PROTOCOL

1 Full title of project

Accelerated development of Cavernomas: A Randomised Efficacy PRECision medicine Platform trial (CARE PREP)

2 Summary of research

Research questions:

- What is the optimal design of an international platform trial of precision medicine with drugs for cerebral cavernous malformations (CCM, also known as brain cavernomas)?
- Is delivery of the optimal platform trial design feasible?

Aims and objectives:

1. Consolidate and initiate international collaborations between CCM researchers, CCM patient and public involvement (PPI) groups, CCM research networks, and commercial partners.
2. Understand regulatory and governance requirements in collaborating countries.
3. 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.
4. Estimate the research, support and treatment costs of the platform trial.

List of abbreviations
CARE: Cavernomas: A Randomised Effectiveness trial
CCM: cerebral cavernous malformation
CTIMP: clinical trial of an investigational medicinal product
FND: focal neurological deficit
ICH: intracerebral haemorrhage
PPI: patient and public involvement
RCT: randomised controlled trial

Anticipated impact and dissemination:

This Acceleration Award will catalyse the design, delivery, and assessment of the feasibility of a protocol and funding application for the first CCM platform trial of drugs. We will produce monthly newsletters for collaborators and PPI groups, and release a final report.

3 Background and rationale

3.1 Why is this research needed now?

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 persist 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 NIHR HTA commissioned a pilot RCT comparing treatment with or without neurosurgery (or stereotactic radiosurgery) for CCM, which is the top uncertainty about the disease.[1] Lead Applicant Salman is the chief investigator of this Cavernomas: A Randomised Effectiveness (CARE) pilot trial, which has recruited 20 participants at 21 UK sites to date (www.ed.ac.uk/care-study) and will continue until August 2023. However, so far 71 eligible patients have been approached for consent

to CARE and the majority of the 52 (73%) eligible patients with symptomatic brain cavernoma who declined indicated a preference for treatment without surgery and would prefer a drug to prevent ICH/FND from CCM, but approved pharmacological therapies do not exist for CCM.

Several drugs might modify CCM prognosis based on studies that co-applicants have done with animal models, humans, drug repurposing,[11] or treatment target approaches.[12] The candidate drugs with the greatest **proof of concept** to date are:

- Propranolol and other beta-blockers, based on animal models,[13-15] human studies,[16-24] and by analogy with infantile haemangioma.[25]
- HMG CoA reductase inhibitors (statins), based on animal[26 27] and human studies.[16 28]
- Antithrombotic (anticoagulant or antiplatelet) drugs based on human studies.[29-31]

Other drug candidates include: combination of a statin and an antiplatelet drug based on human studies[31]; Rho-associated protein kinase inhibition with fasudil in animal models[26 32]; rapamycin in animal models[33]; non-steroidal anti-inflammatory drugs in human studies[30]; selective serotonin reuptake inhibitors in human studies[29]; vitamin D in human studies[29]; or fish oil in human studies.[29]

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. Our preliminary plan for a precision medicine approach will be to stratify participants 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), since the findings about drug effects in animal models are restricted to CCM genetic knockouts. Additional precision medicine targets for consideration during this award are molecular[34] and magnetic resonance imaging (MRI) biomarkers (quantitative susceptibility mapping [QSM] and dynamic contrast-enhanced quantitative perfusion [DCEQP])[35] that may indicate specific pathophysiological processes that could be targeted by particular drugs.[36 37]

Stratification criteria are planned to 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 create four prognostic categories according to CCM anatomic location and history of ICH.[5]

3.2 What is the knowledge gap this research will address?

A systematic review of publications in OVID Medline and Embase to 30 June 2022 with literature search terms for CCM used by the Lead Applicant's 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 (see 3.1 above), proof of concept in human cohort studies (including the Lead Applicant's prospective, population-based inception cohort study[16]) seems strongest for beta-blocker, statin, and antithrombotic (antiplatelet or anticoagulant) drugs:

Cohort study	Participants (number)	Intervention	Comparator	Outcome	Association with outcome
Goldberg et al. 2018[19]	Any CCM (n=408)	Any beta-blocker	No beta-blockers	ICH	HR 1.19 (95% CI 0.49-2.90)
Gomez-Paz et al. 2020[18]	Any CCM (n=438)	Any beta-blockers	No beta-blockers	ICH	OR 0.71 (95% CI 0.39-1.30)
Zuurbier et al. 2022[16]	Any CCM (n=300)	Any statin	No statin	ICH/FND	aHR 0.37 (95% CI 0.01-1.07)
Zuurbier et al. 2022[16]	Any CCM (n=300)	Any beta-blocker	No beta-blockers	ICH/FND	aHR 0.09 [95% CI, 0.01-0.66
Zuurbier et al. 2019[38]	Any CCM (n=1,342 meta-analysis)	Any antithrombotic drug	No antithrombotic drugs	ICH	RR 0.25 (95% CI 0.13-0.51)

