Trial Readiness in Cavernous Angioma with Symptomatic Hemorrhage (CASH)

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Principal Investigator: Dr. Issam Awad, Dr. Kelly Flemming, Dr. Helen Kim

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Trial Readiness in Cavernous Angiomas with Symptomatic Hemorrhage
Study Description:	This U01 project will address gaps in knowledge and barriers to clinical trial readiness in cerebral cavernous angioma patients with recent symptomatic hemorrhage (CASH)
Objectives:	Primary Objectives: 1. To assess enrollment rates, harmonize data and determine baseline characteristics of patients with CASH across sites 2. MRI Biomarker Validations 3. Rate of recurrent symptomatic hemorrhage over 2 years in patients with CASH. Secondary Objectives: Functional status of CASH cases at enrollment and during follow-up; impact of bleed on functional status
Endpoints:	Primary Endpoint (Aim 3): • Recurrent bleeding during follow-up, homogeneity in years 1 and 2 Secondary Endpoints (Aim 3): • Biomarker changes during follow-up, homogeneity in years 1 and 2 • Functional status and quality of life change in years 1 and 2 compared to baseline
Study Population:	Adult patients with cerebral cavernous malformations (CCMs) who have had a symptomatic hemorrhage within the prior year, where the bleeding lesion has not been excised or radiated
Phase:	Trial readiness
Description of Sites/Facilities Enrolling Participants:	Seven high volume cavernous angioma clinical centers University of Chicago, Mayo Clinic, University of Utah, University of New Mexico, Barrow Neurological Institute and University of San Francisco and Johns Hopkins University. Additional sites may be added as needed to reach enrollment goals.
Description of Study Intervention:	This is an observational cohort study of CASH cases with no intervention.
Study Duration:	The study will last 5 years.
Participant Duration:	Patients enrolled in the Screening and Clinical Assessment (SCA) arm will have a single, baseline visit. Patients enrolled in the Follow-up and

Biomarker Validation (FUBV) arm will have a baseline visit, along with two yearly follow-up visits, for a total of 3 visits. This is an observational study and all study visits can be completed remotely via telephone and/or telemedicine platforms.

In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions

1.2 SCHEMA

Timeline of study visit and procedures performed.	**Baseline**	**1 year** (12 months ± 1 month)*	**2 year** (24 months ± 1 month)*
Type of Visit	In Person/Remote	In Person/Remote	In Person/Remote
Informed Consent	X		
Baseline clinical and radiographic data	X		
Verify clinical features (timing of prior SH,	X	X	X
mRS score assessment	X	X	X
EQ-5D questionnaire	X	X	X
PROMIS29	X	X	X
NIH stroke scale	X	X	X
QSM/DCEQP MRI sequences*	X	X	X
MRI standard sequences*	X	X	X

(*) to be performed on subset of cases in the FUBV arm

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening	Enrollment/baseline	**1 year** (12 months ± 1 month)*	**2 year** (24 months ± 1 month)*

Type of Visit	In Person/Remote	In Person / Remote	**In Person/Remote**	**In Person/Remote**
Informed consent	X			
Demographics	X			
Medical history	X			
Verify clinical and radiographic data		X	X	X
Physical exam		X	X	X
Vital signs		X	X	X
Height		X	X	X
Weight		X	X	X
mRS score assessment		X	X	X

EQ-5D questionnaire		X	X	X
PROMIS29		X	X	X
NIH Stroke Scale		X	X	X
QSM/DCEQP MRI sequences*		X	X	X
MRI standard sequences*		X	X	X

(*) to be performed on subset of cases in the FUBV arm

For this trial, some sites will recruit subjects for the SCA arm only while other sites recruit subjects for the FUBV arm. Subjects who are screened for the FUBV arm and do not qualify, will be screened and offered potential enrollment in the SCA study arm, if applicable.

Subjects enrolled in the SCA arm will have one visit only: the baseline visit. It is anticipated the visit will last less than an hour and include consenting, medical and radiographic history review, a physical, vitals and neurological assessments. The visit information and neurological assessments will be completed via interview with the site coordinator who will enter the data into the electronic case report forms. Subjects enrolled in the SCA arm will not have a standard MRI done at the baseline visit. Instead, data will be collected from their latest MRI scan, from which the CASH lesion was identified.

Subjects enrolled in FUBV arm will have three study visits: Baseline, Year 1 and Year 2. It is anticipated that each visit will last about 2 hours. The visits will include consenting (Baseline only), medical and radiographic history review, a physical, vitals and neurological assessments. The visit information and neurological assessments will be completed via interview either in person or via telephone with the site coordinator who will enter the data into the electronic case report forms. Subjects will have a standard MRI with additional research sequences. MRI with the additional research sequences will be completed when the participant has a regularly scheduled standard of care appointment. The MRI sequences include T1, T2, SWI/VenBold, and post-contrast scans. The research MRI sequences are QSM and DCEQP sequences. No additional gadolinium is required for the additional research sequences.

