Medical management and surgery versus medical management alone for symptomatic cerebral cavernous malformation (CARE): a feasibility study and randomised, open, pragmatic, pilot phase trial

*CARE pilot trial collaboration**

Summary

Background The highest priority uncertainty for people with symptomatic cerebral cavernous malformation is whether to have medical management and surgery or medical management alone. We conducted a pilot phase randomised controlled trial to assess the feasibility of addressing this uncertainty in a definitive trial.

Methods The CARE pilot trial was a prospective, randomised, open-label, assessor-blinded, parallel-group trial at neuroscience centres in the UK and Ireland. We aimed to recruit 60 people of any age, sex, and ethnicity who had mental capacity, were resident in the UK or Ireland, and had a symptomatic cerebral cavernous malformation. Computerised, web-based randomisation assigned participants (1:1) to medical management and surgery (neurosurgical resection or stereotactic radiosurgery) or medical management alone, stratified by the neurosurgeon's and participant's consensus about the intended type of surgery before randomisation. Assignment was open to investigators, participants, and carers, but not clinical outcome event adjudicators. Feasibility outcomes included site engagement, recruitment, choice of surgical management, retention, adherence, data quality, clinical outcome event rate, and protocol implementation. The primary clinical outcome was symptomatic intracranial haemorrhage or new persistent or progressive non-haemorrhagic focal neurological deficit due to cerebral cavernous malformation or surgery during at least 6 months of follow-up. We analysed data from all randomly assigned participants according to assigned management. This trial is registered with ISRCTN (ISRCTN41647111) and has been completed.

Findings Between Sept 27, 2021, and April 28, 2023, 28 (70%) of 40 sites took part, at which investigators screened 511 patients, of whom 322 (63%) were eligible, 202 were approached for recruitment, and 96 had collective uncertainty with their neurosurgeon about whether to have surgery for a symptomatic cerebral cavernous malformation. 72 (22%) of 322 eligible patients were randomly assigned (mean recruitment rate 0·2 [SD 0·25] participants per site per month) at a median of 287 (IQR 67–591) days since the most recent symptomatic presentation. Participants' median age was 50·6 (IQR 38·6–59·2) years, 68 (94%) of 72 participants were adults, 41 (57%) were female, 66 (92%) were White, 56 (78%) had a previous intracranial haemorrhage, and 28 (39%) had a previous epileptic seizure. The intended type of surgery before randomisation was neurosurgical resection for 19 (26%) of 72, stereotactic radiosurgery for 44 (61%), and no preference for nine (13%). Baseline clinical and imaging data were complete for all participants. 36 participants were randomly assigned to medical management and surgery (12 to neurosurgical resection and 24 to stereotactic radiosurgery) and 36 to medical management alone. Three (4%) of 72 participants withdrew, one was lost to follow-up, and one declined face-to-face follow-up, leaving 67 (93%) retained at 6-months' clinical follow-up. 61 (91%) of 67 participants with follow-up adhered to the assigned management strategy. The primary clinical outcome occurred in two (6%) of 33 participants randomly assigned to medical management and surgery (8·0%, 95% CI 2·0–32·1 per year) and in two (6%) of 34 participants randomly assigned to medical management alone (7·5%, 1·9–30·1 per year). Investigators reported no deaths, no serious adverse events, one protocol violation, and 61 protocol deviations.

Interpretation This pilot phase trial exceeded its recruitment target, but a definitive trial will require extensive international engagement.

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*Members of the CARE pilot trial collaboration are listed at the end of the paper

Correspondence to:
Prof Rustam Al-Shahi Salman, Centre for Clinical Brain Sciences, The University of Edinburgh, Edinburgh EH16 4SB, UK
rustam.al-shahi@ed.ac.uk

Introduction

Cerebral cavernous malformations are present without symptoms in 0·16% of the population.[1] The incidence of symptomatic cerebral cavernous malformation is at least 0·24 per 100 000 people per year,[2] meaning approximately 160 people are newly diagnosed in the UK annually. After diagnosis following epileptic seizure[3] or stroke (due to intracranial haemorrhage or a focal neurological deficit that did not appear to be due to haemorrhage),[4] the 5-year risk of symptomatic intracranial haemorrhage ranges

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Research in context

Evidence before this study

On Nov 24, 2023, we searched for randomised controlled trials of management approaches for cerebral cavernous malformation in the Cochrane Central Register of Controlled Trials (from database inception), MEDLINE Ovid (from 1946), Embase Ovid (from 1974), online registers of clinical trials, and bibliographies of relevant publications using search terms detailed in the appendix (pp 5–6). We found randomised trials of pharmacological treatments that were completed (NCT01764451 and NCT03589014) or ongoing (NCT02603328, NCT05085561, and ChiCTR2100043189), but none involving surgery. Observational cohort studies of people with cerebral cavernous malformation comparing the outcome after medical management and surgery (using neurosurgical resection or stereotactic radiosurgery) with outcome after medical management alone in concurrent controls have not identified substantial effects of surgery that would preclude the need for a randomised trial. Meta-analyses of cohort studies after neurosurgical resection or stereotactic radiosurgery for cerebral cavernous malformation have found similar outcomes, yet stereotactic radiosurgery remains controversial because some neurosurgeons are strongly opposed to the intervention. Guidelines have been unable to make strong recommendations about surgery for cerebral cavernous malformation.

Added value of this study

To our knowledge, this study is the first randomised controlled trial comparing medical management and surgery with medical management alone for people with symptomatic cerebral cavernous malformation. This pilot study integrated a QuinteT Recruitment Intervention and quantified several estimates of recruitment, retention, surgical preference (stereotactic radiosurgery was chosen twice as often as neurosurgical resection), adherence, outcome event rates, intervention effects, and trial conduct to assess the feasibility of a definitive randomised controlled trial.

