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Research Article

Developing a Randomised Efficacy PREcision medicine Platform trial design for Cavernomas: the CARE PREP study

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Abstract

Background: Symptomatic cerebral cavernous malformations are a rare sporadic or familial disease, which may cause haemorrhagic strokes or epileptic seizures. In 2015, a James Lind Alliance Priority Setting Partnership ranked targeted drug therapies as fourth of the top 10 research priorities for cerebral cavernous malformations. There are no disease-modifying drugs for cerebral cavernous malformations, but there are several promising candidates with proof of concept in human and animal studies. There are no platform trials for cerebral cavernous malformations.

Objectives: (1) Consolidate and initiate international collaborations between cerebral cavernous malformations researchers, cerebral cavernous malformations patient and public involvement groups, cerebral cavernous malformations research networks, and commercial partners; (2) Finalise a protocol for an efficient, international platform trial of multiple drugs using precision medicine (sporadic vs. familial cerebral cavernous malformations) that is both feasible and acceptable to patients and regulators; (3) Estimate the research, support and treatment costs of the platform trial and apply to the National Institute for Health and Care Research Efficacy and Mechanism Evaluation Programme.

Methods: A National Institute for Health and Care Research Efficacy and Mechanism Evaluation Application Acceleration Award funded this project from September 2022 to August 2023. A trial manager supported the Chief Investigator in growing and leading a multidisciplinary international collaboration, including a patient and public involvement advisory group, in a series of meetings to optimise study design, equality, diversity and inclusion. Edinburgh Innovations established connections with commercial partners with candidate drugs. We assessed feasibility by scoping potential funding agencies, and clinical networks that might support recruitment internationally. We agreed upon a final design and sample size through a process of consensus, enlightened by scenarios simulated by statisticians varying key parameters, which informed a comprehensive estimate of the budget for a stage 1 submission to the National Institute for Health and Care Research Efficacy and Mechanism Evaluation programme.

Setting: International collaboration.

Participants: Clinicians, researchers, patient and public involvement groups, cerebral cavernous malformations research networks, and commercial partners.

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Results: There was one face-to-face meeting, nine virtual meetings of the co-applicants, and five meetings of the patient and public involvement advisory group. We identified 14 countries with clinical leadership, a cerebral cavernous malformation research network, and a funding agency that could support an international trial. We contacted three potential commercial partners and obtained one letter of collaboration. We sent monthly newsletters to collaborators. Our meetings and simulations concluded that a three-arm, two-stage multiarm multistage adaptive treatment selection randomised trial design was suitable for evaluating aspirin and propranolol as the first two interventions compared with standard care in a platform trial. We submitted a stage 1 proposal for this Cavernous malformations A Randomised Efficacy MAster Protocol study to the National Institute for Health and Care Research Efficacy and Mechanism Evaluation call 23/15 in May 2023, and a resubmission was encouraged.
Limitations: The National Institute for Health and Care Research Efficacy and Mechanism Evaluation funding committee would have required further justification for the choice of the intermediate phenotype used for treatment selection, biomarker validation work, and details about the pipeline of interventions.
Future work: We have addressed these limitations and re-applied to the National Institute for Health and Care Research Efficacy and Mechanism Evaluation programme.
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Background

The major unmet need for people with cerebral cavernous malformation (CCM) – which is a raspberry-like capillary microangiopathy in the brain – is targeted drug treatment, which was fourth of the top 10 research priorities in a recent James Lind Alliance Priority Setting Partnership.[1] Although asymptomatic CCM occur in ~107,500 people in the UK (prevalence 1 in ~625)[2,3] symptomatic CCM are a rare disease leading to approximately 160 new diagnoses in the UK each year (incidence 0.24 per 100,000 per year).[4] The burden of CCM is disproportionately high because they are usually diagnosed in young adults of working age who are at risk of recurrent stroke due to intracerebral haemorrhage (ICH),[5] new non-haemorrhagic focal neurological deficits (FND),[6] or epileptic seizures that recur in ~50% of people affected despite anti-epileptic drugs.[7] These risks may be reduced by neurosurgical excision of CCM, but surgery has a ~4% risk of death, ICH or FND in the following year, which is higher still for CCM in the brainstem or CCM that have caused ICH, and this complication rate has not changed over time.[8] CCM that are too hazardous for neurosurgical excision (e.g. in the brainstem) are sometimes treated with stereotactic radiosurgery, which seems to have similar risks to neurosurgery.[9] However, guidelines have been unable to make level A recommendations about these treatments because there are no randomised controlled trials (RCTs).[10]

The National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme commissioned a pilot RCT comparing treatment with or without neurosurgery (or stereotactic radiosurgery) for CCM, which is the top uncertainty about the disease.[1] This Cavernomas A Randomised Effectiveness (CARE) pilot trial recruited 72 participants at 29 UK sites (www.ed.ac.uk/care-study) and reported on the feasibility and design of a definitive RCT.[11] Three-quarters of the eligible patients with symptomatic CCM who were approached and who declined to participate in the CARE pilot trial indicated a preference for treatment without surgery,[11,12] so a drug to prevent ICH/FND from CCM might be more suitable for them, but specific pharmacological therapies do not exist for CCM.

Several drugs might modify CCM prognosis based on studies of animal models, humans, drug repurposing[13] or treatment target approaches.[14] The three leading drug candidates are:

- Propranolol and other beta-blockers, based on animal models,[15–17] human studies,[18–26] and by analogy with infantile haemangioma[27]
- 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG CoA) reductase inhibitors (statins), based on animal models[28,29] and human studies[18,30]
- Antithrombotic (anticoagulant or antiplatelet) drugs based on human studies[31–33]

Other drug candidates include combination of a statin and an antiplatelet drug based on human studies;[33] Rho-associated protein kinase inhibition with fasudil in animal models;[28,34] rapamycin in animal models;[35] non-steroidal anti-inflammatory drugs in human studies;[32] selective serotonin reuptake inhibitors in human studies;[31] vitamin D in human studies;[31] and fish oil in human studies.[31]

Precision medicine to prevent ICH/FND from CCM using these drugs could arise from targeting drug treatments at distinct aetiological or pathophysiological groups of patients with CCM, such as by presence/absence of one of the three heterozygous germline mutations with autosomal

dominant inheritance that lead to 20% of CCM being familial (*CCM1* OMIM 116860, *CCM2* OMIM 603284, *CCM3* OMIM 603285, ORPHA:221061). People with these genetic mutations have multiple CCM that can grow both in number and size over time; the number of familial CCM is associated with the rate of ICH,[36] and there are specific genotype–phenotype differences; for example, people with *CCM3* mutations have higher risk of ICH at an earlier age and greater CCM burden compared to people with *CCM1* mutations, *CCM2* mutations, or sporadic CCM.[37,38] Additional precision medicine targets for consideration include molecular[39] and magnetic resonance imaging (MRI) biomarkers [quantitative susceptibility mapping (QSM) and dynamic contrast-enhanced quantitative perfusion][40] that measure relevant pathophysiological processes (iron deposition and vascular permeability, respectively) that could be targeted by particular drugs.[41,42]

Stratification criteria could include CCM location (brainstem CCM have a higher risk of ICH than CCM located elsewhere in the brain) and prior presentation with symptomatic ICH due to CCM (which conveys a higher risk of future ICH than not having prior ICH), which together create four prognostic categories according to CCM anatomic location and history of ICH.[5]

A systematic review of publications in Ovid MEDLINE and EMBASE to 30 June 2022 with literature search terms for CCM used by earlier systematic reviews[5,8,9] identified case reports, cross-sectional studies and cohort studies of drugs for CCM in humans, but no definitive RCTs. Alongside studies in animal models, proof of concept in human cohort studies seems strongest for beta-blocker, statin, and antithrombotic (antiplatelet or anticoagulant) drugs (*Table 1*).

A search of ClinicalTrials.gov on 30 June 2022 identified six relevant RCTs, although two proposed RCTs of Propranolol (NCT03474614 and NCT03523650) never began (*Table 2*). Two phase 2 RCTs have been completed: one showed a non-significant effect of simvastatin on MRI permeability of CCM,[30] and the other showed a promising effect of Propranolol on new ICH or FND [hazard ratio (HR) 0.43, 80% confidence interval (CI) 0.18 to 0.98].[19,44] There are two ongoing Phase II RCTs of Atorvastatin[45] and REC-994 (a superoxide scavenger)[13] for CCM, but these RCTs are unlikely to identify effects definitively because of their small sample sizes. Therefore, there is no definitive platform RCT using precision medicine approaches for CCM registered in ClinicalTrials.gov.

TABLE 1 Observational studies of the associations between drugs and outcomes for humans with CCM, identified by a systematic review on 30 June 2022

Cohort study	Participants (number)	Intervention	Comparator	Outcome	Association with outcome
Goldberg *et al.* 2018[21]	Any CCM (*n* = 408)	Any beta-blocker	No beta-blockers	ICH	HR 1.19 (95% CI 0.49 to 2.90)
Gomez-Paz *et al.* 2020[20]	Any CCM (*n* = 438)	Any beta-blockers	No beta-blockers	ICH	OR 0.71 (95% CI 0.39 to 1.30)
Zuurbier *et al.* 2022[18]	Any CCM (*n* = 300)	Any statin	No statin	ICH/FND	aHR 0.37 (95% CI 0.01 to 1.07)
Zuurbier *et al.* 2022[18]	Any CCM (*n* = 300)	Any beta-blocker	No beta-blockers	ICH/FND	aHR 0.09 (95% CI 0.01 to 0.66)
Zuurbier *et al.* 2019[43]	Any CCM (*n* = 1342 meta-analysis)	Any antithrombotic drug	No antithrombotic drugs	ICH	RR 0.25 (95% CI 0.13 to 0.51)

aHR, adjusted hazard ratio; OR, odds ratio; RR, relative risk.