Subjects will not be compensated for their participation. A large percentage of subjects will be coming in as part of their clinical care and we do not anticipate special costs for subjects for these visits. To promote retention and follow up visit compliance, subjects enrolling in the FUBV arm will receive travel reimbursement for each of the 3 study visits.

Data elements to be collected include: the subject's age, gender, race and disease-related history. We will also collect information about their clinical MRI scans, including the number of lesions seen on the scan, as well as, (for FUBV subjects,) the MRI QSM and permeability values, calculated during post-processing. This data will be shared with the DCC. Any personal identifiers, including the subject's name, date of birth, and medical record number, will be held locally, separately from the study file, in locked cabinets in private offices per institutional guidelines.

2 INTRODUCTION

2.1 STUDY RATIONALE

There are fewer than 200,000 cases of brain cavernous angiomas (CA) in North America today who have suffered a symptomatic hemorrhage (SH). Cavernous angiomas with symptomatic hemorrhage (CASH) are most likely to re-bleed and cause further neurologic sequelae. Among these are smaller cohorts of CASH with different genotypes, lesion locations, or other characteristics portending variable disease severity or prospective risk. Surgical resection of CASH is associated with substantial morbidity and cost, particularly in deep and brainstem lesions, which are also more likely to bleed, and cause serious disability. **It would be desirable to develop a drug that stabilizes CASH, and prevent recurrent bleeding.** CASH with recent bleed, where surgical resection is not undertaken, are the most likely cases to be followed expectantly per current evidence based guidelines, with **clinical equipoise for testing novel therapies to prevent re-bleeding**.

Candidate Therapeutics Under Development. Several candidate therapeutics have emerged in recent years, aimed at targeting signaling aberrations related to the loss of CCM gene function, and associated vascular permeability, angiogenic activity and inflammatory response. Several drugs have already been shown to prevent lesion development or hemorrhage in preclinical experiments meeting the most stringent NINDS criteria of rigor and objectivity. Novel agents are being pursued by the pharmaceutical industry specifically for this disease, and are currently at various stages of development. Other drugs in current clinical use for other applications are being explored for proof of concept effect, with the aim of potential repurposing. All these candidate drugs will ultimately require dose optimization and testing of safety and efficacy in multi-site clinical trials.

Opportunities in Clinical Research. Much progress has been made in understanding the epidemiology and natural history of CAs, and several outcome assessment tools have been proposed, including an adjudicated definition of SH during clinical follow-up. Advanced magnetic resonance imaging techniques have applied dynamic contrast enhanced quantitative perfusion (DCEQP) and quantitative susceptibility mapping (QSM) to measure vascular leak and lesional iron content in CAs, and these have been linked to clinical activity in longitudinal follow-up, holding promise as sensitive biomarkers of lesional hemorrhage. There is a strong collaborative culture among major researchers in this disease, catalyzed by a very engaged patient advocacy and support group, the Angioma Alliance.

Gaps in Trial Readiness. Established CA research databases have not considered CASH specifically. The ability to screen and enroll cases with CASH, particularly those whose lesion has not been resected, has never been assessed at multiple sites, nor the spectrum of their baseline characteristics, including time from SH, hemorrhagic lesion location, disability status, and demographic features such as gender. Quality of life (QOL) has never been systematically evaluated in CAs, and it is unclear what functional status instruments best capture the clinical impact of CASH. Biomarkers of vascular permeability and iron leak in CAs have never been deployed or validated at multiple sites using uniform protocols. These and

clinical outcomes instruments have not been harmonized, nor evaluated for their relative sensitivity and reliability, yet are essential to the planning of needed clinical trials. Without this information, clinical trials could use false assumptions and likely fail.

In response to these gaps in trial readiness, we propose **Specific Aim 1** to harmonize data entry, and to assess detection rates and baseline characteristics of CASH cases at multiple sites with high volume and clinical interest in CAs. **Specific Aim 2** shall deploy rigorous tests of feasibility, accuracy, precision and reproducibility of biomarker measurements at multiple sites, critical to their potential application as surrogate outcomes in clinical trials. **Specific Aim 3** shall assess rates of clinical events versus changes in biomarkers and functional status/QOL measures during prospective follow-up. Leading CA research teams have been assembled with expertise in the questions being tackled, including rigorous statistical approaches, sample size estimates, and a data coordinating center with a proven record in trial planning and execution. An Executive Committee with broad expertise will advise and make suggestions regarding trial design, data capture and collection as a collaborative effort with NINDS. They will offer suggestions prior to and during the progress of each aim, propose revisions, help us interpret emerging results, and ultimately approve and prioritize workable trial models. There is no DSMB for this non-interventional trial.