Implications of all the available evidence

This pilot phase randomised trial in the UK and Ireland met its targets for participation by neuroscience centres, investigators, and people with symptomatic cerebral cavernous malformation. Although the generalisability of the findings outside the UK and Ireland 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 cerebral cavernous malformation, the recruitment of a fifth of eligible patients who were approached to take part, and the frequency of outcome events.

from approximately 3·8% for people with cerebral cavernous malformation who have presented without a stroke to approximately 30·8% for people with a brainstem cavernous malformation who have presented with stroke.[5] People with cerebral cavernous malformation who present with an epileptic seizure almost inevitably develop epilepsy within 1 year, and only half of the people with cerebral cavernous malformation-related epilepsy achieve 2-year seizure-freedom.[6]

In standard care, medical management includes drugs for epilepsy, pain, and spasticity, as well as therapies such as physiotherapy, occupational therapy, speech and language therapy, and psychology.[7,8] Neurosurgical resection is used for long-term prevention of intracranial haemorrhage or epileptic seizures,[9] whereas stereotactic radiosurgery can be used if neurosurgical access is impossible, hazardous, or patients prefer non-invasive management.[10] Surgery with either technique carries the risk of complications that can be fatal or disabling,[9–13] similar to the risks of medical management alone,[5] although long-term outcomes are uncertain. There are no randomised controlled trials comparing surgery with medical management alone and only a few cohort studies with concurrent comparisons of outcomes after surgery with medical management alone,[14–23] none of which showed substantial effects of surgery.[24] Consequently, guidelines have been unable to make strong recommendations about surgery for clinical practice,[7,8,25] and a James Lind Alliance Priority Setting Partnership found that the top research priority for people with cavernous malformation was, "Does treatment (with neurosurgery or stereotactic radiosurgery) or no treatment improve outcome for people diagnosed with brain or spine cavernoma?"[26]

Although a randomised trial to test the superiority of medical management and surgery (using neurosurgical resection or stereotactic radiosurgery) over medical management alone for symptomatic cerebral cavernous malformation is justified, several challenges exist. The condition is rare.[2,27] Most patients recover well after intracranial haemorrhage[28] and epilepsy is usually not intractable.[6] Neurosurgical resection and stereotactic radiosurgery are already available in standard practice.[7,8] Equipoise poses intellectual and emotional challenges for doctors that are barriers to recruitment to randomised trials,[29] especially those comparing surgery with non-surgical management.[30] These challenges were encountered in previous pragmatic randomised trials comparing invasive treatments with medical management for other intracranial vascular malformations.[31,32] Therefore, we aimed to determine the feasibility of conducting a definitive randomised trial comparing medical management and surgery with medical management alone for symptomatic cerebral cavernous malformation.

Methods

Study design

The Cavernomas malformations A Randomised Effectiveness (CARE) study was a feasibility study

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including an embedded QuinteT Recruitment Intervention[33] within a randomised, open, parallel group, pragmatic pilot phase trial comparing medical management and surgery (with neurosurgical resection or stereotactic radiosurgery) with medical management alone for symptomatic cerebral cavernous malformation. The Leeds East Research Ethics Committee approved the trial protocol (version 2.0, March 22, 2021). The trial co-sponsors were the University of Edinburgh and the NHS Lothian Health Board. A patient, carer, and public involvement advisory group co-designed the study materials and reviewed progress. The trial steering committee and sponsor approved the trial protocol (version 2.0, March 22, 2021) before the close of recruitment,[34] and the statistical analysis plan (final version 1.0, Dec 8, 2022) and health economics analysis plan (final version 2.0, Nov 10, 2023) before data lock and analysis. Patients, or the parent of a child (ie, those younger than 16 years in the UK and those younger than 18 years in Ireland) if required by locally applicable laws, provided written or electronic informed consent before randomisation.

The primary objective was to assess the feasibility of performing a definitive randomised trial. The secondary objectives were to set up a collaboration at neuroscience centres throughout the UK and Ireland, conduct a QuinteT Recruitment Intervention[33] to address barriers and identify facilitators to recruitment (which is reported elsewhere),[35] and recruit approximately 60 participants to the pilot trial over 18 months. The trial is registered (ISRCTN41647111) and is complete.

Participants

We recruited people of any age (children or adults with mental capacity), with at least one cerebral cavernous malformation that had never been completely resected or obliterated by surgery and had caused epileptic seizures or stroke (due to intracranial haemorrhage or a focal neurological deficit that did not appear to be due to haemorrhage) at any time, and had not been randomised in the CARE pilot trial previously. Investigators were doctors and research nurses who identified eligible patients in standard clinical practice (ie, inpatients, outpatients, and via multidisciplinary team meeting records), approached them by email, video consultation, or in person, and recruited participants at neuroscience centres throughout the UK and Ireland. Patient support organisations (Cavernoma Alliance UK and Cavernoma Ireland) shared information about the trial through their websites, social media platforms, and other communication channels, and supported patients to identify active sites in the trial and make decisions about participation.

Randomisation and masking

Because of preferences for type of surgery according to the anatomical location of the cerebral cavernous malformation, concerns about exposing children to radiation, and scepticism about the effects of stereotactic radiosurgery, we stratified randomisation by intended type of surgery. Before randomisation, investigators prespecified the consensus between the patient and their neurosurgeon about the intended type of surgery if the patient was randomly assigned to medical management and surgery (neurosurgical resection, stereotactic radiosurgery, or no preference); if there was no preference, a computer algorithm randomly assigned neurosurgical resection or stereotactic radiosurgery as the intended type of surgery. After obtaining a participant's written informed consent, investigators supplied complete information about participants' demographics, socioeconomic status, medical history, comorbidities, treatment, imaging, and questionnaire data (ie, 5-level EuroQol-5D questionnaire or 5-level EuroQol-5D youth questionnaire; modified Rankin Scale score; National Institutes of Health Stroke Scale (NIHSS) score; Karnofsky Performance Status or Lansky Play-Performance scale; and Liverpool Seizure Severity scale if they had experienced an epileptic seizure within the preceding 4 weeks) via a secure web interface with in-built validation. A central, web-based, computerised randomisation system with permuted block sizes of two or four incorporating a stratification algorithm by the intended type of surgery randomly assigned participants (1:1) to either medical management and surgery or medical management alone. The web interface displayed each participant's unique study identification number and their assignment, which was also sent in an email to all investigators at the hospital site, having been concealed until that point. If the participant was assigned to medical management and surgery, the protocol requested, but did not mandate, that investigators should arrange surgery within 3 months.

Assignment was known to investigators, participants, and carers, because of the practical and ethical problems of sham procedures. The clinical outcome event adjudicators were masked to participant identity, treatment assignment, and conduct of surgery by redaction of this information from source documents.

Procedures

Investigators kept electronic logs of the characteristics of people who were screened for the trial, their eligibility, whether they were approached for inclusion, whether the patient and their doctor were uncertain about surgery, whether consent was provided, and whether they were randomly assigned. After randomisation, investigators sent brain imaging scans done previously that confirmed the mode of presentation and cerebral cavernous malformation diagnosis, or any imaging relating to clinical outcome events in Digital Imaging and Communications in Medicine format, to the Systematic Management, Archiving & Reviewing of Trial Images Service[36] so that an experienced consultant neuroradiologist (PMW) could confirm the certainty of cerebral

For more on **Cavernoma Alliance UK** see https://cavernoma.org.uk/

For more on **Cavernoma Ireland** see https://www.facebook.com/CavernomaIrelandSupport/

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cavernous malformation diagnosis and support the adjudication of outcome events blinded to treatment assignment.