TABLE 2 Randomised controlled trials of drugs for CCM that were registered in ClinicalTrials.gov on 30 June 2022 and had been initiated

Identifier	Principal investigator	Intervention vs. comparator	Target sample size	Status	Sample size achieved
NCT01764451	Mabray[30]	Simvastatin vs. standard care	12	Complete	12
NCT03589014	Latini[19,44]	Propranolol vs. standard care	60	Complete	83
NCT02603328	Awad[45]	Atorvastatin vs. placebo	80	Complete	80
NCT05085561	Recursion Pharmaceuticals[13]	REC-994 400 mg vs. 200 mg vs. placebo	60	Complete	62

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Altogether, proof of concept from animal models, human cohort studies[18,43] in sporadic and familial CCM, and pilot phase RCTs in humans with familial CCM[19,30] lead us to hypothesise that antithrombotic, beta-blocker, and statin drugs are promising treatments to repurpose for CCM, and many others may be beneficial based on preclinical, drug repurposing or target-driven studies.

Aims and objectives

This Application Acceleration Award funded us to address three main aims and objectives, in order to catalyse the design, delivery, and assessment of the feasibility of a protocol and funding application for the first CCM platform trial of drugs:

1. Consolidate and initiate international collaborations between CCM researchers, CCM patient and public involvement (PPI) groups, CCM research networks, and commercial partners.
2. Finalise a protocol for an efficient, international platform trial of multiple drugs using precision medicine (sporadic vs. familial CCM) that is feasible and acceptable to patients and regulators.
3. Estimate the research, support and treatment costs of the platform trial and apply to the NIHR Efficacy and Mechanism Evaluation (EME) programme.

Methods

We followed the project plan proposed in the funding application (*Figure 1*), established a Steering Committee and a Patient, carer and public involvement and engagement Advisory Group (PAG), and used the following methods to address our aims and objectives.

1. International collaboration

In September 2022, we initiated a novel, inclusive academic collaboration of researchers and PPI co-applicants for the first platform RCT for CCM. The co-applicants have prior experience (Kim),[30] recent experience (Latini),[19] and ongoing experience (Salman, White, Lee, Kim and Awad) of CCM RCTs. During the award, we identified international networks of research-ready clinical sites that care for people with CCM (such as those that have expressed interest in an international main phase of the NIHR HTA CARE trial, the NIH Brain Vascular Malformation Consortium CCM project,[36,46] or are involved in the Cavernous Angiomas With Symptomatic Haemorrhage trial readiness project[47,48]). International involvement will ensure the feasibility of recruiting people with a rare disease, generalisability and investigate the external validity of UK findings. The project manager worked with our international collaborators to determine whether there were any specific local regulatory requirements for the conduct of platform RCTs involving licensed and unlicensed drugs in Phase II (safety and dose-finding) and

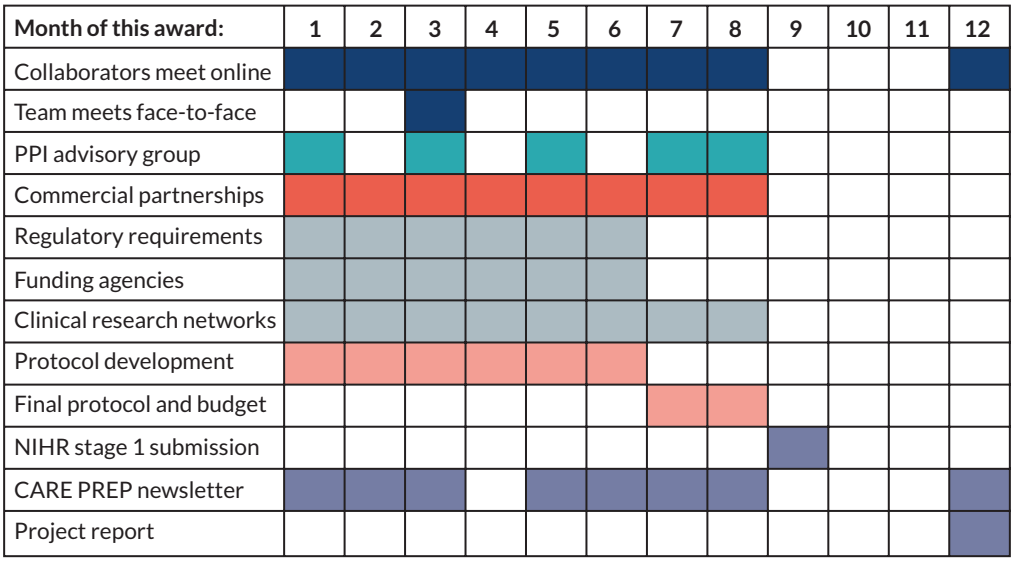

FIGURE 1 Project timetable.

Phase III (efficacy) clinical trials of investigational medicinal products, but did not find any specific requirements, so this aspect is not dealt with further in this report. The collaborators met as follows:

- August 2022: In a pre-funding meeting, the PPI co-applicants met to make recommendations to the Steering Committee on the Terms of Reference for PAG, its size and membership. It proposed that PAG should consist of two additional members, Carlos Casaus and João Próspero Luís, to provide more voices with lived experience and greater geographical diversity.
- September 2022: We agreed on the project plan (see *Figure 1*) and set up a series of virtual meetings to adhere to the project plan. The PAG discussed the information (evaluation criteria) we would collect on national patient networks, including the likely numbers of patients, with which clinical centres and clinicians they are networked and their structure. PAG identified which European clinical research networks could aid recruitment, and who might be clinical partners.
- October 2022: We contacted international CCM researchers and patient advocacy organisations to assess the feasibility of an international platform RCT based on the existence of relevant networks and stakeholders in countries with a track record of CCM clinical research (*Table 3*). We met with Recursion Pharmaceuticals (a potential commercial partner) and LifeArc (a charity) to discuss their potential partnership with a platform RCT for CCM.
- November 2022: We continued to explore international feasibility and local regulatory requirements. We met with Neurelis and Cervello (potential commercial partners). The co-applicants met face to face at the International CCM Scientific Meeting, hosted by Alliance to Cure Cavernous Malformation Scientific Meeting in Durham, North Carolina (www.alliancetocure.org/for-professionals/researchers/ccm-scientific-meeting/past-ccm-scientific-meetings/). Rustam Al-Shahi Salman gave presentations about the NIHR HTA CARE pilot trial and our plans for an international precision medicine platform trial for CCM. The PAG analysed the details of national patient networks identified by the PAG and the discussion and comments made by the steering group, grouping them on their availability of the resources required to support an international platform trial in a preliminary version of *Table 3*. We discussed general issues important to patients during a platform trial.
- December 2022–February 2023: We developed the design of the international precision medicine platform trial for CCM at and between monthly meetings. Discussion points included key design criteria for platform RCTs (*Figure 2*), including eligibility criteria, stratification, precision medicine, interventions, comparators, randomisation, outcomes and adaptive trial design. We considered the proof of concept for the potential drug therapies and the mechanistic component of the trial.
- January 2023: The PAG meeting focussed on the structure of PPI involvement in the platform trial, including the need for and roles of a PAG co-ordinating board and individual nations' PAG co-ordinators, for effective translation of all patient-facing documents. In addition, we discussed whether the trial should have primary and secondary outcomes and their content, and highlighted the need for a mobile App for patient recording.
- March–April 2023: These meetings focused on the final protocol and budget required for the grant application. We discussed the design of the international precision medicine platform trial for CCM with Professor Mahesh Parmar and Dr Babak Choodari-Oskooei in an appointment with their multiarm multistage (MAMS) clinic (www.mrcctu.ucl.ac.uk/our-research/methodology/design/more-about-mams/mams-clinic/), after which they joined our grant application as co-applicants. We met with the Edinburgh Clinical Trials Unit, Edinburgh Research Office, and NHS Lothian Research and Development Finance to develop the budget for the platform trial proposal.
- March 2023: The bulk of the PAG meeting was devoted to the drugs to be included in the platform trial, particularly of aspirin and the feasibility of patient recruitment with a drug well known as a blood thinner. PAG also considered its role in reviewing the full application.
- April 2023: The PAG considered the duration and international involvement in the platform trial, and the need for international funding. PAG also discussed the outcome of two focus groups set up to understand patients' views on the inclusion of three drugs and showed the challenges faced regarding preconceptions, opinions and beliefs.
- May 2023: We submitted an NIHR EME stage 1 proposal for the Cavernomas A Randomised Efficacy

TABLE 3 Availability of the resources required to support an international platform trial

	Clinical lead	CCM patient network	CCM research network	Early career researchers	Funding agency
UK					
USA					
Canada					
Brazil					
Germany					
Belgium					
Australia					
Ireland					
Sweden					
The Netherlands					
France					
Austria					
Greece					
Switzerland					
Italy					
Mexico					
Spain					
Finland					
Portugal					
South Africa					
Norway					

Green, yes; amber, maybe; red, no.

MAster Protocol (CARE MAP) in response to NIHR EME call 23/15 'Precision medicine platform studies to efficiently evaluate the efficacy of interventions'.
- We sent monthly e-mail newsletters to update all of our partners about the project's progress.