Specific milestones are proposed and go/no-go decisions based on interim analyses and results of these aims. Data from this project will insure the most stringent rigor in trial assumptions, including validated detection rates and baseline features specific to CASH. We will endorse or reject outcome instruments or biomarkers based on empiric observations, hypothesizing a clinically meaningful impact of putative therapies. And we will determine the sample size, cogent stratification for relevant subgroups, length of follow-up, and the number of sites needed to test trial hypotheses. Corollary goals are to ready pilot sites with expertise in these facets of disease evaluation and follow-up, to be deployed and emulated in prospective clinical trials. Other goals are to complete preparatory and regulatory milestones needed before launching actual trials, and to assemble research core teams who would oversee and manage prospective trials. Such a comprehensive project has never been undertaken in this disease. The timing cannot be more opportune, with therapeutic targets identified, unmatched collaboration among stakeholders, and several drugs ready to benefit from the proposed trial readiness.

2.2 BACKGROUND

Cavernous Angioma: A Common Lesion, an Uncommon Disease. Cavernous angioma (CA) of the brain is also referred to in the literature as cerebral cavernous malformation (CCM), hemangioma or cavernoma. The lesion consists of clustered, giant, blood-filled capillary spaces (“caverns”), lined by endothelium, and separated by an amorphous matrix lacking mature vessel wall angioarchitecture[1]. CA occurs in a sporadic form, manifesting a solitary lesion or a cluster of lesions associated with a venous developmental anomaly[2]. The disease is familial in 20-30% of cases, associated with multiple lesions that develop over time throughout the patient’s brain[3]. The familial form (OMIM #116860;

http://omim.org/entry/116860) exhibits a Mendelian autosomal dominant inheritance due to a heterozygous loss-of-function mutation in one of 3 genes (*CCM1*/*KRIT1*, *CCM2*/*Malcavernin*, and *CCM3*/*PDCD10*)[4-10]. Multiple cavernomas may also develop after cranial irradiation. Magnetic resonance imaging (MRI) is the hallmark diagnostic modality for these lesions, including sequences revealing chronic and acute hemorrhage, and tiny occult lesions. CAs are histologically identical in familial and sporadic cases, and harbor somatic mutations in the same three genes[11-13].

CAs are often detected incidentally, or in association with seizures or non-specific symptoms[14-16]. The natural history of such lesions is exceedingly benign, with <0.5% annual risk of clinically significant hemorrhage, and there is consensus about these cases not needing interventions beyond symptom management and surveillance[17]. But once a lesion has manifested a symptomatic hemorrhage (SH), its untreated clinical course is quite serious, with a 42% (CI 27-58) rate of recurrent bleeding or focal neurologic deficit within 5 years[17-19]. CASH is hence a singular clinical entity, distinguishing lesions with a unique risk profile, impacting a patient's life and meriting clinical intervention. The adjudicated definition of CASH[20] requires diagnostic evidence of new lesional bleeding or hemorrhagic growth, in association with directly attributable symptoms.

Lesions in the brainstem and deep brain locations are more likely than other CAs to bleed[21], rebleed[18], and cause severe disability[19, 22]. It is unclear if this greater propensity to SH simply reflects the clinical impact of bleeds in those locations, while lesions in less eloquent brain regions may bleed at similar rates but more likely without symptoms. Per current clinical practice and evidence-based guidelines, CAs are typically observed expectantly, and surgically excised only *after significant clinical sequelae* (typically one or more hemorrhagic strokes) particularly in deep or brainstem locations[17, 23]. Healthcare costs of hemorrhagic stroke can reach up to $27,400/case in the first 90 days (2007 dollars), excluding socioeconomic impact of lost productivity[24].

While brain surgery for lesion excision may benefit some patients, it can be associated with significant cost and morbidity. It is expensive, with a typical craniotomy costing $37,438 in 2011 dollars[25], excluding the cost of complications. More concerning are complications and morbidity with CA surgical excision, particularly with brainstem lesions, associated with a particularly alarming rate of surgical adverse events[23]. In a non-randomized population-based cohort study, lesion excision was associated with significantly worse functional outcomes and greater complications compared to conservative management[23]. Stereotactic radiosurgery has been proposed but there is controversy about its effectiveness and concern about complications and radiation-induced genesis of new CAs[26, 27].

The rates of development of new lesions, and of first SH in asymptomatic CAs, are far too low to allow meaningful testing or to compel primary prevention strategies for CASH. Cases with recent SH, where surgical resection is not undertaken (mostly in deep and brainstem locations), are the most likely to be followed expectantly per current evidence based guidelines[17], with clinical equipoise for testing novel therapies aimed at preventing re-bleeding. It would be desirable to develop a drug that stabilizes CASH, and prevent recurrent bleeding. It would mitigate neurologic sequelae of re-bleeds and the complications of surgical resection in many patients. Based on current knowledge of natural history, the

likelihood of therapeutic benefit for secondary prevention (symptomatic re-bleed) would be greatest within 2-3 years after a SH[17-19].

2.3 RISK/BENEFIT ASSESSMENT

This is an observational cohort study with no planned intervention.