Medical management constituted standard medical care according to UK guidelines,[8] which could include anti-seizure drugs,[3] methods of rehabilitation of neurological deficits (eg, physiotherapy and speech and language therapy), medical treatment of other neurological symptoms (eg, headache, body pain, spasticity, and dysaesthesia), and psychological support (eg, cognitive behavioural therapy, counselling, or guided self-help). Surgery included neurosurgical resection or gamma knife stereotactic radiosurgery in addition to medical management, accessed and delivered according to what is available in standard clinical practice. The technique used for neurosurgical resection was that used by the neurosurgeon in their standard clinical practice, using adjuncts at their discretion such as image direction, microscopy, ultrasonic aspiration, awake or general anaesthesia surgery, cortical mapping or stimulation, and intraoperative MRI. Stereotactic radiosurgery was performed at the National Centre for Stereotactic Radiosurgery in Sheffield or the Queen Square Radiosurgery Centre in London, which are the two referral centres in the UK that are commissioned to provide gamma knife stereotactic radiosurgery for cerebral cavernous malformation.[37] We encouraged investigators to obtain confirmation from one of these referral centres that stereotactic radiosurgery could be performed, before a patient was randomly assigned in the trial. The two referral centres used standard clinical treatment protocols to target the cerebral cavernous malformation, but not the surrounding haemosiderin ring, using a radiation dose of 12–16 Gy depending on the size, shape, definition, and site of the cerebral cavernous malformation. Investigators were sent an email prompt 3 months after randomisation to report whether surgery was performed, regardless of randomised assignment.

See Online for appendix

Investigators were asked to assess participants face-to-face 6 months after being randomly assigned, to assess clinical outcomes, complete questionnaires (using the same scales measured before randomisation), record conduct and details of surgery, perform brain MRI scans, record health service use, and record other social and economic outcomes. This information was collected every 6 months thereafter via post or telephone by research staff at the Trial Coordinating Centre until the end of the funded period of follow-up (Oct 31, 2023). Investigators were asked to record and report only clinical outcomes and relevant serious adverse events related to medical management and surgery that occurred between randomisation and each participant's final 6-month follow-up.

Participants were free to completely withdraw, or discontinue any individual component of the trial, at any point; we retained data collected until the time of withdrawal. Investigators reported protocol deviations and violations to the sponsor.

Outcomes

We collected several outcomes to inform an assessment of the feasibility of a definitive randomised trial. These included: site participation and recruitment; investigators' correct implementation of trial procedures; proportion of screened patients who were eligible; proportions of eligible patients who were approached and were randomly assigned; distribution of participants between neurosurgical resection and stereotactic radiosurgery; adherence to the assigned management and retention; completeness of baseline, imaging, and outcome data; clinical outcome event rates; generalisability of baseline characteristics, outcome event rates, and differences between treatment groups; estimates of effect size and variability to design a definitive randomised trial; the sample size needed for a trial to address the overall question over a 10-year follow-up; and whether the trial data can develop a robust economic model to evaluate cost-effectiveness in a definitive randomised trial.

The primary clinical outcome was symptomatic intracranial haemorrhage or new persistent or progressive focal neurological deficit due to cerebral cavernous malformation or surgery, whether fatal (leading to death within 30 days of the outcome event) or non-fatal.[4] The secondary clinical outcomes were: death not due to a primary clinical outcome; modified Rankin Scale score; NIHSS score; 5-level EuroQol-5D questionnaire in adults and EuroQol-5D youth questionnaire in children; Karnofsky Performance Status scale in adults and Lanksy Play-Performance Scale in children; Liverpool Seizure Severity Scale and frequency of previous epileptic seizures; and data to estimate health service use and health-care and socioeconomic costs during follow-up.

Statistical analysis

We estimated that approximately 240 people with symptomatic cerebral cavernous malformations would be newly diagnosed during 18 months of recruitment at 40 neuroscience centres in the UK and Ireland (eight sites activated per month over 5 months),[2] 10% would be missed, 10% would decline to participate, and 31% of the eligible patients would be randomised,[38] such that at least 60 patients would be randomised in the CARE pilot trial, for a recruitment rate of 0·114 participants per site per month. There is no estimate of the minimal clinically important difference in our primary clinical outcome.

Throughout the recruitment period, the unmasked trial statistician supplied the independent data monitoring committee with analyses of the accumulating baseline and follow-up data in strict confidence at least once every year, so that they could assess trial conduct, safety, and efficacy, and make recommendations about stopping, modifying, or continuing the trial to the steering committee. There was no formal fixed schedule of interim analyses and no prespecified stopping rule.

Two statisticians (JS and SCL) and the chief investigator (RA-SS) prepared a prespecified statistical analysis plan

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without reference to data by randomised allocation; the trial steering committee approved the statistical analysis plan before database lock. Health economists (ARN, PH, AS, and AB) prepared a prespecified health economic analysis plan without reference to data by randomised allocation.

The analysis dataset included all screened, eligible, approached, consented, and randomised participants. In this feasibility study, analyses were descriptive only (frequencies, proportions with 95% CI to reflect their precision, and mean or median as measures of central tendency, as appropriate). Outcome event rates were quantified using the number and proportion of participants with an event, the number of events, and the average event rate per participant per year. There were no formal statistical significance tests.

The primary analysis (performed by JS) used the intention-to-treat population. Statistical analyses were performed using SAS (version 9.4 or later).

Role of the funding source

The funder of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From April 1, 2021, onwards, we approached 40 neurosurgical sites in the UK and Ireland, of which 30 (75%) were given research ethics committee approval, although the research ethics committee at one site rejected the study because stereotactic radiosurgery could not be provided for research (appendix pp 7–8). 28 (70%) sites obtained all regulatory approvals to be activated over a median of 276 (IQR 219–543) days per site between Aug 30, 2021, and April 26, 2023 (appendix p 9). The impact of the COVID-19 pandemic on capacity in research governance, clinical, and research teams in the UK and Ireland accounted for most of the sites that were not activated (appendix pp 7–8); these processes took much longer than anticipated when planning the study before the pandemic, so a 5-month extension of recruitment was granted by the funder to permit attainment of the recruitment target (appendix pp 10–13).