A search of ClinicalTrials.gov on 30 June 2022 identified six relevant RCTs. Two proposed RCTs of Propranolol (NCT03474614 and NCT03523650) never began. Two phase 2 RCTs have completed: one showed a non-significant effect of simvastatin on MRI permeability of CCM,[28] and the other showed a promising effect of Propranolol on new ICH or FND (HR 0.43, 80%CI 0.18-0.98; under review by *The Lancet Neurology*).[17] There are two ongoing phase 2 RCTs of Atorvastatin[39] and REC-994 (a superoxide scavenger)[11] for CCM, but these small parallel group RCTs will not be definitive. **A novel approach that will determine drug effects on CCM definitively and quickly is an international precision medicine platform RCT.**

Identifier	Lead author (role in this application)	Intervention *vs* comparator	Target sample size	Status	Sample size achieved
NCT01764451	Mabray (including co-applicant Kim)[28]	Simvastatin *vs* standard care	12	Complete	12
NCT03589014	Latini (co-applicant)[17]	Propranolol *vs* standard care	60	Complete	83
NCT02603328	Awad (co-applicant)[39]	Atorvastatin *vs* placebo	80	Ongoing	-
NCT05085561	Recursion Pharmaceuticals (collaborator)[11]	REC-994 400mg *vs* 200mg *vs* placebo	60	Ongoing	-

Altogether, proof of concept from animal models, human cohort studies[16 38] in sporadic and familial CCM, and pilot phase RCTs in humans with familial CCM[17 28] 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.

4 Aims and objectives

4.1 Consolidate and initiate international collaborations between researchers, CCM patient and public involvement (PPI) groups, CCM research networks, and commercial partners.

4.2 Understand regulatory and governance requirements across collaborating countries.

4.3 Finalise a protocol for an efficient, international platform trial of precision medicine with antithrombotic, beta-blocker, and statin drugs for CCM, which is feasible; acceptable to patients and regulators; and has a hypothesis-driven mechanistic component.

4.4 Estimate the budget for research, support and treatment costs of the platform trial.

5 Research plan / methods

5.1 International collaboration

This award will consolidate existing collaborations and initiate a novel, all-inclusive collaboration of researchers and PPI co-applicants for the first platform RCT for CCM. Co-applicants have prior experience (Kim),[28] recent experience (Latini),[17] and ongoing experience (Salman, White, Lee, Kim and Awad) of CCM RCTs. During the award, we will identify 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, or are involved in the Cavernous Angioma With Symptomatic Haemorrhage [CASH] trial readiness project[40 41]). We will establish the number of sites in each network, annual caseload, recruitment rates based on recent and ongoing drug RCTs for CCM,[17 41] and any competing RCTs. International involvement will ensure the feasibility of rare disease recruitment, generalisability and investigate the external validity of UK findings.

5.2 Regulatory and governance requirements

The trial manager will work with our international collaborators' research governance departments and Sponsors to understand the local regulatory requirements for the conduct of platform RCTs

involving licensed and unlicensed drugs in phase 2 (safety and dose-finding) and phase 3 (efficacy) clinical trials of investigational medicinal products (CTIMPs). Decisions about a single or modular master protocol, trial conduct,[42] operational aspects,[43] and data management[44] will be informed by longstanding platform RCTs and the lived experience of the PPI Advisory Group.

5.3 Protocol for a precision medicine platform trial

We intend for this platform RCT to be an efficient strategy for evaluating many drugs concurrently[45] and provide proof of clinical efficacy, effect size, and safety with a precision medicine approach to RCT design and stratification of the analysis. We will reach consensus about the uncertainties that we face about the first international, precision medicine platform trial for CCM (see flow diagram):

Research design: Having considered the proof of concept for the potential drug therapies, and information from the pilot phase RCTs,[17 28] we will agree the type of adaptive platform biomarker-guided trial design (BiGTeD), most likely a multi-arm, multi-stage (MAMS) RCT (see flow diagram). We will consider whether to stop treatments for futility or efficacy, and whether we will re-estimate sample size at interim analyses. We will agree the aspects of inter-individual variability that may influence treatment effects as well as pragmatic considerations (e.g. current use 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: The eligibility criteria will be broad to increase inclusion, and we will consider how to maximise and record equality and diversity (e.g. age, sex, ethnicity, disability) with the PPI Advisory Group, whilst allowing stratification factors to permit investigation of specific effects in sub-groups. We will apply what we have learned about successful approaches to this patient group in the ongoing NIHR HTA CARE pilot trial via an embedded QuinteT Recruitment Intervention.[46] We will assess the suitability of data platforms for identifying participants and detecting clinical outcomes, according to their adoption of the recent ICD-11 revision, which is the first to include a code for CCM (8B22.41). The PPI Advisory Group and co-applicants leading CCM RCTs will plan support for participants, data capture from them,[44] and minimising drop-out.