Risks to participants of this study are minimal and include loss of privacy and confidentiality, and risks associated with MRI and intravenous gadolinium administration. To minimize risk to participants, follow up visits have the option of being done remotely. Visits that require MRI scans, the scans will be completed during the participants standard of care visit. Protection against these minimal risks shall be insured by each site's PI and the project's central institutional review board (cIRB).

Protection against loss of privacy and confidentiality. The main risk to study participants is loss of privacy, which is minimized through utilization of sound confidentiality procedures. All study personnel will undergo certification on the protection of human subjects, currently through CITI, as well as HIPAA certification. All study records will be kept locally in locked files in private offices. Electronic files will be kept on secured drives managed at each institution, with access limited to key study personnel. All study data will be entered on a secure, password-protected database managed by the Data Coordinating Center at Johns Hopkins University.

Reasons for exclusion for screened patients not enrolled into the trial will be recorded. Each participating site will enter screening data into the trial's EDC system for review of screening and eligibility performance. Data to be collected for screen failed patients will include, age (numerical), gender, race, type of disease (sporadic or familial), and reason for exclusion from the study. Once all fields are completed, or an inclusion/exclusion criterion is failed, the system will either document the subject as a screen failure or prompt the coordinator to enroll the eligible subject. Ineligible patients will be assigned **a unique screening number with no protected health information** (e.g., name, medical record number, date of birth, etc.) stored in the system. Following written informed consent each enrolled subject is then assigned a **unique study number, which contains a unique site number**, by the EDC for data collection purposes. A list of enrolled subjects including identifiable information (name, medical record number, contact information, etc.) mapped to unique study number, along with signed consent forms, will be maintained in a secure location by local study personnel at the site, outside of the EDC, for local tracking purposes. Data analyzed on enrolled cases in Aims 1-3 shall be conducted without any access to any information about subject identity.

Because patients being studied already carry the diagnosis of CA, we do not believe that participation in this study will adversely affect the patient's ability to obtain life or medical insurance or employment. Information from this research will remain anonymous and confidential in the research database, and security measures will be in place to prevent unauthorized access to the system and data.

Protection against risk of gadolinium enhanced MRI. Patients in the follow-up cohort (FUBV) will

be consented specifically for undergoing three contrast enhanced MRI scans over 2 years, as a

requirement for the study (contrast to be used is called MultiHance). Patients with CASH have likely undergone numerous prior MRI studies as part of standard of care diagnosis and management of their disease. Those with gadolinium allergy, or who cannot tolerate MRI scans because of claustrophobia will be excluded. Patients with retained metal objects are also excluded unless the metal object can be positively confirmed to be MRI compatible, as per standard clinical MRI procedures. Per institutional policy, every patient will be screened and excluded for pregnancy, where safety of high field MRI and gadolinium contrast agents have not been established.

Gadolinium-based contrast agents have been used for diagnosis and treatment guidance in more than 100 million patients worldwide over the past 25 years, with a spectacular safety record, and no known untoward clinical effect except in rare instances and only in patients with renal insufficiency. We shall use **current U.S. FDA guidelines** to screen for and exclude patients with renal insufficiency, which are at risk of developing rare nephrogenic systemic fibrosis. There is currently no known clinical significance, nor any restriction of gadolinium use by the U.S. FDA despite reports of potential accumulation of trace gadolinium molecule in the human brain. If evidence emerges during the trial of clinical harmful effects of gadolinium or formal U.S. FDA injunction against its use, we would cease its use and obtain IRB and NINDS approval to modify the protocol to continue the study without gadolinium permeability biomarker. This would not impact the **QSM lesional iron concentration biomarker, which does not require gadolinium contrast**.

There will be no direct benefits to patients for participating in this study. However, the information gained from this study may lead to successful clinical trials testing novel therapies in patients with cerebral cavernous angiomas.

3 OBJECTIVES AND ENDPOINTS

Specific Aim 1: To harmonize data entry, and assess prospective enrollment rates and baseline characteristics of CASH cases at multiple high volume sites with clinical interest in CAs.

Specific Aim 2: To test the feasibility, accuracy, precision and reproducibility of MRI biomarker measurements at multiple sites, critical to their potential application as predictive, diagnostic or outcome measures.

Specific Aim 3: To assess rates of symptomatic hemorrhage and changes in biomarkers and functional status/QOL measures during prospective follow-up.

Specific milestones are proposed and go/no-go decisions based on interim analyses and results of these aims. Data from this project will insure the most stringent rigor in trial assumptions, including validated enrollment rates and baseline features specific to CASH. Results will endorse or reject outcome instruments or biomarkers based on empiric observations, hypothesizing a clinically meaningful impact of putative therapies.