Between Sept 27, 2021, and April 28, 2023, investigators screened 511 people, of whom 322 (63%) were eligible (figure 1). Investigators approached 202 (63%) of 322 eligible adults or parents or guardians of an eligible child, but did not approach 120 people mostly because the doctor or patient were reportedly certain about whether or not to go ahead with surgery. 96 (48%) of 202 people approached had collective uncertainty with a neurosurgeon about whether to have surgery, but for the

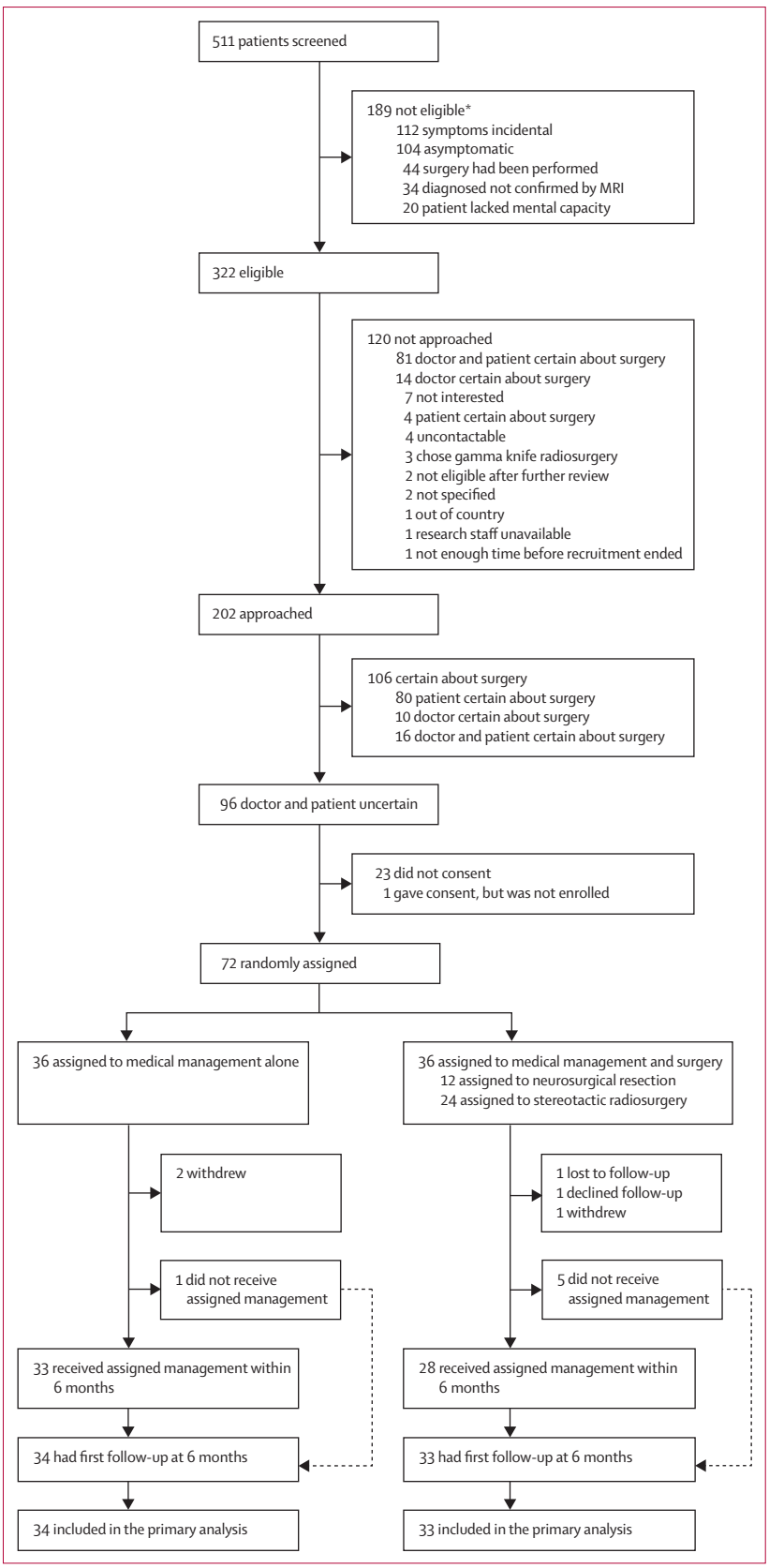

Figure 1: **Trial profile**
*Some patients had more than one reason for being ineligible.

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	Medical management and surgery (n=36)	Medical management alone (n=36)
Age of adults at randomisation, years (n=68)	51·0 (43·0–58·7)	52·4 (37·3–62·0)
Age of children at randomisation, years (n=4)	10·2 (10·2–10·2)	7·1 (3·2–8·6)
Sex		
Female	21 (58%)	20 (56%)
Male	15 (42%)	16 (44%)
Ethnicity		
White	31 (86%)	35 (97%)
Black	0	0
Asian	1 (3%)	0
Mixed	1 (3%)	0
Other	3 (8%)	1 (3%)
History of symptomatic intracranial haemorrhage from cerebral cavernous malformation		
None	8 (22%)	8 (22%)
One	22 (61%)	21 (58%)
More than one	6 (17%)	7 (19%)
History of non-haemorrhagic focal neurological deficit from cerebral cavernous malformation		
None	26 (72%)	19 (53%)
One	7 (19%)	7 (19%)
More than one	3 (8%)	10 (28%)
History of epileptic seizures related to cerebral cavernous malformation		
None	22 (61%)	22 (61%)
Solitary seizure	3 (8%)	1 (3%)
Epilepsy, seizure-free ≥1year	3 (8%)	4 (11%)
Epilepsy, not seizure-free ≥1year	8 (22%)	9 (25%)
Number of major comorbidities		
None	19 (53%)	20 (56%)
One	11 (31%)	6 (17%)
Two or more	6 (17%)	10 (28%)
Family history of cerebral cavernous malformation	1 (3%)	4 (11%)
Number of cerebral cavernous malformations		
Single	30 (83%)	27 (75%)
Multiple	6 (17%)	9 (25%)
Side of symptomatic cerebral cavernous malformation		
Left	13 (36%)	14 (39%)
Right	18 (50%)	15 (42%)
Midline	5 (14%)	7 (19%)
Location of symptomatic cerebral cavernous malformation		
Supratentorial lobar	15 (42%)	18 (50%)
Supratentorial deep grey matter	8 (22%)	5 (14%)
Brainstem	9 (25%)	9 (25%)
Cerebellum	4 (11%)	4 (11%)
Depth of symptomatic cerebral cavernous malformation		
Superficial cortical	7 (19%)	12 (33%)
Superficial subcortical	12 (33%)	8 (22%)
Deep	17 (47%)	16 (44%)

Data are n (%) or median (IQR).