2. Protocol for an international precision medicine platform trial

We designed a platform RCT to be an efficient strategy for evaluating many drugs concurrently,[50] and provide proof of clinical efficacy, effect size, and safety with a precision medicine approach to RCT design and stratification of the analysis. At our collaborators' meetings, we reached consensus about:

- **Research design:** We planned for a MAMS RCT. We considered whether to stop treatments for futility or efficacy and whether we would re-estimate sample size at interim analyses. We considered aspects of inter-individual variability that may influence treatment effects as well as pragmatic considerations (e.g. current use of any of the drugs, contraindications to candidate drugs, or intolerance of the mode of drug delivery) that may influence eligibility, randomisation and subsequent analyses.
- **Participants:** We sought broad eligibility criteria to increase inclusion, and we considered how to maximise and record equality and diversity (e.g. age, sex, ethnicity, disability) with the PPI Advisory Group, while allowing stratification factors to permit investigation of specific effects in subgroups. We applied what we have learnt about successful approaches to this patient group in the ongoing NIHR HTA CARE pilot trial via an embedded QuinteT Recruitment Intervention.[51] The PPI Advisory Group

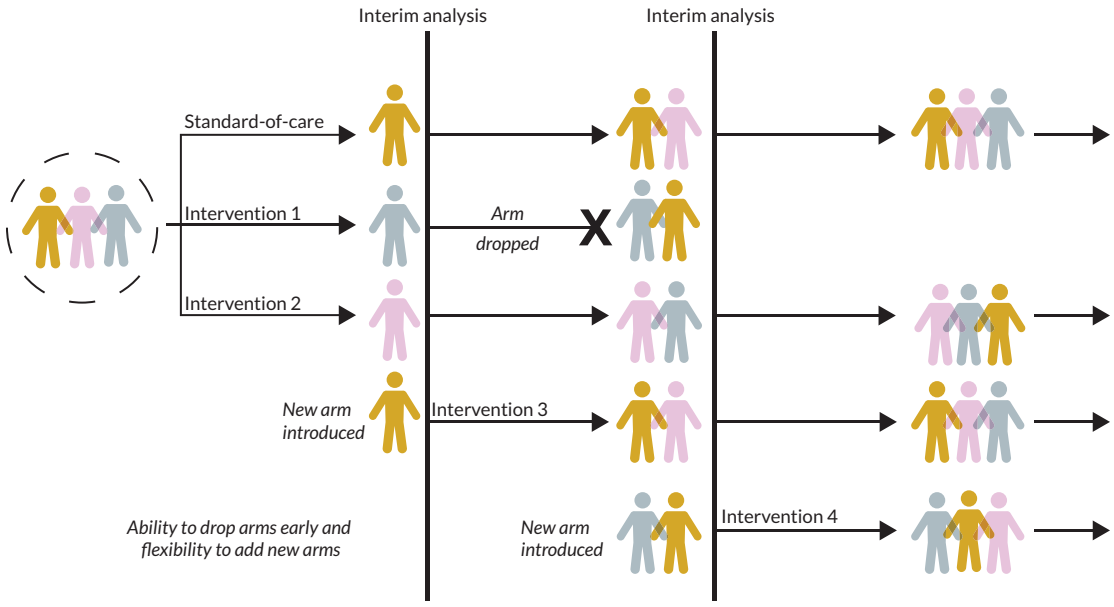

FIGURE 2 Generic illustration of a multi-arm, multi-stage adaptive platform design with some of the design considerations to be addressed by the Application Acceleration Award. Examples of considerations to be addressed: Participant eligibility criteria; Stratification/selection criteria according to genotype/phenotype/biomarker; Intervention allocation ratios, target sample sizes; Initial number and type of interventions to be compared with standard care (e.g. a beta-blocker, a statin and aspirin); New interventions to be added (e.g. unlicensed drugs such as REC-994), setting up the pipeline to identify new interventions, plans for assessing combinations of interventions; Efficacy, safety and futility criteria at interim analysis; Contingency plans for standard of care changing over time; Intermediate phenotypes and clinical outcomes. Reproduced with permission from Park *et al.*[49] This is an Open Access article distributed in accordance with the terms of the Creative Commons CC BY NC-ND licence, which permits non-commercial use of the work as published, without adaptation or alteration provided the work is fully attributed. See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

and co-applicants leading CCM RCTs considered support for participants, data capture from them,[52] and minimising drop-out.

- **Interventions:** We discussed at length which drugs will be the first to be evaluated, and estimated likely adherence and attrition based on other CCM RCTs.[19,45] We investigated setting up a living systematic review as a pipeline for discovering additional drugs that might be added to the master protocol with colleagues at The University of Edinburgh. We reviewed knowledge about the dosing of drugs (e.g. propranolol[15]) to determine whether the platform must include both Phase II and Phase III RCTs. We considered the risk of performance and detection biases when deciding whether the platform RCT should use placebo or open control. We foresaw the evaluation of combinations of drugs and effects in subgroups.
- **Assignment:** We discussed the allocation ratio mindful of statistical issues (e.g. maximising power by setting the ratio of control: intervention according to the number of interventions concurrently being studied in the platform) and acceptability to patients.
- **Outcomes:** While the major clinical outcomes of interest (ICH, FND and epileptic seizures) are well defined[6,53] and were confirmed by the PAG, we sought more information about the validation of disease-specific measures of global outcomes that are still under development (e.g. CCM Health Index). We sought to understand the mechanism of treatment effect via intermediate phenotypes, such as QSM on brain MRI (under consideration by the US Food and Drug Administration as a monitoring biomarker of drug effects on haemorrhage from CCM) to quantify haemosiderin leakage by CCM and other circulating biomarkers,[41] and whether these are surrogate markers of clinical outcomes.[54]
- **Statistical analyses:** Co-applicant Weir supervised a senior statistician (Parker) to perform simulations across a range of platform RCT scenarios, agreed in consultation with the co-applicants and PAG, according to variations in the choice of adaptive design, participant eligibility criteria, number of interventions, outcome type/frequency/distribution, and sample size required to explore heterogeneity of effects in subgroups according to stratification criteria.[55,56] These simulations helped to determine an efficient, pragmatic, platform RCT design, defining its operating characteristics with regard to statistical power and type 1 error for given interim analysis progression criteria. We also confirmed the deliverability of the RCT, according to the recruitment base established.
- **Mechanistic component:** A key objective of the efficacy platform RCT will be to embed hypothesis-testing mechanistic studies to

understand the mechanism of action of the interventions, the causes of differing responses, and whether intermediate phenotypes are reliable surrogate outcomes.

3. Estimate budget for an international precision medicine platform trial

We used published examples,[52,57,58] our own experience,[59] and projections for the international scope of the efficacy platform RCT to estimate the budget required for international coordination, UK conduct, and international conduct, focusing on value for money and design efficiencies.[60]

Patient and public involvement or community engagement, and involvement

Extensive involvement from our PAG informed us about patients' preferences for study design, and recommended how to maximise equality, diversity and inclusion. The Group included three PPI co-applicants [Lee (USA), White (UK) – both carers – and Bergholtz (Sweden) who is a CCM patient/service user, all involved with non-profit CCM organisations], Carlos Casaus (relative) from the Alliance to Cure Cavernous Malformation (USA), and João Próspero Luís (relative) of Cavernoma Portugal. The PAG took part in monthly co-applicants' meetings as well as 2-monthly PAG meetings. The PAG members defined the aims and responsibilities of the group, membership criteria, a shared learning approach and the working methods using a partnership-focused framework for PPI.[61] The PAG helped to identify patient networks worldwide. PAG members discussed the role of the PAG for the platform RCT as well as what was expected from PAG co-coordinators for each nation and how to reimburse their work. Members discussed a consistent patient-orientated document set, eligibility, inclusion, interventions (in particular feelings and evidence about antiplatelet agents) and outcomes. Cavernoma Alliance UK (CAUK) hosted a Focus Group with 10 contributing patients with symptomatic CCM to explore their perspectives on three drugs for treating CCM and the extent to which these perspectives changed when current clinical information was shared. The 2-monthly PAG meetings provided an opportunity to explore tools for evaluating the impact of PPI throughout the proposed research (e.g. https://ceppp.ca/en/evaluation-toolkit/). Lee and her team from Alliance to Cure Cavernous Malformation organised the International Alliance to Cure Cavernous Malformation Scientific Meeting in Durham, US where the CARE PREP group met face to face.

Equality, diversity and inclusion

We sought to identify as many countries as possible with the requirements to contribute to an international platform RCT (see *Table 3*), regardless of their geographical location and income status, while recognising that MRI needs to be available to diagnose CCM (making diagnosis a challenge in low-middle income countries with few MRI facilities) and not all countries have CCM support groups. For the platform RCT, we will invite all eligible people to take part regardless of their protected characteristics, adhering to the INCLUDE ethnicity framework.

Results

We developed a proposal for 'Cavernous malformations: A Randomised Efficacy MAster Protocol (CARE MAP) precision medicine platform study' and submitted a stage 1 application to NIHR EME in May 2023 to establish the CARE MAP infrastructure, UK recruitment to evaluate aspirin and propranolol, and preparation for international extension. We intended CARE MAP to be a large, ambitious, master protocol study including a MAMS adaptive RCT of the efficacy and safety of targeted drugs for symptomatic CCM, including mechanistic studies using MRI and blood biomarkers, initiated in the UK and aspiring to be international. We chose a MAMS design because it efficiently evaluates many drugs and no such RCT exists for CCM. MRI and blood biomarkers will provide insight into drugs' mechanisms of action. QSM MRI reflects the occurrence and risk of ICH, so we thought that it would be a suitable continuous intermediate outcome to inform adaptive drug selection.[62] We planned to compare blood biomarkers and MRI characteristics of the symptomatic CCM between randomisation and 1-year follow-up to indicate drug effects on thrombosis within CCM (signal and volume), haemorrhage within/outside CCM (signal, volume and mean magnetic susceptibility), and angiogenesis (CCM volume and the number of genetic CCM) for a MAMS treatment selection design (*Figure 3*).

Timing of CARE MAP

We concluded that our proposed design for CARE MAP was needed at the time of application because: targeted drugs are a research priority for CCM;[1] proof of concept existed for several drugs (see below)[14] and small parallel group RCTs were complete or ongoing (see below); QSM MRI seemed a suitable intermediate outcome for CCM (see CARE MAP outcomes, below);[63] and our NIHR EME Acceleration Award had grown a large international collaboration of countries committed to joining and seeking funding for CARE MAP (see *Table 3*).