4.1 OVERALL DESIGN

This is an observational cohort study of CASH cases with no intervention. Seven high-volume cavernous angioma sites have been identified for this project. We propose to activate sites and prepare data structure in year 1, then prospectively screen and enroll 200 CASH cases in years 2-5 at multiple sites. We shall collect harmonized baseline data, and enroll a subset of approximately 120 cases into the follow-up and imaging biomarker validation (FUBV) arm at 4 or so sites to assess and compare clinical outcomes, biomarker outcomes, and functional status and patient-reported quality of life outcomes for potential use in future clinical trials.

Clinical Coordinating Center (CCC):

The Clinical Coordinating Center, located at the University of Chicago, will train site coordinators on the protocol and data entry, as well as track enrollment rates. The CCC will also be responsible for answering site questions about enrollment and subject eligibility.

Data Coordinating Center (DCC):

The Data Coordinating Center, located at Johns Hopkins University, will develop and oversee the trial electronic data system to ensure the integrity of data collection, safety and coordination of data storage and access. Study site staff will be trained, sites activated and pilot cases completed in year 1 and data collection thereafter for years 2-5. The DCC shall performed data monitoring and generate data reports for analysis by Investigators as proposed in the respective Specific Aims 1-3. The DCC will review the online case forms for completeness, logic, and consistency, then verify the entered data against the uploaded source records/data collection worksheets in a random 5% sample of cases. Routine queries identified in this process will be entered into the EDC system (triggering an automated notice to the site). The monitors will then work with the site personnel to obtain correction of all data errors and resolution of the corresponding queries.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Justification of Rare Disease. Brain CA lesion prevalence has been estimated at 0.46-0.63% of the population based on consecutive imaging studies in the MRI era[27-29]. A 0.5% lesion prevalence was confirmed by the detection of 131 CAs among 24,535 consecutive autopsies[30]. In these consecutive imaging or autopsy studies, consistently <10% of lesions had manifested a SH. In the one prospective population based study in the MRI era, 12% of detected CAs presented with a SH[19]. Based on <10-12% CASH prevalence among all cavernomas and assuming 0.5% of 325 million adults of the U.S. population harbor a CA, it is projected that fewer than 162,500 to 195,000 adults are living with a cavernoma that has bled at least once. Fewer numbers would harbor a CA with a more recent SH, warranting therapeutic targeting. Based on an estimated prevalence of 60,000 cavernomas in the U.S. with clinical symptoms warranting therapeutic intervention, Recursion Pharmaceuticals received Orphan Drug Designation in 2010 from the U.S. Food and Drug Administration (FDA) (http://www.pr.com/press-release/640210).

Similarly, the European Consortium Orphanet has designated brain CA as a rare disease, Orpha164 (http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=164).

Knowledge Gaps Regarding the Prevalence of CASH and Baseline Characteristics. For planning and executing multi-site clinical trials, it is unclear what fraction of CA patients would meet the likely trial eligibility criteria of SH within the prior year with an unresected lesion. That prevalence varied between 10-25% in the three largest ongoing CA research databases at U.S. institutions, with different referral patterns and enrollment criteria. This might vary further at other institutions, and with systematic screening. **Prospective prevalence of CASH in systematic screening of CAs, and enrollment rates at multiple sites are not known.** These data are essential for the proper design of clinical trials, including the number of prospective sites needed. It is further unclear how CASH cases might vary by age, sex, familial versus sporadic, lesion size and location, associated venous anomaly, past bleeds, and baseline disability. These features varied or were not assessed consistently in the 3 active prospective CA research databases in the U.S. More importantly, the **assessment of these features at multiple sites has never been harmonized or adjudicated. Further, it is unclear what functional status and Quality of Life (QoL) instruments best capture the clinical impact of CASH**. Inclusion/exclusion criteria and stratification for these characteristics will be important in clinical trials, as they will impact natural risk, and potentially the effect of putative therapies. These critical knowledge gaps will be addressed in Specific Aim 1 of this proposal.

Opportunities and Challenges with Novel Biomarkers Linked to Clinical Bleeding in CAs. Vascular leak is a fundamental feature of CAs, mediating hemorrhage and the associated accumulation of non-heme iron (including hemosiderin). Pre-clinical studies demonstrated rescue of vascular permeability and decreased lesional iron deposition with ROCK inhibitors and statins[31], and B-cell depletion therapy[32] in murine CA models recapitulating the human disease. Awad's group in Chicago implemented a novel MRI application of assessing iron deposition in human CAs using quantitative susceptibility mapping (QSM)[33-36]. Mean lesional QSM was shown to reflect actual iron concentrations assessed by mass spectroscopy in resected human CA specimens[35]. Researchers in Chicago and New Mexico optimized a second technique, dynamic contrast enhanced quantitative perfusion (DCEQP) measure on MRI in human subjects, reflecting mechanistically postulated vascular hyper-permeability[33, 34, 37-39]. The Awad team used both QSM and DCEQP successfully in over 200 CA subjects and showed strong inter-observer agreement in QSM and DCEQP measurements, stability of both measurements in clinically stable lesions, and reproducibility across MRI instrument platforms at the Chicago site[36, 38]. As predicted by the conservation of mass hypothesis, CA lesions with greater permeability (K_i) had higher lesional iron content (QSM)[36], and lesional iron content was greater in older patients and in CAs with prior SH[36]. More recent studies demonstrated **a** significant increase of mean lesional QSM and DCEQP K_i in human CA lesions manifesting interval SH or growth during longitudinal follow-up, while these did not change in stable lesions[33]. There were tight, sensitive and specific thresholds of QSM and DCEQP increases in association with clinical events[33]. Therefore, it is postulated that the QSM and DCEQP may be used as *in vivo* measures of hemorrhagic activity and vascular leak, respectively, and may reflect sensitive, clinically meaningful therapeutic effect in human CAs. No other biomarkers have been as linked mechanistically to CA, nor associated as closely with clinical events.