Table 1: **Baseline characteristics reported by investigators**

	Medical management and surgery (n=36)	Medical management alone (n=36)
Treatment before enrolment		
Previous craniospinal irradiation	0	0
Previous surgical treatment of the symptomatic cerebral cavernous malformation		
None	35 (97%)	34 (94%)
Neurosurgical resection	0	2 (6%)
Stereotactic radiosurgery	0	0
Both	1 (3%)	0
Antiseizure medication	12 (33%)	15 (42%)
Antiplatelet agent	1 (3%)	0
Oral anticoagulant	0	0
Oral analgesia	4 (11%)	4 (11%)
Oral muscle relaxant	1 (3%)	1 (3%)
Propranolol	2 (6%)	1 (3%)
Statin	1 (3%)	4 (11%)
Vitamin D	2 (6%)	3 (8%)
Combined oral contraceptive or hormone replacement therapy	2 (6%)	1 (3%)
Physiotherapy	3 (8%)	6 (17%)
Speech and language therapy	0	2 (6%)
Psychology	1 (3%)	1 (3%)
Occupational therapy	2 (6%)	4 (11%)
Prespecified consensus about intended type of surgery, if randomly assigned to medical management and surgery		
Neurosurgical resection	11 (31%)	8 (22%)
Stereotactic radiosurgery	22 (61%)	22 (61%)
No preference	3 (8%)	6 (17%)
Distribution of participants by stratified randomisation, according to prespecified consensus about intended type of surgery		
Neurosurgical resection	12 (33%)	12 (33%)
Stereotactic radiosurgery	24 (67%)	24 (67%)

Data are n (%) or median (IQR).

Table 2: **Interventions before and after enrolment**

majority without collective uncertainty the patient was reported to be certain about whether to have surgery. 23 eligible patients who were approached and had collective uncertainty with a neurosurgeon did not consent (seven did not respond, five remained undecided, and 11 had one of a variety of other reasons), leaving 69 eligible adults and four eligible children (n=73, 76%) who gave consent to join the trial, either in person (n=57, 78%), electronically (n=9, 12%), or remotely (n=7, 10%). One patient gave consent, but investigators at the National Centre for Stereotactic Radiosurgery could not identify a cerebral cavernous malformation that could be treated with stereotactic radiosurgery so this person was not enrolled. 72 (22%) of 322 eligible patients were randomly assigned at 22 (79%) of 28 active sites over 368 site-months of recruitment (appendix p 14), for an overall mean recruitment rate of 0·2 (SD 0·25) participants per site per month. The characteristics of

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participants who were randomly assigned were similar to people who were eligible but not randomly assigned (appendix p 15).

68 adults and four children (median age 50·6 years [IQR 38·6–59·2]) were enrolled, of whom 41 (57%) were female, 66 (92%) were White, and 56 (78%) had previous symptomatic intracranial haemorrhage, 27 (38%) had previous symptomatic persistent or progressive non-haemorrhagic focal neurological deficit, and 28 (39%) had previous epileptic seizures related to a cerebral cavernous malformation (table 1). 57 (79%) participants had a solitary cerebral cavernous malformation, and the symptomatic cerebral cavernous malformation was most often in a supratentorial lobar brain region (n=33, 46%) and deep below the pial surface of the brain region (n=33, 46%; table 1). An independent review of diagnostic brain imaging confirmed definite certainty of cerebral cavernous malformation diagnosis in 70 (97%) participants and probable certainty in two (3%) participants. Randomisation occurred at a median of 287 (IQR 67–591) days since most recent symptomatic presentation and was stratified by prespecified consensus about intended type of surgery (table 2). 36 participants were randomly assigned to medical management and surgery and 36 to medical management alone (figure 1). Participants in the stratum randomly assigned to medical management and neurosurgical resection versus medical management alone (n=24), when compared with those in the stratum randomly assigned to medical management and stereotactic radiosurgery versus medical management alone (n=48), was less likely to have previous intracranial haemorrhage (15 [63%] of 24 *vs* 41 [85%] of 48), more likely to have previous epileptic seizures (16 [67%] *vs* 12 [25%]), more likely to have a symptomatic cerebral cavernous malformation in a lobar region (20 [83%] *vs* 13 [27%]), and less likely to have a symptomatic cerebral cavernous malformation deep below the pial surface (two [8%] *vs* 31 [65%]; appendix pp 16–19).

After randomisation, three (4%) of 72 participants withdrew completely (one because of cognitive decline, another because they were assigned to medical management alone but chose to have surgery, and the other did not give a reason), one was lost to follow-up, and one declined face-to-face follow-up, leaving 67 (93%) retained at 6-month clinical follow-up. Small proportions of participants declined other trial procedures (appendix p 20). 61 (91%) of 67 participants with follow-up adhered to the assigned management strategy: 28 (85%) of 33 assigned to medical management and surgery and 33 (97%) of 34 assigned to medical management alone (appendix p 21). 29 participants had surgery at a median of 119 (72–193) days after being randomly assigned and all of them received the prespecified type of surgery; nine had neurosurgical resection and 20 had stereotactic radiosurgery (appendix pp 22–23), and none had novel approaches such as thermal or laser ablation therapy. Co-interventions before randomisation and during follow-up were similar in both groups (table 2; appendix p 24).

During all available follow-up, four (6%) of 67 participants had a primary clinical outcome attributable to a cerebral cavernous malformation or surgery due to a new intracranial haemorrhage (two [6%] of 34 after assignment to medical management alone; overall event rate was 3·8%, 95% CI 1·0–15·1 per year) or progressive or persistent non-haemorrhagic focal neurological deficit

