric Stroke Organisation
    c. Radiation versus Observation following surgical resection of Atypical Meningioma: a randomised controlled trial (the ROAM trial)
    d. UK Society of British Neurological Surgeons
    e. European Association of Neurosurgical Societies (EANS) vascular section
    f. EANS research committee
    g. European Stroke Organisation
    h. Italy Treat_CCM collaboration[50]
    i. Canadian HEmorrhagic Stroke trIals initiatiVE
    j. Australian neurology network
    k. Australia neurosurgery network
    l. Brazil neurology network
    m. France neurology network
    n. Germany neurosurgery network
    o. Germany neurology network
    p. Italy radiosurgery network
    q. USA neurosurgery network

r. South Africa neurosurgery network
s. Spain radiosurgery network
t. Netherlands Collaboration Of New TReatments for Acute Stroke

2. Patients
   a. European Cavernoma Alliance
   b. Republic of Ireland
   c. Italy
   d. Sweden
   e. USA
   f. Spain
   g. France
   h. Germany
   i. UK

Conclusions

The CARE pilot RCT recruited successfully, provided insights into the barriers to informed consent and recruitment, tested interventions to address these barriers and generated a variety of estimates to inform the design of a definitive RCT. It seems that a definitive RCT would be feasible if the large number of international clinical and patient communities that expressed interest in a definitive RCT remain in equipoise after the dissemination of the CARE pilot RCT results, although extensive international involvement and shared support from multiple funding agencies will be needed.

Additional information

CRediT contribution statement

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Data-sharing statement

A de-identified individual participant data set will be prepared for sharing purposes. All requests for study data will need to be made in writing via e-mail to ECTUdatashare@ed.ac.uk. Access to the de-identified data may be granted following review by Chief Investigator and the Edinburgh Clinical Trials Unit Portfolio Management Committee.

Ethics statement

The Leeds East Research Ethics Committee (REC) approved the trial protocol (version 2.0, 22 March 2021) on 31 March 2021 (REC reference 21/YH/0046).

Information governance statement

The University of Edinburgh and NHS Lothian are committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, The University of Edinburgh and NHS Lothian are joint Data Controllers, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data

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Protection Officer here www.accord.scot/data-protection/our-privacy-notices.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/GJRS5321.

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Philip M White reports being immediate past Chair of the UK Neurointerventional Group.

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This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Trial registration

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Award publications

This synopsis reports on one component of the research award *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*. Other articles published as part of this thread are:

CARE pilot trial collaboration. Medical management and surgery versus medical management alone for symptomatic cerebral cavernous malformation (CARE): a feasibility study and randomised, open, pragmatic, pilot phase trial. *Lancet Neurol* 2024;**23**: 565–76. https://doi.org/10.1016/S1474-4422(24)00096-6

Wade J, Farrar N, Realpe AX, Donovan JL, Forsyth L, Harkness KA, *et al*. Addressing barriers and identifying facilitators to support informed consent and recruitment in the Cavernous malformations A Randomised Effectiveness (CARE) pilot phase trial: insights from the integrated QuinteT Recruitment Intervention (QRI). *EClinicalMedicine* 2024;**71**:102557. https://doi.org/10.1016/j.eclinm.2024.102557

For more information about this research please view the award page (www.fundingawards.nihr.ac.uk/award/NIHR128694).

Additional outputs

Loan JJM, Bacon A, van Beijnum J, Bhatt P, Bjornson A, Broomes N, *et al*. Feasibility of comparing medical management and surgery (with neurosurgery or stereotactic radiosurgery) with medical management alone in people with symptomatic brain cavernoma – protocol for the cavernomas: a randomised effectiveness (CARE) pilot trial. *BMJ Open* 2023;**13**:e075187. https://doi.org/10.1136/bmjopen-2023-075187

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List of supplementary material

Report Supplementary Material 1
NIHR Commissioning brief

Report Supplementary Material 2
NIHR Commissioning brief supplement

Report Supplementary Material 3
Trial Steering Committee charter

Report Supplementary Material 4
Data Monitoring Committee charter

Report Supplementary Material 5
Patient and public involvement and engagement Advisory Group terms of reference

Report Supplementary Material 6
Statistical analysis plan

Report Supplementary Material 7
Health economic analysis plan

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/GJRS5321).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

CARE	Cavernomas A Randomised Effectiveness
CAUK	Cavernoma Alliance UK
DNA	deoxyribonucleic acid
EANS	European Association of Neurosurgical Societies
FND	focal neurological deficit
ICH	intracranial haemorrhage
MRI	magnetic resonance imaging
NIHSS	National Institute of Health Stroke Scale
PAG	Patient, carer and public involvement and engagement Advisory Group
PCPI	Patient, Carer and Public Involvement
PI	principal investigator
QRI	QuinteT Recruitment Intervention
QuinteT	Qualitative research integrated within Trials
RCT	randomised controlled trial

REC	Research Ethics Committee
SAE	serious adverse event
SOP	standard operating procedure
TMG	Trial Management Group
TSC	Trial Steering Committee

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