However, the QSM validations and clinical correlations in CAs have been conducted at a single site to date, and DCEQP was applied to CAs at only two sites using slightly different protocols. FDA approved image acquisition sequences of QSM and DCEQP have been implemented on different MRI instruments from major manufacturers, but their validation at multiple sites have not been reported, nor specifically in CAs. The feasibility, accuracy, precision and reproducibility of biomarker measurements at multiple sites are critical to their potential application as outcomes instruments in clinical trials. We propose a rigorous approach to address these gaps in Specific Aim 2 of this project.

Knowledge Gaps Regarding Follow- and Outcomes Assessment. Reducing the rate of recurrent SH as a clinical outcome would decrease the burden of disease, since a single SH can lead to devastating neurologic sequelae. This would be an approvable outcome, adjudicated, readily defined and easy to measure. Yet there are many knowledge gaps and potential obstacles to planning clinical trials based on this primary outcome. Attempting to power a study based on recurrent SH would require at least a 1- to 2-year study and a significant number of patients (Table). The relative mix of lesions with different re-bleed rates will greatly influence the sample size needed to show treatment effect based on this primary outcome. Limiting trials to brainstem lesions would enhance statistical power, but also restrict recruitment and prevent generalizability of a drug's effects to other CASH cases that could benefit. Other studies suggest an equally high rate of SH in deep supra-tentorial and possibly cerebellar CAs[21]. **The rates of recurrent SH have never been assessed prospectively at multiple sites in CASH trial candidates**.

Table. Power Calculation Models
Numbers of patients needed, based on different re-bleed rates. Calculated by Parexel, 90% power, 1-sided, Type 1 error 0.025, treatment allocation 1:1, dropout rate 10%.

Annual rate of SH in control	Follow-up period	Reduction in SH rate (%)	Sample size/group
6%	1.5 yrs	25%	3341
	1.5 yrs	50%	720
15%	1.5 yrs	25%	1161
	1.5 yrs	50%	253
30%	1.5 yrs	25%	435
	1.5 yrs	50%	98

Moderate to severe disability after SH has been reported in 11-22% of patients[17, 40-42]. A CA re-bleed causes significantly greater disability than initial SH[22]. The proportion of CASH cases with any functional disability varied between 26 and 65% at U Chicago, Mayo and BVMC cohorts. Only two studies assessed QOL in CAs, and both were limited to surgical patients. One study[43] used Karnofsky performance scale, Patzold Rating and SF-36, and the second[44] used only SF-36. Newer QoL scores (e.g. EQ-5D and PROMIS 29) have been validated and are more specific for stroke patients compared to SF-36[45-53], and easier to obtain than the Patzold Rating[54]. No study to date has reported QOL measures or their changes over time in CASH patients observed without surgery. **It would be useful to assess functional outcome and QOL measures at baseline and document their change over time with or without a symptomatic re-bleed**. One or more may be fit for use as a putative outcome in clinical trials of pharmacotherapies, and may even be useful in future surgical trials. As to the QSM and DCEQP biomarkers of lesional hemorrhage and permeability, even if they are successfully and reliably deployed at multiple sites, **it remains unclear how they change during longitudinal follow-up in cases with CASH, and whether their changes are more sensitive than clinical events**. The gaps of knowledge regarding outcome measures in clinical trials are addressed in Specific Aim 3 of this proposal.

Urgent Need for Clinical Trial Readiness. Potential drug development for CASH is very promising, but also illustrates what past-NINDS Director Story Landis, PhD described as "an embarrassment of riches". As with many rare neurologic diseases, fundamental discoveries have identified cogent mechanistic targets for therapies, but their development into viable clinical solutions invariably meets obstacles and uncertainties in trial readiness. In this disease, there is a huge opportunity through clinical equipoise to target CAs with recent SH, where surgical resection of lesion is not undertaken, with the aim of preventing recurrent bleeding within 2-3 years. There are unique collaborations among major experts and stakeholders in place, yet a critical "Valley of Death" awaits drug development in the absence of readiness for multi-site clinical trials. Obstacles include a lack of harmonization of screening, baseline cohort characterization, prevalence rates and screen/enroll ratios, risk stratification and the assessment of clinical, functional and biomarker outcomes at multiple sites. Further gaps include the unknown rate and sensitivity (fitness for purpose) of outcome parameters during follow-up, needed to postulate treatment effects. These obstacles and gaps are readily addressed by the proposed clinical readiness project. The timing cannot be more opportune, with therapeutic targets identified, and several drugs ready to benefit from a track to clinical testing in about five years.