	Medical management and surgery	Medical management alone
Primary clinical outcome		
Intracranial haemorrhage or new persistent or progressive focal neurological deficit due to cerebral cavernous malformation or surgery	2/33	2/34
Secondary clinical outcomes		
Death not due to a primary clinical outcome	0/33	0/34
National Institutes of Health Stroke Scale score (face-to-face assessments only)		
Baseline (n=50)	0 (0–1)	1 (0–2)
6-month follow-up (n=58)	0 (0–1)	1 (0–3)
Modified Rankin Scale score		
Baseline (n=72)	1 (0–1)	1 (1–2)
6-month follow-up (n=67)	1 (0–1)	1 (0–1)
12-month follow-up (n=33)	1 (0–2)	2 (1–2)
18-month follow-up (n=8)	1 (0–1)	1 (1–1)
Karnofsky performance scale (adults)		
Baseline (n=68)	90 (80–100)	90 (80–90)
6-month follow-up (n=63)	90 (80–100)	90 (80–90)
12-month follow-up (n=33)	80 (80–100)	80 (70–90)
18-month follow-up (n=6)	100 (90–100)	90 (60–100)
Lansky play performance scale (children)		
Baseline (n=4)	60 (60–60)	90 (70–100)
6-month follow-up (n=4)	50 (50–50)	100 (80–100)
12-month follow-up (n=3)	80 (80–80)	95 (90–100)
18-month follow-up (n=2)	..	95 (90–100)
5-level EuroQol-5D questionnaire (adults)		
Baseline (n=67)	0·8 (0·7–0·9)	0·8 (0·6–1·0)
6-month follow-up (n=62)	0·9 (0·7–1·0)	0·8 (0·5–0·9)
12-month follow-up (n=29)	0·8 (0·6–1·0)	0·6 (0·2–0·9)
18-month follow-up (n=6)	1·0 (1·0–1·0)	0·8 (0·5–0·8)
5-level EuroQol-5D youth questionnaire (children)		
Baseline (n=4)	0·5 (0·5–0·5)	0·9 (0·7–1·0)
6-month follow-up (n=4)	0·3 (0·3–0·3)	1·0 (0·5–1·0)
12-month follow-up (n=2)	..	0·8 (0·6–0·9)
18-month follow-up (n=2)	..	0·8 (0·6–0·9)
Liverpool seizure severity scale (participants with previous epileptic seizures only)		
Baseline (n=28)	0 (0–0)	0 (0–35)
6-month follow-up (n=27)	0 (0-0)	0 (0–45)
12-month follow-up (n=13)	0 (0–0)	0 (0–50)
18-month follow-up (n=3)	0 (0–0)	48
Serious adverse events	0/33	0/34

Data are n/N or median (IQR).

Table 3: **Clinical scales at baseline and clinical outcomes and serious adverse events during follow-up**

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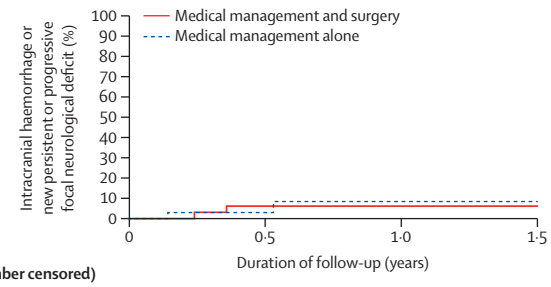

Patients at risk (number censored)				
Medical management and surgery	33 (0)	24 (7)	8 (23)	1 (30)
Medical management alone	34 (0)	27 (6)	8 (24)	1 (31)
Patients at risk (cumulative number of events)				
Medical management and surgery	33 (0)	24 (2)	8 (2)	1 (2)
Medical management alone	34 (0)	27 (1)	8 (2)	1 (2)

Figure 2: **Kaplan–Meier plot of the first occurrence of symptomatic intracranial haemorrhage or new persistent or progressive non-haemorrhagic focal neurological deficit due to cerebral cavernous malformation or surgery after randomisation**

Numbers at risk refer to survivors under follow-up at the start of each year according to assigned treatment. Number censored indicates the cumulative number censored due to withdrawal, end of follow-up, or death not due to a primary clinical outcome according to assigned treatment. Cumulative number of events indicates the participants in follow-up with a first primary clinical outcome according to assigned management.

(two [6%] of 33 after assignment to medical management and surgery; 3·8%, 1·0–15·1 per year) for an overall primary clinical outcome event rate of 7·8% (95% CI 2·9–20·7) per year. No participant died (table 3). The primary clinical outcome occurred in two (6%) of 33 participants randomly assigned to medical management and surgery (8·0%, 95% CI 2·0–32·1 per year) and in two (6%) of 34 participants randomly assigned to medical management alone (7·5%, 1·9–30·1 per year; figure 2). The distributions of primary clinical outcomes by the randomisation stratification variable of prespecified consensus for intended type of surgery are provided in the appendix (p 25); in the neurosurgical resection stratum, two outcomes occurred after medical management and neurosurgical resection but none occurred after medical management, whereas in the stereotactic radiosurgery stratum, two outcomes occurred after medical management but none after medical management and stereotactic radiosurgery. Investigators did not report any serious adverse events (table 3). Functional outcomes are reported in table 3 and the appendix (p 26). Follow-up brain imaging at 6 months was received for 69 (96%) of 72 participants, which revealed persistence of the symptomatic cerebral cavernous malformation in three (27%) of 11 participants assigned to medical management and neurosurgical resection, 23 (100%) of 23 participants assigned to medical management and stereotactic radiosurgery, and 35 (100%) of 35 participants assigned to medical management alone (appendix p 27).

Investigators reported one protocol violation (QuinteT Recruitment Intervention consent form not completed) and 61 protocol deviations (DNA sample not provided [n=11]; consent form errors [n=10]; delegation log errors [n=10]; baseline NIHSS score not 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]; appendix p 28).

The data about care pathways and outcomes that were collected by investigators, participants, parents, carers, and trial coordinating centre staff (appendix pp 29–32) were sufficient to estimate resource use and costs per participant (appendix pp 33–44), and could be used to update a published Markov model (appendix pp 45–50).[39] To estimate the sample size that might be required for a definitive randomised trial using the same primary clinical outcome as this pilot randomised trial, we assumed a recruitment duration of 5 years, two estimates 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, drop-out, and death rate of 7% per year, a duration of follow-up of 10 years, two-sided p=0·05, and 90% power. We used two estimates of a beneficial effect of surgery in reducing the primary clinical outcome (hazard ratios of 0·60 and 0·75), that are similar to associations between surgery and a reduction in the primary clinical outcome in non-randomised observational cohort studies.[16,17,23] These parameters suggested that a definitive randomised trial might require 590 participants (recruited at 36–56 sites) or 1900 participants (recruited at 166–259 sites). Feasibility outcomes and metrics are summarised in the panel.

Discussion

The findings of the CARE pilot trial showed that a randomised trial of surgery for symptomatic cerebral cavernous malformation could be done. A fifth of potentially eligible patients who were approached took part, such that the trial exceeded its recruitment target. The trial achieved good retention and adherence and provided estimates of preference for the type of surgery 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 there was no evidence of the inferiority of either management strategy.