Interventions: We will agree which drugs will be the first to be evaluated, and estimate likely adherence and attrition based on other CCM RCTs.[17 39] We have identified one industry collaborator (Recursion Pharmaceuticals; see 3.2 above) and will take an un-biased, systematic approach to identifying others (e.g. Neurelis Inc. NRL-1049), supported by Edinburgh Innovations (attached). We will investigate 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 will review knowledge about the dosing of drugs (e.g. propranolol[13]) to determine whether the platform must include both phase 2 and phase 3 RCTs. We will consider the risk of performance and detection biases when deciding whether the platform RCT should use placebo or open control, consider evolution of standard care, and consider the use of combinations of drugs.

Assignment: We will use web-based randomisation with allocation concealment from researchers to assign treatments. We will decide on 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: Whilst the major clinical outcomes of interest (ICH, FND, and epileptic seizures) are well defined,[6 47] we will monitor the validation of disease-specific measures of global outcome that are still under development (e.g. CCM Health Index). We are interested to understand mechanism of treatment effect via intermediate phenotypes, such as co-applicant Awad's use of quantitative susceptibility mapping on brain MRI to quantify haemosiderin leakage by CCM and other circulating biomarkers,[36] and whether these are surrogate markers of clinical outcomes.[48]

Statistical analyses: Co-applicant Weir and a senior statistician will simulate across a range of platform trial scenarios, agreed in consultation with the co-applicants and PPI Advisory Group, according to variations in the choice of platform/adaptive design, Bayesian/frequentist approach, participant eligibility criteria, number of interventions, outcome type/frequency/distribution, and sample size needed to explore heterogeneity of effects in sub-groups by stratification criteria.[49 50] These simulations will help determine the most efficient platform trial design, define its operating characteristics, and its deliverability according to the recruitment base established (see 5.1 above).

Mechanistic component: A key objective of the efficacy platform RCT will be to embed hypothesis-testing mechanistic studies to understand mechanism of action of the interventions, causes of differing responses, and whether intermediate phenotypes are reliable surrogate outcomes. Ultimately, we intend to gain extra insight from these observations in humans by exploring their mechanistic pathways in CCM animal models ('reverse translation').

5.4 Estimate budget for the precision medicine platform trial

We will use published examples,[42-44] our own experience,[51] and projections for the international scope of the efficacy platform RCT to estimate the budget required for international coordination, UK conduct, and international conduct, focussing on value for money and design efficiencies.[52]

6 Dissemination, outputs and anticipated impact

We will produce a short report reflecting the achievement of our aims, including learning generalisable to the planning, setup and conduct of international platform studies, such as differences in contemporary regulatory approaches. We will finalise a protocol for the CCM platform trial by month 8 of the award in order to submit a stage 1 NIHR EME application by May 2023. We will work with PPI co-applicants to produce a report of our findings in plain English, and disseminate these as updates after each 2-monthly PPI Advisory Group meeting and as a final report at meetings of the PPI organisations in countries supporting the international platform RCT.

7 Project / research timetable:

Year:	**2022**				**2023**												**2024**			
Month:	**Sep**	**Oct**	**Nov**	**Dec**	**Jan**	**Feb**	**Mar**	**Apr**	**May**	**Jun**	**Jul**	**Aug**	**Sep**	**Oct**	**Nov**	**Dec**	**Jan**	**Feb**	**Mar**	**Apr**
Month of this award:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**								
NIHR HTA CARE trial																				
Collaborators meet online																				
Team meets face-to-face																				
PPI Advisory Group																				
Commercial partnerships																				
Regulatory requirements																				
Funding agencies																				
Clinical research networks																				
Protocol development																				
Final protocol and budget																				
NIHR stage 1 submission																				
CARE PREP newsletter																				
Project report																				
NIHR stage 2 submission																				
NIHR stage 2 decision																				
CARE PREP starts																				