4.3 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

Cases whose CASH lesion has been resected will be considered to have reached endpoint, and will not be followed further during the study. The indication for surgery shall be noted, including any SH prior to CASH lesion resection.

Cases who develop a recurrent SH during follow-up, and their CASH lesion has not been excised, will remain in the study until they complete follow- up, and will undergo all scheduled assessments.

If an enrolled subject decides to discontinue the study, fails follow-up, or develops an exclusion criterion after enrollment in the study (becomes pregnant, undergoes CASH lesion excision, etc.), he/she will be considered an attrition after recording the causative event. Data collected prior to the attrition shall still be included in the study and no further patient follow-up will take place. An allowance in sample size calculation is made for up to 30% attrition or missing data from any cause.

5 Study Population

5.1 INCLUSION CRITERIA

(1) 18 years of age and older.
(2) diagnosed with a brain CA (single or multiple).
(3) had a SH within the past year (with demonstrated new lesional bleeding or hemorrhagic growth >3mm on diagnostic studies AND attributable new symptoms).
(4)~~no prior treatment of the symptomatic lesion (after neurosurgical consultation).~~ Subject is able to provide informed consent.

5.2 EXCLUSION CRITERIA

(1) have symptomatic spinal CA's
(2) have received prior brain irradiation.
(3) cases where verification of SH with clinical and imaging review cannot be accomplished.
(4) No prior or planned treatment of the symptomatic lesion (after neurosurgical consultation)

Subjects meeting these eligibility criteria are considered eligible for the SCA arm.

Additional FUBV Arm Exclusion Criteria. To be eligible for Aims 2 and 3, CASH cases enrolled in Aim 1 will be further excluded from FUBV arm inclusion for the following reasons:
(1) unable to undergo MRI with contrast and/or because of contraindications (e.g. pacemaker, metallic foreign body, pregnancy) or other reasons (severe claustrophobia, too large or too heavy for MRI scanner).
(2) pregnant or breastfeeding women due to unknown harm to fetus/child from MRI.
(3) Subject will be unable/unlikely to return for follow-up visit

5.4 SCREEN FAILURES

Sites will enter all patients with CCM disease seen at their institution. The study database (VISION-EDC) will include a list of possible exclusions from which the study team will choose for all patients found to be not eligible for the trial. The most common reason for exclusion is likely to be a lack of ymptomatic hemorrhage within the last year.

This a non-interventional study.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Cases whose CASH lesion has been resected will be considered to have reached endpoint, and will not be followed further during the study. The indication for surgery shall be noted, including any SH prior to CASH lesion resection.

Cases who develop a recurrent SH during follow-up, and their CASH lesion has not been excised, will remain in the study until they complete follow-up. They will undergo the scheduled follow-up assessments at Years 1 and 2.

Participants are free to withdraw from participation in the study at any time upon request.

7.2 LOST TO FOLLOW-UP

If an enrolled subject decides to discontinue the study, fails follow-up, or develops an exclusion criterion after enrollment in the study (becomes pregnant, undergoes CASH lesion excision, etc.), he/she will be considered an attrition after recording the causative event. Data collected prior to the attrition shall still be included in the study. An allowance in sample size calculation is made for up to 30% attrition or missing data from any cause.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit [within 2 months of the study window] and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

All eligible subjects will be identified by the study team at each site. Based on clinic schedules and current patient databases, all CCM patients with a symptomatic hemorrhage within the last 12 months (of screening) are eligible for the trial. Sites will screen neurology, neurosurgery, and neurointerventional radiology clinic schedules, MRI schedules, and attend Neurovascular rounds to help identify potential subjects. Additionally, study sites will rely on referrals from the various services listed above, or self-referrals via web searches and through the Angioma Alliance, a patient support group. Once identified, the study coordinator at each site, along with the site PI, will screen the subject for basic eligibility. Screened subjects not scheduled to come in for a clinical visit within their eligibility window will be contacted by the study coordinator or PI to explain the study and determine if the subject is interested. When the subject comes in, either for a standard clinic visit or for a study visit, the study team will review the subject's medical history to ensure the subject meets the inclusion criteria. The trial will be explained and informed consent obtained. After consent is obtained a physical exam (height, weight, vital signs) will be completed, a baseline modified Rankin Score obtained, and EQ-5D, PROMIS 29, and NIH stroke scale assessments completed. The study team will also collect information about the subject's history, pertinent to the disease (history of seizure, resection of other lesions, etc.). All subjects at the FUBV sites (enrolled to the FUBV arm) will have a MRI scan including the additional sequences for research as specified in Specific Aim 2 (QSM/DCEQP). All women of childbearing age will undergo a urine or serum beta-HCG pregnancy test prior to MRI to confirm no pregnancy, per local institutional guidelines.