The trial exceeded its target recruitment after a 5-month extension (to compensate for the impact of the COVID-19 pandemic on site activations and their capacity to recruit) with a mean recruitment rate of 0·2 (SD 0·25) participants per site per month, which aligned with our original projections. We anticipated that recruitment would also be challenging because symptomatic cerebral cavernous malformation is a rare disease[2,27] and small proportions of eligible people with other intracranial vascular malformations have participated in randomised trials comparing medical management to invasive treatments before.[32,38] Therefore, we worked in close partnership with patient support organisations to maximise patients' awareness and understanding of the trial and to support them with their decisions to

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Panel: **Feasibility outcomes and metrics**

What proportion of the collaborating sites take part and recruit participants to the CARE pilot trial?
30 (75%) of 40 sites obtained research ethics committee approval, 28 (70%) sites were activated, and 22 (55%) sites recruited one or more participants

Do investigators implement trial procedures correctly?
Definite diagnosis of cerebral cavernous malformation was confirmed for 70 (97%) of 72 participants; there were 61 protocol deviations and one protocol violation

What proportion of screened patients is eligible?
322 (63%) of 511 screened participants

What proportions of eligible patients are approached and randomly assigned (and why are eligible patients not approached or not randomly assigned)?
202 (63%) of 322 eligible patients were approached and 72 (22%) were randomly assigned; certainty about whether to have surgery was the main reason that patients were not approached or not randomised

What is the distribution of participants between neurosurgical resection and stereotactic radiosurgery?
Intended type of surgery that was prespecified before randomly assigning the 72 participants: neurosurgical resection 19 (26%) of 72 participants, stereotactic radiosurgery 44 (61%), and no preference nine (13%)

Do participants adhere to the assigned management and follow-up?
67 (93%) of 72 participants completed 6-month follow-up; 61 (91%) of 67 participants adhered to assigned management; and 29 (100%) of 29 participants assigned to surgery and medical management adhered to the prespecified type of surgery

How complete are baseline, imaging, and outcome data?
The baseline clinical case report form was completed for 72 (100%) of 72 participants; baseline brain imaging was received for 72 (100%) participants; 6-month clinical follow-up was completed for 67 (93%) participants; and 6-month brain imaging was received for 69 (96%) participants

What are the outcome event rates? (event rate per participant per year)
The rate of first new symptomatic intracranial haemorrhage or new persistent or progressive non-haemorrhagic focal neurological deficit was 7·8% (95% CI 2·9–20·7); the rate of first new symptomatic intracranial haemorrhage was 3·8% (1·0–15·1); the rate of first new persistent or progressive non-haemorrhagic focal neurological deficit was 3·8% (1·0–15·1); and death not due to a primary outcome was 0%.

How do the baseline characteristics, outcome event rates, and differences between treatment groups compare with observational data about outcomes during medical management alone or after surgery and medical management?
Baseline demographic, clinical, and imaging characteristics were similar to systematic reviews and meta-analyses of untreated clinical course[5] and after surgery;[9,10] outcome event rates were similar to rates described in the untreated clinical course[5] and after surgery;[9,10] association between medical management and surgery versus medical management alone with subsequent new symptomatic intracranial haemorrhage or new persistent or progressive non-haemorrhagic focal neurological deficit in cohort studies: risk ratio (RR) 0·6 (95% CI 0·2–1·7) over approximately 5 years,[16] 0·6 (0·1–2·6) over approximately 4 years,[17] hazard ratio 0·76 (95% CI 0·4–1·4),[23] RR 1·9 (95% CI 0·6–6·0) over approximately 6 years,[18] adjusted hazard ratio 3·6 (95% CI 1·3–10·0) over approximately 5 years,[15] and RR 7·8 (1·1–57·4) over approximately 4 years[19]

What estimates of effect size and variability should be used in the design of the CARE definitive randomised trial?
A clinically meaningful reduction in the primary clinical outcome with medical management and surgery would be a hazard ratio of 0·60–0·75

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 (appendix pp 29–32) were sufficient to estimate mean resource use and costs per participant (appendix pp 33–44) and to be used by a published Markov model[39]

participate. Furthermore, we sought to identify and address barriers and enhance facilitators in an embedded QuinteT Recruitment Intervention within this trial,[33] which involved the co-design of the participant information leaflets, discussions at site initiation visits, the monitoring of sites' screening logs, audio recordings of recruitment consultations between patients and health-care professionals, interviews (with health-care professionals and patients who declined or withdrew from participation), discussions at investigator meetings, and observation of trial management group meetings.[35] This 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 the short follow-up in the trial; and challenges with organising stereotactic radiosurgery. This substudy identified several

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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, including: a balanced portrayal of the two trial groups in the participant information leaflet; emphasis on screening and explicit discussions about recruitment and equipoise at site initiation visits; videos to coach investigators in screening and recruitment; tips and guidance documents for investigators; and investigator meetings.[35] A definitive trial would benefit from repeating the collaboration with patient support organisations and implementing the actions from the QuinteT Recruitment Intervention.

The generalisability of our findings outside the UK and Ireland is unknown because this study is, to the best of our knowledge, the first randomised controlled trial comparing medical management and surgery with medical management alone for people with symptomatic cerebral cavernous malformation. Standard practice varies around the world according to the interpretation of available evidence, available resources, clinical traditions, and the organisation and funding of health services. In a project assessing readiness for drug trials at five neuroscience centres in the USA, restricted to people aged older than 18 years with symptomatic haemorrhage from a cerebral cavernous malformation over the preceding year, participants seemed younger, more ethnically diverse, more likely to have a brainstem cavernous malformation, and more likely to have a family history than in the CARE pilot trial, but other characteristics and the outcome event rate were similar.[40]

The strengths of this pilot phase trial were that it was conducted in partnership with patients and carers and we embedded a QuinteT Recruitment Intervention to understand and improve recruitment, which helped investigators to exceed the recruitment target despite the impact of COVID-19 on most clinical trials at the time.[41] We did not find evidence of selection bias on the basis of the similarities between eligible patients who declined and those who participated. Recruitment of women reflected their prevalence at diagnosis.[5] Characteristics of participants by intended type of surgery reflected their appropriate selection for each type of surgery. Characteristics of surgery reflected standard practice in the UK. Stereotactic radiosurgery was accepted within the context of a trial and chosen twice as often as neurosurgical resection. Measures of data completeness, retention, adherence to assigned treatment, and adherence to the protocol were generally good. The limitations of this study were that the sample size was small even though it exceeded its target, only four (6%) of 72 participants were children, and participants' ethnicities were less diverse than the UK.[42,43]

In conclusion, we found that it was possible to perform a pilot randomised trial of medical management with or without surgery for people with symptomatic cerebral cavernous malformation. A parallel group trial with stratification of randomisation by intended type of surgery was acceptable to neurosurgeons and participants, although additional stratification or minimisation by two key prognostic factors (eg, cavernous malformation location and previous symptomatic haemorrhage) would be desirable and possible in a much larger definitive trial.[5] We did not detect any safety concerns about either management strategy. A definitive trial will benefit from designing its investigator training and participant information informed by the QuinteT Recruitment Intervention in this feasibility study. A definitive trial will need to be multicentre and international (involving between 36 and 259 sites) given the sample size required (between 590 and 1900 participants), the recruitment rate in this pilot trial, and traditional durations of recruitment expected by funding agencies.