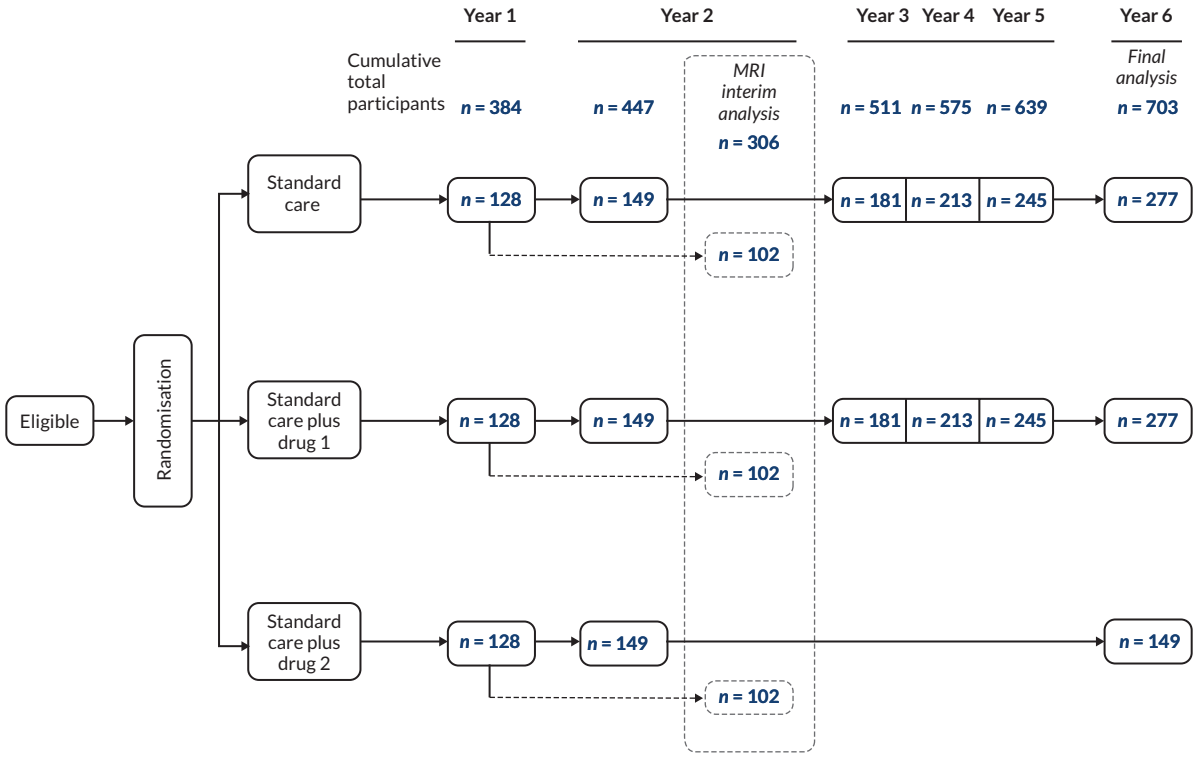

FIGURE 3 Cavernous malformations A Randomised Efficacy MAster Protocol precision medicine platform study.

Proof of concept

We updated our systematic review[5] to 28 April 2023 during this award, and identified three drugs with promising comparative data in humans:

- Propranolol: CCM1/2 knockout mice display angiogenesis due to altered cadherin distribution and Notch inhibition. Propranolol is an anti-angiogenic agent, effective for infantile haemangioma.[27] Co-applicant Latini's Treat_CCM RCT of propranolol versus open control in 83 people with genetic CCM, involving lead applicant Salman, showed a non-significant reduction in ICH/FND (HR 0.43, 80% CI 0.18 to 0.98), tolerability (95% adherence, > 50% tolerating ≥ 40 mg twice daily), and fewer de novo CCM (median 4 vs. 5) with propranolol.[44] Lead applicant Salman's population-based cohort found an association between beta-blocker use and a lower risk of ICH/FND from CCM (HR 0.09, 95% CI 0.01 to 0.66).[18]
- Antithrombotic drugs: The brain endothelium in CCM3 knockout mice is pro-thrombotic. Antithrombotic drug use is less frequent when CCM are diagnosed with ICH versus other presentations,[32,33,64,65] and subsequent antithrombotic drug use (84% antiplatelet, 16% anticoagulant) was associated with a lower risk of ICH/FND in lead applicant Salman's population-based cohort (with adjustment for confounders), in a meta-analysis [relative risk (RR) 0.25, 95% CI 0.13 to 0.51],[43] and in recent cohorts.[31,64]
- Statins: These pleiotropic drugs rescued the cellular phenotype and barrier function in CCM2 heterozygous mice. A RCT of simvastatin 20–40 mg versus open control in 12 participants did not show an effect of simvastatin on dynamic contrast-enhanced MRI permeability of CCM.[30] Lead applicant Salman's population-based cohort found a non-significant association between statin use and a lower risk of ICH/FND (HR 0.37, 95% CI 0.01 to 1.07).[18]

Trial Register searches

An updated search of World Health Organization International Clinical Trials Registry Platform with 'cavernous malformation' on 14 April 2023 found a small 1 : 1 parallel group of ongoing RCTs:

- An academic RCT of atorvastatin has recruited all 80 participants, who were in follow-up until July 2024.[45]
- A commercial RCT of REC-994 (a free-radical scavenger) recruited 62 participants (NCT05085561).
- A commercial crossover RCT of rapamycin (a mechanistic target of rapamycin kinase inhibitor) seeks 20 participants (ChiCTR2100043189).

This article should be referenced as follows:
Al-Shahi Salman R, Adamczuk K, Parker RA, Weir CJ, Latini R, Kim H, *et al.* Developing a Randomised Efficacy PREcision medicine Platform trial design for Cavernomas: the CARE PREP study [published online ahead of print March 26 2025]. *Efficacy Mech Eval* 2025. https://doi.org/10.3310/TYUP6982

- Two RCTs of propranolol never began (NCT03474614 and NCT03523650).

CARE MAP clinical objectives

1. Initiate the first master protocol platform study for CCM.
2. Compare propranolol and aspirin to standard care using a MAMS platform RCT.
3. Pick the most promising drug at interim analysis using QSM MRI.
4. Test the efficacy and safety of the most promising drug.

CARE MAP mechanistic hypotheses

5. Thrombosis and inflammation within CCM trigger ICH {by comparing change in MRI CCM volume/signal and plasma biomarkers [interleukin (IL)-1β, IL-6, soluble cluster of differentiation 14 (sCD14)14] at 1 year, and rate of ICH/FND after randomisation to aspirin vs. standard care}.
6. Propranolol reduces CCM angiogenesis {by comparing change in CCM volume and number on MRI and plasma biomarkers [vascular endothelial growth factor (VEGF), sROBO4] at 1 year after randomisation to propranolol vs. standard care}.
7. People with genetic CCM benefit more from propranolol than people with sporadic CCM, because of its anti-angiogenic effects on CCM formation.

CARE MAP deliverables (by objective/hypothesis number)

- Obtain regulatory approvals for the master protocol (1–4).
- Activate 27 sites in the UK (1–4).
- Recruit 306 adults with symptomatic CCM for an interim analysis using MRI after 2 years (3).
- Recruit 703 people with CCM in total over 6 years, obtain plasma biomarkers to establish mechanism of drugs' effects (5, 6), and follow-up for ≥ 1 year to establish efficacy and safety of the selected drug (4).
- Seek funding to recruit internationally (1–4).
- Investigate precision medicine by genotype (7).
- Recruitment study-within-a-trial (SWAT) of video information (1–4).

CARE MAP population

Our sites are geographically, ethnically and socioeconomically diverse. We will invite all eligible people to take part regardless of their protected characteristics, adhering to the INCLUDE ethnicity framework and the NIHR Race and Equality Framework.

Inclusion criteria: (1) age ≥ 18 years; (2) at least one sporadic/familial CCM diagnosed by MRI; (3) CCM previously/currently symptomatic from stroke due to ICH, FND or epilepsy within 5 years before randomisation; (4) symptomatic CCM has not been removed surgically or treated with stereotactic radiosurgery; (5) MRI, or a formal report, that confirms the CCM diagnosis (and prior ICH, if it occurred) available; (6) retained mental capacity; (7) informed consent provided. Exclusion criteria: (1) intention to treat the symptomatic CCM with surgery or stereotactic radiosurgery; (2) MRI intolerance/contraindication; (3) known hypersensitivity/contraindication to any study drug; (4) already taking a study drug regularly and will not discontinue; (5) women who are pregnant, breastfeeding, or of childbearing potential and not using contraception; (6) unlikely to survive > 1 year; (7) enrolled in another drug RCT.

Due to the low anticipated event rate of the efficacy outcome, which limits statistical power, we did not plan to use an adaptive enrichment design (whereby the target population is modified as the RCT evolves).

CARE MAP interventions

We propose two repurposed drugs that are widely available in the NHS, based on current proof of concept (see above), avoidance of duplication of ongoing RCTs (see above), and a 10-patient focus group conducted by Cavernoma Alliance UK on 20 April 23:

- Propranolol: Oral administration (target dose 80 mg twice daily), which was tolerable in the RCT of propranolol for genetic CCM[44] and should inhibit beta-1 adrenergic receptors.[17]
- Aspirin: Oral administration of 75 mg once daily. In our meta-analysis of cohorts, 82% used an antiplatelet drug (mostly aspirin at this standard dose for secondary prevention of thrombotic disease), which was associated with a lower risk of ICH (RR 0.30, 95% CI 0.15 to 0.62) than no antithrombotic drug use.[43]
- Pipeline: We will create a living systematic review to identify drugs beyond propranolol, aspirin, and statins for repurposing.[14] We will consider atorvastatin when the ongoing RCT reports as this platform study begins.[45] We will consolidate our commercial partnership (Recursion Pharmaceuticals), and appoint an Intervention Prioritisation Committee to decide which new drug(s) to add as others are dropped at interim analyses.

CARE MAP comparator

Standard care without any of the study drugs.