8 Project management

Chief investigator: Leadership, protocol development and delivery, grant application. **Trial manager:** delivery of the project plan, coordination of co-applicants and collaborators, scoping of

regulatory requirements and funding available, dissemination via newsletters. **PPI Advisory Group:** Consideration of patient preferences, EDI, and trial design. **Co-applicants:** Attendance at monthly online meetings and one face-to-face meeting (International CCM Scientific Meeting, North Carolina, USA, 17-18 November 2022), guidance on regulatory requirements, identification of potential funding sources, connection with clinical research networks. **Statistician:** Leadership on methodological aspects of the platform trial design and protocol, and supervision of simulation analyses. **Edinburgh Innovations and Tech Transfer office:** commercial partnerships.

9 Ethics/regulatory approvals

We will scope the regulatory and governance approvals, their timelines, costs and any conflicts that would require resolution for a single, unified CARE PREP protocol to apply in participating countries. We will resolve any contractual, intellectual property, and financial considerations about commercial partnerships. Regulatory approvals are not needed for this accelerator award.

10 Project/research expertise

SALMAN: Clinical director of Edinburgh Clinical Trials Unit (ECTU) and the UKCRC network of registered CTUs. Chief investigator of the ongoing NIHR HTA CARE pilot trial (ISRCTN41647111), ENRICH-AF trial (NCT03950076), TRIDENT trial (NCT02699645), and ASPIRING pilot trial (NCT04522102). Trial steering committee member for the Treat_CCM trial (NCT03589014). Clinical expertise in CCM, stroke, and neurology. **WEIR:** Trial statistician for several adaptive (DEXFEM NCT01769820) and platform (MND-SMART NCT04302870) RCTs. Co-lead of the Outcomes Working Group of the MRC-NIHR Trials Methodology Research Partnership. Academic expertise in medical statistics and clinical trials methodology, with a focus on adaptive trial designs and evaluation of surrogate outcomes. **WHITE:** Carer of wife with symptomatic CCM. Trustee and Treasurer of Cavernoma Alliance UK (CAUK). Chair Patient Advisory Group, CARE pilot trial. Founder member and UK representative in the informal network of patient organisations, European Cavernoma Alliance. Retired (2009). Currently working as honorary CEO of CAUK. **BERGHOLTZ:** Patient with CCM. Chair and CEO of Cavernöst Angiom Sverige. Initiator / Swedish representative in the informal network of patient organisations, European Cavernoma Alliance. Patient representative at Gothenburg University for a mapping review of systematic reviews on PPI in healthcare. Patient representative at Rare Diseases Sweden. **LEE:** Founder/CEO of Alliance to Cure Cavernous Malformation. Carer. Clinical Advisory Board member: Recursion REC-994 Sycamore Trial (NCT05085561), Treat_CCM (NCT03589014), CASH Trial Readiness (NCT03652181). Organizer, annual International CCM Scientific Meeting. DEI and recruitment expertise. **LATINI:** Head of the Department of Cardiovascular Medicine, of the Mario Negri Institute since 2013, expert in cardiovascular pharmacology. Trial Steering Committee for several RCTs (ALOFT, ValHeFT, GISSI-HF, GISSI-AF, CandHeart, CYCLE, ALBIOS, ICOS-ONE, REBOOT), including Treat_CCM (NCT03589014), the first completed pilot phase RCT of propranolol for CCM. **KIM:** Research expertise in vascular malformations, including CCM, clinical and genetic epidemiology, and conducting clinical/translational research studies. Principal investigator of the ongoing NIH-funded Brain Vascular Malformation Consortium, which includes a longitudinal cohort study of familial CCM (NCT01764529) and funds pilot drug trials for CCM (NCT01764451). **AWAD:** Researcher who has identified several CCM-related signalling aberrations, therapeutic targets and biomarkers. He leads the largest CCM clinical centre of excellence in the USA (http://uchicagomedicine.org/ccm). PI of several USA NIH/NINDS-funded projects, including a multisite trial readiness initiative for CCM and the ongoing AT CASH EPOC RCT (NCT02603328).

11 Success criteria and barriers to proposed work

11.1 Measurements of success: Quorate attendance at collaborator and PPI Advisory Group meetings; timely completion of all milestones in section 7; design of a protocol that will satisfy all international regulatory requirements; agreement about final protocol; submission of a feasible and affordable stage 1 application to NIHR EME.

11.2 Risks and intended mitigations: Lack of agreement about final protocol, mitigated by achieving consensus; insufficient international coverage amongst the collaboration to be funded or feasible, mitigated by involving additional collaborators.

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