The CARE pilot trial collaboration

Writing group Rustam Al-Shahi Salman, Laura Forsyth, Steff C Lewis, James J M Loan, Aileen R Neilson, Jacqueline Stephen (The University of Edinburgh, Edinburgh, UK); Neil Kitchen (National Hospital for Neurology and Neurosurgery, London, UK); Kirsty A Harkness (Royal Hallamshire Hospital, Sheffield, UK); Peter J A Hutchinson (The University of Cambridge, Cambridge, UK); Conor Mallucci (Alder Hey Children's Hospital, Liverpool, UK); Julia Wade (University of Bristol, Bristol, UK); Philip M White (Newcastle University, Newcastle-upon-Tyne, UK).

Trial management group R Al-Shahi Salman, M Eriksson, L Forsyth, P Hall, R Hayat, E Kinsella, K Lewis, SC Lewis, J J M Loan, A R Neilson (The University of Edinburgh, Edinburgh, UK); N Kitchen (National Hospital for Neurology and Neurosurgery, London, UK); V Ganesan (Great Ormond Street Hospital, London, UK); K A Harkness, M Radatz (Royal Hallamshire Hospital, Sheffield, UK); P J A Hutchinson, C Turner (The University of Cambridge, Cambridge, UK); C Mallucci (Alder Hey Children's Hospital, Liverpool, UK); J Wade (University of Bristol, Bristol, UK); D C S White (Cavernoma Alliance UK, Watlington, UK); P M White (Newcastle University, Newcastle-upon-Tyne, UK).

Observers of the trial management group J Boyd, A Bullen, M Maclean, A Stoddart (The University of Edinburgh, Edinburgh, UK); S Phair (Cavernoma Ireland, Ireland); H Evans, J Noakes (Cavernoma Alliance UK, Watlington, UK).

Trial coordinating centre R Al-Shahi Salman, D Alexander, M Eriksson, L Forsyth, P Hall, R Hayat, C Keerie, E Kinsella, K Lewis, S Lewis, C Linsley, M Maclean, G Milne, J Norrie, J Stephen (The University of Edinburgh, Edinburgh, UK).

Independent trial steering committee members G Cruickshank (chairperson; University of Birmingham, Birmingham, UK), D C S White (carer representative; Cavernoma Alliance UK, Watlington, UK), I Stuart and K Douthwaite (patient representative; Cavernoma Alliance UK, Watlington, UK), R Kerr (Oxford University Hospitals NHS Foundation Trust, Oxford, UK), C Hewitt (University of York, York, UK), H Shakur-Still (London School of Hygiene and Tropical Medicine, London, UK).

Non-independent trial steering committee members N Kitchen (National Hospital for Neurology and Neurosurgery, London, UK).

Observers of the trial steering committee R Al-Shahi Salman, S C Lewis, L Forsyth (The University of Edinburgh, Edinburgh, UK), J Wade (University of Bristol, Bristol, UK), and H Evans and J Noakes (Cavernoma Alliance UK, Watlington, UK).

Independent data monitoring committee J Bamford (chairperson, University of Leeds, Leeds, UK), A D Mendelow (Newcastle University, Newcastle-upon-Tyne, UK), N Baker (AstraZeneca, Cambridge, UK).

Clinical outcome event adjudication committee R Al-Shahi Salman,

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J J M Loan (The University of Edinburgh, Edinburgh, UK), N Kitchen (National Hospital for Neurology and Neurosurgery, London, UK), K A Harkness (Royal Hallamshire Hospital, Sheffield, UK), and V Ganesan (Great Ormond Street Hospital, London, UK).
Qualitative Research Integrated within Trials (QuinteT) Recruitment Intervention group J Wade, N Farrar, A X Realpe, J L Donovan (University of Bristol, Bristol, UK).
Patient, carer, and public involvement advisory group D C S White (chairperson), A Atkins, J Bunch, K Douthwaite, J Hogg, D Scott, P Spallone, I Stuart, S Temple, J Thompson (Cavernoma Alliance UK, Watlington, UK) and S Phair (Cavernoma Ireland, Ireland).
Observers of the patient, carer, and public involvement advisory group R Al-Shahi Salman, S C Lewis, L Forsyth (The University of Edinburgh, Edinburgh, UK), J Wade (University of Bristol, Bristol, UK), and H Evans and J Noakes (Cavernoma Alliance UK, Watlington, UK).
Brain imaging assessor P M White (Newcastle University and Newcastle-upon-Tyne Hospitals NHS Trust, Newcastle-upon-Tyne, UK).
Systematic management, archiving, and reviewing of trial images service J M Wardlaw, J Palmer, and E Sakka (The University of Edinburgh, Edinburgh, UK).
Sponsor's representative C Coner (The University of Edinburgh and NHS Lothian, Edinburgh, UK).
Funder's research manager A Marshall (National Institute for Health and Care Research, Southampton, UK).
Investigators at sites that recruited participants are listed in the appendix (pp 3–4).

Contributors

RA-SS (chief investigator) and NK (co-chief investigator) had the idea for the study. RA-SS (lead applicant) obtained funding and developed the protocol. RA-SS designed and implemented the study, with the trial management group. SCL was the masked trial statistician. JS was the unmasked trial statistician who did the data analyses. All authors had access to raw data. JS and SCL verified the underlying data. RA-SS wrote the first draft of the manuscript. All members of the writing committee reviewed the analyses and drafts of this manuscript and approved its final version.

Declaration of interests

KAH reports an unrestricted educational grant from Medtronic. NK reports receiving personal income from consultancy with Amethyst UK. PW reports being immediate past chair of the UK neurointerventional group. RA-SS reports funding from the National Institute for Health and Care Research for this project, paid to The University of Edinburgh; consulting fees from Recursion Pharmaceuticals and Bioxodes, paid to The University of Edinburgh; lecture fees from the European Stroke Masters, paid to The University of Edinburgh; fees for participation in endpoint adjudication for Novo Nordisk, paid to The University of Edinburgh; and secondment as the clinical director of the UK Clinical Research Collaboration network of registered Clinical Trials Units, paid to The University of Edinburgh. SCL reports membership of the National Institute for Health and Care Research Health Technology Assessment general funding committee. JJML reports fellowship funding from the Wellcome Trust. All other members of the writing group declare no competing interests.

Data sharing

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

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