CARE MAP outcomes

We decided on the following outcomes based on a process of consensus involving reviews of the existing evidence about CCM and the opinions of the collaborators and the PAG.

Mechanistic

- Change in symptomatic CCM on MRI between randomisation and 1 year to indicate drug effects on thrombosis (signal and volume), haemorrhage (signal, volume and mean magnetic susceptibility), inflammation (T2/Fluid-attenuated inversion recovery signal), and angiogenesis (volume and number in genetic CCM).
- Change in blood biomarkers between randomisation and 1 year will explore the mechanisms of action of the drugs on inflammation, thrombosis, and angiogenesis (IL-1β, IL-6, sCD14, VEGF and sROBO4), and their effect on the predicted probability of ICH using a validated model including these biomarkers.[66]

Intermediate

- Change in CCM susceptibility on QSM MRI at 1 year, and efficacy and safety outcomes. QSM MRI has been validated as a quantitative measure of iron deposition in CCM using phantoms, ex vivo and in vivo studies at multiple sites with different MRI manufacturers (97% were useable[47]). In humans, CCM with prior ICH have ~10% higher mean susceptibility than CCM without prior ICH,[54] and CCMs with growth or new ICH show a 6–44% increase in mean susceptibility per CCM over ~1 year.[63,67]

Efficacy

- New symptomatic stroke due to ICH or persistent/progressive non-haemorrhagic FND due to CCM throughout follow-up.
- Epilepsy.

Safety

- Serious adverse events throughout follow-up.

Effectiveness

- Modified Rankin Scale,[47] EuroQol-5 Dimensions, five-level version,[47] and Patient-Reported Outcomes Measurement Information System (PROMIS)-29,[47] to inform us about their likely sensitivity to treatment effects and utility in a definitive RCT.

CARE MAP risk of bias and randomisation

We will minimise bias with a web-based, concealed, random allocation sequence; tenacious clinical follow-up and assiduous attention to quality control of MRI acquisition; outcome adjudication blinded to treatment allocation; and complete outcome reporting. Randomisation will assign participants 1 : 1 : 1 to standard care, aspirin or propranolol, stratified by the two predictors of the efficacy outcome [CCM location (brainstem vs. other) and prior ICH (yes vs. no)].[5]

CARE MAP statistical methods

Design

Three-arm, two-stage MAMS adaptive treatment selection design.

Sample size

Derived by co-applicant Parker using 5000 trials simulated in R (The R Foundation for Statistical Computing, Vienna, Austria) and nQuery v8.0 (Statistical Solutions, Saugus, MA, USA). nQuery v8.0 software was used to determine sample size and power for the interim analysis (based on the intermediate continuous outcome, change in CCM susceptibility on QSM MRI) and a simulation approach (using R software) was implemented for the survival outcome of time until first ICH/FND. The reason for using a simulation method for the ICH/FND outcome was to consider additional complexity involving changes to ICH/FND rates over the duration of follow-up and changes in recruitment rates over time; it was not possible to incorporate these elements into standard software such as nQuery.

We chose an intervention effect of 20% absolute difference in mean change in CCM susceptibility on QSM MRI as the intermediate outcome because this difference was deemed to be both clinically relevant and realistic by the collaboration, existing studies of QSM MRI, and the ongoing Atorvastatin Treatment of Cavernous Angiomas With Symptomatic Haemorrhage Exploratory Proof of Concept (AT CASH EPOC) RCT.[45] We chose an intervention effect of HR 0.35 on the efficacy outcome of time to first ICH/FND, which was conservative compared with the association between antithrombotic agents and lower risk of ICH/FND in our meta-analysis.[43]

Stage 1

The continuation criterion for each drug will be a statistically significant (one-sided 20% alpha) improvement over standard care in the mean reduction in MRI susceptibility between baseline and 1 year. By trial month 33, 447 participants will have been randomised 1 : 1 : 1

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to standard care, aspirin or propranolol and 383 will have reached 1-year follow-up. A conservative estimate of 20% attrition due to missing/failed acquisition of MRI gives an interim analysis sample size of 306 (102 per group). This provides 92% power to detect a 20% absolute difference in mean change in MRI susceptibility, assuming a standard deviation of 61% (data from an ongoing RCT; NCT02603328), ≤ 5% non-adherence to allocated drug and a two-group *t*-test. If both drugs meet the continuation criterion, the Data Monitoring Committee will select one drug to continue based on a holistic consideration of mechanistic, efficacy and safety outcomes. If neither drug meets the criterion, both would be dropped from the trial and drug(s) identified by the Intervention Prioritisation Committee would be added to the platform.

Stage 2

If one drug is selected, a further 256 participants will be randomised 1 : 1 to standard care or the selected drug (n = 277 per group in total). We estimate that 6% of participants will record an efficacy outcome of ICH or FND during follow-up in the standard care group (annual rate 4% per year after incident CCM diagnosis), based on their expected risk factor profile and the time between their most recent symptomatic presentation and randomisation.[5] Assuming 5% attrition in clinical follow-up, ≤ 5% non-adherence to treatment and a two-sided 5% significance level, simulations showed that 703 participants will provide 91% power to detect a HR of 0.35 on the efficacy outcome (or 85% power for a HR of 0.40), analysing by Cox proportional hazards (PH) model adjusting for recruitment stage and stratification criteria.

Analysis

Stage 1: We will analyse the intermediate outcome using a linear model, adjusting for the stratification variables and including a factor for randomised treatment. Stage 2: Cox Proportional Hazards model, adjusting for recruitment stage and stratification variables. Efficacy versus standard care reported as HR (95% CI). Mechanistic: We will explore heterogeneity of treatment effect by predicted risk using the stratification criteria, and according to genetic versus sporadic CCM, by testing for the interaction term in the Cox model. Since statistical power will be much lower for these interaction tests (approximately 42% to detect an HR of 0.35 for the sporadic vs. genetic CCM interaction test), we would interpret results (especially non-significant findings) with great caution and consider any observed effects as exploratory only. The relationship between the effect of randomised treatment on efficacy outcome and plasma biomarker change at 1 year will be assessed using mixed models for surrogate outcome evaluation.[68]

CARE MAP recruitment plan

Investigators at 27 NIHR HTA CARE pilot trial sites will recruit participants in inpatient/outpatient settings. Of the 160 people newly diagnosed with symptomatic CCM in the UK annually, 80% (n = 128) are not treated with neurosurgery or stereotactic radiosurgery.[69] We expect 50% to participate, for a recruitment rate of ~64 per year. We will enrol patients who were first diagnosed in the 5 years preceding the start of recruitment (n = 320) and incident patients during 6 years of recruitment (n = 383) for a total of 703 participants. Feasibility of recruitment is ensured by: engagement of the patient community by Cavernoma Alliance UK by PPI co-applicant Evans (> 3500 registered members) as we have done in the CARE pilot trial; identifying patients by screening clinical databases as sites did in the CARE pilot trial; broad inclusion criteria; low screen failure rates (due to infrequency of use of the two drugs); low anticipated attrition; and an extensive international collaboration (see *Table 3*) that could ensure or accelerate recruitment to target.

CARE MAP timeline (by month)

0–9: regulatory approvals, contracts, investigator training, initiate first site and SWAT
10–33: site set-up and recruitment
15: progression criteria (set-up and recruitment)
27: progression criteria (recruitment and international funding)
33: interim analysis of MAMS RCT and SWAT; assess drug pipeline and prioritise next drug(s)
34–81: complete recruitment
82: seek funding for new drug(s) to be added to the platform
82–93: complete follow-up
94–99: complete, analyse and disseminate aspirin/propranolol RCT; continue RCT with new drug(s)

CARE MAP study within a trial

Platform studies are complex, which might discourage potential participants, but an intervention to improve their understanding might increase recruitment. Interview-style videos improve participant understanding and satisfaction,[70] but no such SWAT in a platform study is in the SWAT Repository Store, so we will do a RCT of a video to improve understanding and recruitment to CARE MAP to generate generalisable learning about an efficient solution to a challenge of platform studies.

CARE MAP budget

The total budget was £5,320,242.12 research costs, £303,506.40 NHS support costs and £39,114.00 NHS excess treatment costs for a 99-month trial. The budget

covered central platform RCT set-up costs as well as activities at sites. We used the Schedule of Events Cost Attribution Tool for non-commercial research studies in the four UK nations to establish site-level costs and full costs per patient for a three-arm RCT in the UK. A key consideration for the budget estimation was the drug cost. We concluded that an open design would offer the best trade-off between cost and risk of bias; placebo control would increase research costs by ~£1.5 m. We considered the cost of drug accountability and compliance as well as shipment to participants. To enhance drug adherence and study retention, text message reminders were included. We costed QSM MRI and blood biomarkers. The MRI management budget included central scan management costs, and sites' radiology set-up costs to make sure compatibility with the imaging protocol as we all scan costs per participant at baseline and 1 year for interim analysis. The blood biomarker budget included DNA and plasma biomarker samples. The Edinburgh Clinical Trials Unit estimated trial management costs including staff salaries as well as study documents, database, archiving and consumables, subsistence for Trial Steering Committee, Data Monitoring Committee, PPI members and travel reimbursement for participants and staff.

A platform study will be an efficient foundation for a perpetual MAMS RCT (i.e. cheaper than separate parallel-group RCTs) of drugs to improve the outcome for people with this rare disease, who often have jobs, caring responsibilities and affected relatives.[4,71] Aspirin and propranolol are cheap drugs that are widely available; understanding their mechanism of action and efficacy will help prioritise therapeutic targets. Using QSM MRI as an early biomarker of drug effects reduces costs and accelerates drug discovery. We developed a budget for the platform infrastructure and costs of a MAMS RCT in the UK informed by experience.[72,73] The budget includes central costs of international coordination, which will be needed only if collaborators leverage international funding by the 2-year progression assessment.

Discussion

Following the submission of a stage 1 application to NIHR EME for CARE MAP on 3 May 2023, which had been informed by the development work in this CARE PREP NIHR EME Application Acceleration Award, the NIHR EME Funding Committee informed us that our outline application would not be invited to stage 2 on 21 July 2023, but they encouraged us to resubmit an outline application addressing their feedback (see *Limitations* below).

Lessons learnt

We found that an Application Acceleration Award was invaluable for growing collaboration and refining the experimental design for an ambitious, international, precision medicine platform trial for a rare design, with extensive PPI involvement. Having a clear project plan and deadline for a stage 1 submission provided a focus to accelerate the development of the proposal.

Patient and public involvement

The PAG were invaluable for: scoping recruitment networks; representing the patient/carer perspective when considering RCT design; recommending how to maximise equality, diversity and inclusion; confirming that a platform RCT is what patients and carers want; and identifying PPI networks to support a platform RCT. We achieved consensus about the design of CARE MAP in the time frame of the award. The PAG members worked effectively and independently, which was aided by their lived experience of PPI in other projects.

Limitations

The NIHR EME Funding Committee's feedback was that the Funding Committee:

1. Would have required further justification for use of QSM MRI as an outcome measure. We have identified further biomarker validation work supporting QSM MRI as an intermediate outcome measure,[74] Furthermore, we plan to add other, simpler intermediate outcomes to inform the treatment selection (CCM size on MRI and the frequency of the efficacy outcomes, above).
2. Would have suggested that further biomarker validation work was required before proceeding to a platform trial. Work validating QSM MRI as an intermediate outcome in RCTs of drugs for CCM is ongoing in the AT CASH EPOC trial.[45]
3. Would have required further information on the pipeline of interventions, including how many are known, how novel interventions would be identified and how they would be prioritised during the interim analysis. From the information provided, the committee was not convinced that there would be sufficient candidates available to justify a platform design on this topic at this time. There is an extensive pipeline of drugs for CCM, documented in a range of recent publications using a variety of approaches to repurposing drugs.[13,14,39,41,75]
4. Would have suggested that consideration was given to weighting randomisation in favour of the invention arms or using historical controls to overcome the issue of recruitment in this rare

disease. The statisticians who are co-designing CARE MAP with us confirmed in simulations that weighting the randomisation ratio would not improve power.

5. Would have required further consideration of how any changes in standard of care during the proposed platform trial would have affected results. We confirm that the comparator will be standard care that is contemporaneous with the intervention if there is a change over time (e.g. if drug interventions become part of standard care), so we plan to monitor standard care and document any changes over time for consideration in analyses.
6. Would have required clarification of the expected rate of efficacy outcome predicted in the standard of care arm and the reason for the stated disparity during the follow-up period versus the annual rate. We estimated that 3% of participants would experience an efficacy outcome during follow-up in the standard care group, based on their expected risk factor profile and the time between their most recent symptomatic presentation and randomisation.[5]
7. Would have suggested that a greater emphasis on Precision Medicine would have been desirable to fit the call brief. We have described our precision medicine approach by genotype and mechanism of action, but we do not have sufficient evidence to justify alternative or additional precision medicine approaches for CCM.
8. Would have suggested further work to engage and support early career researchers was required. We asked all international collaborators to identify early career researchers who could become involved, and would seek to do so if funded, but there was insufficient space to explain this in the application.
9. Would have required further reassurance that the international partners were fully committed to supporting this application. The international collaborators we describe above are fully committed, but there was insufficient space to explain this in the application.

The Funding Committee stated,

> *If you can respond to the above feedback, we would encourage you to re-apply to the EME Researcher Led call with a new Stage 1 application. In any future application, please consider whether your question is best answered as a platform, or another study design. Please also note that the other constraints of the previous call brief, specifically the need for precision medicine and international collaboration, would not be essential for a Researcher-led application, although this can still be included as appropriate.*

Future research

We will resubmit CARE MAP for funding to NIHR EME having addressed these limitations.

Conclusions

Key learning points

We have benefited from co-development and co-design of a MAMS platform RCT with extensive PPI involvement, including identification of international patient support networks, support for a platform RCT design, and discussion about the initial interventions in PAG meetings and focus groups with patients and carers. The availability of suitable intermediate phenotypes/outcomes remains a challenge, because evidence of their surrogacy for outcome prediction and treatment effect is often imperfect,[76] especially in rare diseases like CCM. International collaboration will be essential to delivering a platform RCT for CCM in a conventional grant duration, but multiagency funding will always be a challenge.

What this adds to existing knowledge

According to our Trial Register searches, CARE MAP remains the only known proposal for a platform RCT of drugs for CCM. We have identified some uncertainties that can inform future research, such as studies of validation and surrogacy of biomarkers and intermediate phenotype/outcomes. A platform RCT, and not just a MAMS RCT, is desirable for the international clinical and patient community, and would be an efficient approach to identifying an effective drug for CCM.

Additional information

CRediT contribution statement

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This article 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.

List of abbreviations

CARE	Cavernomas A Randomised Effectiveness

CARE MAP	Cavernomas A Randomised Efficacy MAster Protocol
CCM	cerebral cavernous malformation
EME	Efficacy and Mechanism Evaluation
FND	focal neurological deficits
HTA	Health Technology Assessment
ICH	intracerebral haemorrhage
IL	interleukin
MAMS	multiarm multistage
MRI	magnetic resonance imaging
NIHR	National Institute for Health and Care Research
PAG	Patient and public involvement Advisory Group
PPI	patient and public involvement
QSM	quantitative susceptibility mapping
RCT	randomised controlled trial
REC	Research Ethics Committee
SWAT	study-within-a-trial
VEGF	vascular endothelial growth factor

References

1. Al-Shahi Salman R, Kitchen N, Thomson J, Ganesan V, Mallucci C, Radatz M; Cavernoma Priority Setting Partnership Steering Group. Top ten research priorities for brain and spine cavernous malformations. *Lancet Neurol* 2016;**15**:354–5. https://doi.org/10.1016/S1474-4422(16)00039-9
2. Morris Z, Whiteley WN, Longstreth WT Jr, Weber F, Lee YC, Tsushima Y, *et al*. Incidental findings on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ* 2009;**339**:b3016. https://doi.org/10.1136/bmj.b3016
3. Flemming KD, Graff-Radford J, Aakre J, Kantarci K, Lanzino G, Brown RD, *et al*. Population-based prevalence of cerebral cavernous malformations in older adults: Mayo Clinic Study of Aging. *JAMA Neurol* 2017;**74**:801–5. https://doi.org/10.1001/jamaneurol.2017.0439
4. Al-Shahi R, Bhattacharya JJ, Currie DG, Papanastassiou V, Ritchie V, Roberts RC, *et al*.; Scottish Intracranial Vascular Malformation Study Collaborators. Prospective, population-based detection of intracranial vascular malformations in adults: the Scottish Intracranial Vascular Malformation Study (SIVMS). *Stroke* 2003;**34**:1163–9. https://doi.org/10.1161/01.STR.0000069018.90456.C9
5. Horne MA, Flemming KD, Su IC, Stapf C, Jeon JP, Li D, *et al*.; Cerebral Cavernous Malformations Individual Patient Data Meta-analysis Collaborators. Clinical course of untreated cerebral cavernous malformations: a meta-analysis of individual patient data. *Lancet Neurol* 2016;**15**:166–73. https://doi.org/10.1016/S1474-4422(15)00303-8
6. Al-Shahi Salman R, Berg MJ, Morrison L, Awad IA; Angioma Alliance Scientific Advisory Board. Hemorrhage from cavernous malformations of the brain: definition and reporting standards. Angioma Alliance Scientific Advisory Board. *Stroke* 2008;**39**:3222–30. https://doi.org/10.1161/STROKEAHA.108.515544
7. Josephson CB, Leach JP, Duncan R, Roberts RC, Counsell CE, Al-Shahi Salman R; Scottish Audit of Intracranial Vascular Malformations (SAIVMs) steering committee and collaborators. Seizure risk from cavernous or arteriovenous malformations: prospective population-based study. *Neurology* 2011;**76**:1548–54. https://doi.org/10.1212/WNL.0b013e3182190f37
8. Harris L, Poorthuis MHF, Grover P, Kitchen N, Al-Shahi Salman R. Surgery for cerebral cavernous malformations: a systematic review and meta-analysis. *Neurosurg Rev* 2022;**45**:231–41. https://doi.org/10.1007/s10143-021-01591-5
9. Poorthuis MHF, Rinkel LA, Lammy S, Al-Shahi Salman R. Stereotactic radiosurgery for cerebral cavernous malformations: a systematic review. *Neurology* 2019;**93**:e1971–9. https://doi.org/10.1212/WNL.0000000000008521
10. Akers A, Al-Shahi Salman R, Issam AA, Dahlem K, Flemming K, Hart B, *et al*. Synopsis of guidelines for the clinical management of cerebral cavernous malformations: consensus recommendations based on systematic literature review by the Angioma Alliance Scientific Advisory Board Clinical Experts Panel. *Neurosurgery* 2017;**80**:665–80. https://doi.org/10.1093/neuros/nyx091
11. CARE pilot trial collaboration. Feasibility of comparing medical management and surgery (using neurosurgical resection or stereotactic radiosurgery) with medical management alone for people with symptomatic cerebral cavernous malformation (CARE): a randomised, open, parallel group, pragmatic, pilot phase trial. *Lancet Neurol* 23:565–76. https://doi.org/10.1016/S1474-4422(24)00096-6
12. 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.

13. Gibson CC, Zhu W, Davis CT, Bowman-Kirigin JA, Chan AC, Ling J, *et al*. Strategy for identifying repurposed drugs for the treatment of cerebral cavernous malformation. *Circulation* 2015;**131**:289–99. https://doi.org/10.1161/CIRCULATIONAHA.114.010403
14. Chohan MO, Marchio S, Morrison LA, Sidman RL, Cavenee WK, Dejana E, *et al*. Emerging pharmacologic targets in cerebral cavernous malformation and potential strategies to alter the natural history of a difficult disease: a review. *JAMA Neurol* 2019;**76**:492–500. https://doi.org/10.1001/jamaneurol.2018.3634
15. Shenkar R, Moore T, Benavides C, Lightle R, Detter MR, Hobson N, *et al*. Propranolol as therapy for cerebral cavernous malformations: a cautionary note. *J Transl Med* 2022;**20**:160. https://doi.org/10.1186/s12967-022-03360-4
16. Oldenburg J, Malinverno M, Globisch MA, Maderna C, Corada M, Orsenigo F, *et al*. Propranolol reduces the development of lesions and rescues barrier function in cerebral cavernous malformations: a preclinical study. *Stroke* 2021;**52**:1418–27. https://doi.org/10.1161/STROKEAHA.120.029676
17. Li W, Shenkar R, Detter MR, Moore T, Benavides C, Lightle R, *et al*. Propranolol inhibits cavernous vascular malformations by beta1 adrenergic receptor antagonism in animal models. *J Clin Invest* 2021;**131**:e144893. https://doi.org/10.1172/JCI144893
18. Zuurbier SM, Hickman CR, Rinkel LA, Berg R, Sure U, Al-Shahi Salman R; Scottish Audit of Intracranial Vascular Malformations Steering Committee and Collaborators. Association between beta-blocker or statin drug use and the risk of hemorrhage from cerebral cavernous malformations. *Stroke* 2022;**53**:2521–7. https://doi.org/10.1161/STROKEAHA.121.037009
19. Lanfranconi S, Scola E, Bertani GA, Zarino B, Pallini R, d'Alessandris G, *et al*.; Treat-CCM Investigators. Propranolol for familial cerebral cavernous malformation (Treat_CCM): study protocol for a randomized controlled pilot trial. *Trials* 2020;**21**:401. https://doi.org/10.1186/s13063-020-4202-x
20. Gomez-Paz S, Maragkos GA, Salem MM, Ascanio LC, Lee M, Enriquez-Marulanda A, *et al*. Symptomatic hemorrhage from cerebral cavernous malformations: evidence from a cohort study. *World Neurosurg* 2020;**135**:e477–87. https://doi.org/10.1016/j.wneu.2019.12.035
21. Goldberg J, Jaeggi C, Schoeni D, Mordasini P, Raabe A, Bervini D. Bleeding risk of cerebral cavernous malformations in patients on beta-blocker medication: a cohort study. *J Neurosurg* 2018;**130**:1931–36. https://doi.org/10.3171/2017.12.JNS172404
22. Zabramski JM, Kalani MYS, Filippidis AS, Spetzler RF. Propranolol treatment of cavernous malformations with symptomatic hemorrhage. *World Neurosurg* 2016;**88**:631–9. https://doi.org/10.1016/j.wneu.2015.11.003
23. Reinhard M, Schuchardt F, Meckel S, Heinz J, Felbor U, Sure U, Geisen U. Propranolol stops progressive multiple cerebral cavernoma in an adult patient. *J Neurol Sci* 2016;**367**:15–7. https://doi.org/10.1016/j.jns.2016.04.053
24. Miquel J, Bruneau B, Dupuy A. Successful treatment of multifocal intracerebral and spinal hemangiomas with propranolol. *J Am Acad Dermatol* 2014;**70**:e83–4. https://doi.org/10.1016/j.jaad.2013.11.006
25. Berti I, Marchetti F, Skabar A, Zennaro F, Zanon D, Ventura A. Propranolol for cerebral cavernous angiomatosis: a magic bullet. *Clin Pediatr (Phila)* 2014;**53**:189–90. https://doi.org/10.1177/0009922813492885
26. Moschovi M, Alexiou GA, Stefanaki K, Tourkantoni N, Prodromou N. Propranolol treatment for a giant infantile brain cavernoma. *J Child Neurol* 2010;**25**:653–5. https://doi.org/10.1177/0883073810363917
27. Leaute-Labreze C, Hoeger P, Mazereeuw-Hautier J, Guibaud L, Baselga E, Posiunas G, *et al*. A randomized, controlled trial of oral propranolol in infantile hemangioma. *N Engl J Med* 2015;**372**:735–46. https://doi.org/10.1056/NEJMoa1404710
28. Shenkar R, Peiper A, Pardo H, Moore T, Lightle R, Girard R, *et al*. Rho kinase inhibition blunts lesion development and hemorrhage in murine models of aggressive Pdcd10/Ccm3 disease. *Stroke* 2019;**50**:738–44. https://doi.org/10.1161/STROKEAHA.118.024058
29. Shenkar R, Shi C, Austin C, Moore T, Lightle R, Cao Y, *et al*. RhoA kinase inhibition with fasudil versus simvastatin in murine models of cerebral cavernous malformations. *Stroke* 2017;**48**:187–94. https://doi.org/10.1161/STROKEAHA.116.015013
30. Mabray MC, Caprihan A, Nelson J, McCulloch CE, Zafar A, Kim H, *et al*. Effect of simvastatin on permeability in cerebral cavernous malformation type 1 patients: results from a pilot small randomized controlled clinical trial. *Transl Stroke Res* 2020;**11**:319–21. https://doi.org/10.1007/s12975-019-00737-4
31. Previch L, Lanzino G, Brown RD Jr, Flemming KD. The influence of select medications on prospective hemorrhage risk in patients with spinal or cerebral cavernous malformations. *World Neurosurg* 2022;**163**:e678–83. https://doi.org/10.1016/j.wneu.2022.03.101

32. Flemming KD, Kumar S, Brown RD Jr, Lanzino G. Predictors of initial presentation with hemorrhage in patients with cavernous malformations. *World Neurosurg* 2020;**133**:e767–73. https://doi.org/10.1016/j.wneu.2019.09.161

33. Gomez-Paz S, Salem MM, Maragkos GA, Ascanio LC, Enriquez-Marulanda A, Lee M, *et al*. Role of aspirin and statin therapy in patients with cerebral cavernous malformations. *J Clin Neurosci* 2020;**78**:246–51. https://doi.org/10.1016/j.jocn.2020.04.012

34. McDonald DA, Shi C, Shenkar R, Stockton RA, Liu F, Ginsberg MH, *et al*. Fasudil decreases lesion burden in a murine model of cerebral cavernous malformation disease. *Stroke* 2012;**43**:571–4. https://doi.org/10.1161/STROKEAHA.111.625467

35. De Luca E, Pedone D, Moglianetti M, Pulcini D, Perrelli A, Retta SF, Pompa PP. Multifunctional platinum@BSA-rapamycin nanocarriers for the combinatorial therapy of cerebral cavernous malformation. *ACS Omega* 2018;**3**:15389–98. https://doi.org/10.1021/acsomega.8b01653

36. Weinsheimer S, Nelson J, Abla AA, Ko NU, Tsang C, Okoye O, *et al*.; Brain Vascular Malformation Consortium Cerebral Cavernous Malformation Investigator Group*. Intracranial hemorrhage rate and lesion burden in patients with familial cerebral cavernous malformation. *J Am Heart Assoc* 2023;**12**:e027572. https://doi.org/10.1161/JAHA.122.027572

37. Denier C, Labauge P, Bergametti F, Marchelli F, Riant F, Arnoult M, *et al*. Genotype-phenotype correlations in cerebral cavernous malformations patients. *Ann Neurol* 2006;**60**:550–6. https://doi.org/10.1002/ana.20947

38. Shenkar R, Shi C, Rebeiz T, Stockton RA, McDonald DA, Mikati AG, *et al*. Exceptional aggressiveness of cerebral cavernous malformation disease associated with PDCD10 mutations. *Genet Med* 2015;**17**:188–96. https://doi.org/10.1038/gim.2014.97

39. Venugopal V, Sumi S. Molecular biomarkers and drug targets in brain arteriovenous and cavernous malformations: where are we? *Stroke* 2022;**53**:279–89. https://doi.org/10.1161/STROKEAHA.121.035654

40. Sone JY, Hobson N, Srinath A, Romanos SG, Li Y, Carrión-Penagos J, *et al*. Perfusion and permeability MRI predicts future cavernous angioma hemorrhage and growth. *J Magn Reson Imaging* 2022;**55**:1440–9. https://doi.org/10.1002/jmri.27935

41. Girard R, Li Y, Stadnik A, Shenkar R, Hobson N, Romanos S, *et al*. A roadmap for developing plasma diagnostic and prognostic biomarkers of cerebral cavernous angioma with symptomatic hemorrhage (CASH). *Neurosurgery* 2021;**88**:686–97. https://doi.org/10.1093/neuros/nyaa478

42. Perrelli A, Fatehbasharzad P, Benedetti V, Ferraris C, Fontanella M, De Luca E, *et al*. Towards precision nanomedicine for cerebrovascular diseases with emphasis on Cerebral Cavernous Malformation (CCM). *Expert Opin Drug Deliv* 2021;**18**:849–76. https://doi.org/10.1080/17425247.2021.1873273

43. Zuurbier SM, Hickman CR, Tolias CS, Rinkel LA, Leyrer R, Flemming KD, *et al*.; Scottish Audit of Intracranial Vascular Malformations Steering Committee. Long-term antithrombotic therapy and risk of intracranial haemorrhage from cerebral cavernous malformations: a population-based cohort study, systematic review, and meta-analysis. *Lancet Neurol* 2019;**18**:935–41. https://doi.org/10.1016/S1474-4422(19)30231-5

44. Lanfranconi S, Scola E, Meessen JMTA, Pallini R, Bertani GA, Al-Shahi Salman R, *et al*.; Treat_CCM Investigators. Safety and efficacy of propranolol for treatment of familial cerebral cavernous malformations (Treat_CCM): a randomised, open-label, blinded-endpoint, phase 2 pilot trial. *Lancet Neurol* 2023;**22**:35–44. https://doi.org/10.1016/S1474-4422(22)00409-4

45. Polster SP, Stadnik A, Akers AL, Cao Y, Christoforidis GA, Fam MD, *et al*. Atorvastatin treatment of cavernous angiomas with symptomatic hemorrhage exploratory proof of concept (AT CASH EPOC) trial. *Neurosurgery* 2019;**85**:843–53. https://doi.org/10.1093/neuros/nyy539

46. Akers AL, Ball KL, Clancy M, Comi AM, Faughnan ME, Gopal-Srivastava R, *et al*. Brain vascular malformation consortium: overview, progress and future directions. *J Rare Disord* 2013;**1**:5.

47. Kim H, Flemming KD, Nelson JA, Lui A, Majersik JJ, Cruz MD, *et al*. Baseline characteristics of patients with cavernous angiomas with symptomatic hemorrhage in multisite trial readiness project. *Stroke* 2021;**52**:3829–38. https://doi.org/10.1161/STROKEAHA.120.033487

48. Polster SP, Cao Y, Carroll T, Flemming K, Girard R, Hanley D, *et al*. Trial readiness in cavernous angiomas with symptomatic hemorrhage (CASH). *Neurosurgery* 2019;**84**:954–64. https://doi.org/10.1093/neuros/nyy108

49. Park JJH, Harari O, Dron L, Lester RT, Thorlund K, Mills EJ. An overview of platform trials with a checklist for clinical readers. *J Clin Epidemiol* 2020;**125**:1–8. https://doi.org/10.1016/j.jclinepi.2020.04.025

50. Park JJH, Siden E, Zoratti MJ, Dron L, Harari O, Singer J, *et al*. Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. *Trials* 2019;**20**:572. https://doi.org/10.1186/s13063-019-3664-1

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51. Rooshenas L, Scott LJ, Blazeby JM, Rogers CA, Tilling KM, Husbands S, *et al.*; By-Band-Sleeve study group. The QuinteT Recruitment Intervention supported five randomized trials to recruit to target: a mixed-methods evaluation. *J Clin Epidemiol* 2019;**106**:108–20. https://doi.org/10.1016/j.jclinepi.2018.10.004

52. Hague D, Townsend S, Masters L, Rauchenberger M, Van Looy N, Diaz-Montana C, *et al.*; STAMPEDE and FOCUS4 investigators. Changing platforms without stopping the train: experiences of data management and data management systems when adapting platform protocols by adding and closing comparisons. *Trials* 2019;**20**:294. https://doi.org/10.1186/s13063-019-3322-7

53. Rosenow F, Alonso-Vanegas MA, Baumgartner C, Blümcke I, Carreño M, Gizewski ER, *et al.*; Surgical Task Force, Commission on Therapeutic Strategies of the ILAE. Cavernoma-related epilepsy: review and recommendations for management – report of the Surgical Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 2013;**54**:2025–35. https://doi.org/10.1111/epi.12402

54. Tan H, Zhang L, Mikati AG, Girard R, Khanna O, Fam MD, *et al*. Quantitative susceptibility mapping in cerebral cavernous malformations: clinical correlations. *AJNR Am J Neuroradiol* 2016;**37**:1209–15. https://doi.org/10.3174/ajnr.A4724

55. Thorlund K, Golchi S, Haggstrom J, Mills E. Highly Efficient Clinical Trials Simulator (HECT): software application for planning and simulating platform adaptive trials. *Gates Open Res* 2019;**3**:780. https://doi.org/10.12688/gatesopenres.12912.2

56. Hummel J, Wang S, Kirkpatrick J. Using simulation to optimize adaptive trial designs: applications in learning and confirmatory phase trials. *Clin Invest* 2015;**5**:401–13. https://doi.org/10.4155/CLI.15.14

57. Morrell L, Hordern J, Brown L, Sydes MR, Amos CL, Kaplan RS, *et al*. Mind the gap? The platform trial as a working environment. *Trials* 2019;**20**:297. https://doi.org/10.1186/s13063-019-3377-5

58. Schiavone F, Bathia R, Letchemanan K, Masters L, Amos C, Bara A, *et al.*; past and present members of the STAMPEDE and FOCUS4 Trial Management Group. This is a platform alteration: a trial management perspective on the operational aspects of adaptive and platform and umbrella protocols. *Trials* 2019;**20**:264. https://doi.org/10.1186/s13063-019-3216-8

59. Pallmann P, Bedding AW, Choodari-Oskooei B, Dimairo M, Flight L, Hampson LV, *et al*. Adaptive designs in clinical trials: why use them, and how to run and report them. *BMC Med* 2018;**16**:29. https://doi.org/10.1186/s12916-018-1017-7

60. Cake C, Ogburn E, Pinches H, Coleman G, Seymour D, Woodard F, *et al.*; UK COVID-19 National Core Studies Consortium. Development and evaluation of rapid data-enabled access to routine clinical information to enhance early recruitment to the national clinical platform trial of COVID-19 community treatments. *Trials* 2022;**23**:62. https://doi.org/10.1186/s13063-021-05965-4

61. Greenhalgh T, Hinton L, Finlay T, Macfarlane A, Fahy N, Clyde B, Chant A. Frameworks for supporting patient and public involvement in research: systematic review and co-design pilot. *Health Expect* 2019;**22**:785–801. https://doi.org/10.1111/hex.12888

62. Choodari-Oskooei B, Thwin SS, Blenkinsop A, Widmer M, Althabe F, Parmar MK. Treatment selection in multi-arm multi-stage designs: with application to a postpartum haemorrhage trial. *Clin Trials* 2023;**20**:71–80. https://doi.org/10.1177/17407745221136527

63. Zeineddine HA, Girard R, Cao Y, Hobson N, Fam MD, Stadnik A, *et al*. Quantitative susceptibility mapping as a monitoring biomarker in cerebral cavernous malformations with recent hemorrhage. *J Magn Reson Imaging* 2018;**47**:1133–8. https://doi.org/10.1002/jmri.25831

64. Wildi S, Nager S, Akeret K, Özkaratufan S, Krayenbühl N, Bozinov O, *et al*. Impact of long-term antithrombotic and statin therapy on the clinical outcome in patients with cavernous malformations of the central nervous system: a single-center case series of 428 patients. *Cerebrovasc Dis* 2023;**52**:634–42. https://doi.org/10.1159/000529511

65. Marques LL, Jaeggi C, Branca M, Raabe A, Bervini D, Goldberg J. Bleeding risk of cerebral cavernous malformations in patients on statin and antiplatelet medication: a cohort study. *Neurosurgery* 2023;**93**:699–705. https://doi.org/10.1227/neu.0000000000002480

66. Girard R, Zeineddine HA, Koskimaki J, Fam MD, Cao Y, Shi C, *et al*. Plasma biomarkers of inflammation and angiogenesis predict cerebral cavernous malformation symptomatic hemorrhage or lesional growth. *Circ Res* 2018;**122**:1716–21. https://doi.org/10.1161/CIRCRESAHA.118.312680

67. Girard R, Fam MD, Zeineddine HA, Tan H, Mikati AG, Shi C, *et al*. Vascular permeability and iron deposition biomarkers in longitudinal follow-up of cerebral cavernous malformations. *J Neurosurg* 2017;**127**:102–10. https://doi.org/10.3171/2016.5.Jns16687

68. Renard D, Geys H, Molenberghs G, Burzykowski T, Buyse M, Vangeneugden T, Bijnens L. Validation of a longitudinally measured surrogate marker for a

time-to-event endpoint. *J Appl Statist* 2003;**30**:235–47. https://doi.org/10.1080/0266476022000023776

69. Moultrie F, Horne MA, Josephson CB, Hall JM, Counsell CE, Bhattacharya JJ, *et al.*; Scottish Audit of Intracranial Vascular Malformations (SAIVMs) steering committee and collaborators. Outcome after surgical or conservative management of cerebral cavernous malformations. *Neurology* 2014;**83**:582–9. https://doi.org/10.1212/WNL.0000000000000684
70. Taylor HA, Washington D, Wang NY, Patel HD, Ford DE, Kass NE, Ali J. Randomized comparison of two interventions to enhance understanding during the informed consent process for research. *Clin Trials* 2021;**18**:466–76. https://doi.org/10.1177/17407745211009529
71. Miller CE, Quayyum Z, McNamee P, Al-Shahi Salman R; SIVMS Steering Committee. Economic burden of intracranial vascular malformations in adults: prospective population-based study. *Stroke* 2009;**40**:1973–9. https://doi.org/10.1161/STROKEAHA.108.539528
72. Love SB, Cafferty F, Snowdon C, Carty K, Savage J, Pallmann P, *et al*. Practical guidance for running late-phase platform protocols for clinical trials: lessons from experienced UK clinical trials units. *Trials* 2022;**23**:757. https://doi.org/10.1186/s13063-022-06680-4
73. Wilson N, Biggs K, Bowden S, Brown J, Dimairo M, Flight L, *et al*. Costs and staffing resource requirements for adaptive clinical trials: quantitative and qualitative results from the Costing Adaptive Trials project. *BMC Med* 2021;**19**:251. https://doi.org/10.1186/s12916-021-02124-z
74. Hage S, Kinkade S, Girard R, Flemming KD, Kim H, Torbey MT, *et al*. Cavernous Angioma Symptomatic Hemorrhage (CASH) Trial Readiness II: imaging biomarkers and trial modeling. *medRxiv* 2023. https://doi.org/10.1101/2023.06.01.23290854
75. Snellings DA, Hong CC, Ren AA, Lopez-Ramirez MA, Girard R, Srinath A, *et al*. Cerebral cavernous malformation: from mechanism to therapy. *Circ Res* 2021;**129**:195–215. https://doi.org/10.1161/CIRCRESAHA.121.318174
76. DeMets DL, Psaty BM, Fleming TR. When can intermediate outcomes be used as surrogate outcomes? *JAMA* 2020;**323**:1184–5. https://doi.org/10.1001/jama.2020.1176

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