Subjects enrolled in the FUBV arm will return for 2 follow up visits: one at 12 months and the other at 24 months. Excluding the informed consent process, all baseline procedures will be repeated. Subjects will have completed their participation upon completion of the baseline visit procedures (SCA arm) or the year 2 visit (FUBV arm). All subjects enrolled in the SCA arm will have one study visit only.

FUBV subjects will receive travel stipends for each of the 3 study visits. Those subjects traveling less than 200 miles to the enrolling site will receive $50 per visit (baseline, Year 1, Year 2). Those traveling more than 200 miles to the enrolling site will receive $500 per visit (baseline, Year 1, Year 2).

9.1 STATISTICAL HYPOTHESES AND PROPOSED ANALYSES

Specific Aim 1. Descriptive statistics (frequencies, min, max, mean, standard deviation) and contingency table analysis will be performed to identify any possible coding errors. Data inconsistencies identified will be sent back to sites for correction. We will calculate the proportion and exact 95% confidence interval (CI) of CASH cases among all CA cases at each SCA site and overall. Baseline characteristics will be summarized using chi-square tests for categorical variables and t-tests for continuous variables. EQ-5D measures are scored on the T-score metric, with a mean of 50 and standard deviation (SD) of 10 in a referent population (mild, moderate, and severe impairment is defined as 0.5-1.0 SD, 1.0-2.0 SD, or 2.0+ worse than the mean, respectively). Spearman correlation coefficients will be calculated between mRS and Euro-QoL and PROMIS29 scales, and mean scores of Euro-QoL and PROMIS29 will be stratified by mRS levels. This analysis will allow us to determine ceiling effects of scores and how well the Euro-QoL and PROMIS29 data are distributed in CASH cases. Functional and QOL scores shall also be analyzed by pre-defined subgroups (sex, genotype and lesion location), to inform stratification or the need for adaptive randomization in clinical trials.

Specific Aim 2. This will follow the same design for QSM and DCEQP data acquired using these phantoms. A $p<0.05$ will be considered a failure, or significant non-zero difference. The accuracy of QSM and DCEQP values will be assessed at each of the sites participating in the FUBV arm by estimating the coefficient of determination r^2 between the observed and known phantom values, with $r^2 \geq 0.95$ needed to validate accuracy of each technique[35]. The Pearson's correlation coefficients r of the FUBV subjects will also be compared using Fisher transformation. The precision of QSM and DCEQP measurements will be tested by comparing two separate measurements acquired at each site, using a paired t-test (7 ferumoxytol concentrations acquired twice by QSM, and 7 permeability values simulated with the phantom twice by DCEQP). The reproducibility of phantom measurements will be evaluated by comparing the QSM and DCEQP simulation values acquired at New Mexico and Mayo Rochester against the values obtained at Chicago, and one another, using a two-sample t-test.

Specific Aim 3. Time to recurrent SH will be analyzed using Kaplan Meier method and Cox proportional hazards regression approach. Rates of recurrent SH/patient/year from initial SH qualifying event, and SH/patient/year from enrollment (potentially more relevant for trial modeling) will be estimated along with 95% CIs. Changes in mean lesional QSM and K_i during 1 and 2-year epochs will be compared using paired t-test or Wilcoxon signed rank test to assess changes within patients over time, including 95% CIs. To test predictive, monitoring or surrogate outcome hypotheses, two sample t-test or Wilcoxon rank sum test will be used to compare such changes between patients with and without recurrent SH. Categorical variables such as proportions of patients with a drop in mRS score ≥ 1 point, difference in EQ-5D and PROMIS 29 scores, NIHSS scores, between patients with and without recurrent SH will be compared using Chi-square or Fisher's exact test. Associations of baseline characteristics (sex, lesion locations, familial/sporadic) and recurrent SH as a binary outcome (yes/no) will be assessed using

univariable and multivariable logistic regression and reported as odds ratios and 95% CIs. Depending on the number of recurrent SH over the 2-year period, we may analyze re-bleeds as a continuous outcome and the associations of baseline features or biomarkers assessed using linear regression. Performance of final model(s) will be assessed using r^2 in the case of linear regression, area under the curve (AUC) and Hosmer Lemeshow goodness of-fit test[55] in the case of logistic regression, or concordance index in the case of Cox proportional hazards regression. AUCs between various models (univariable) will be compared using the method proposed by DeLong et al[56]. For biomarkers, we will create a binary variable (yes/no) depending on whether the % change in mean lesional QSM or K_i during 1-year epochs exceed previously defined respective thresholds (+ 5.8% QSM and +39.6% for K_i)[33] that were significantly associated with new clinical events at high sensitivity and specificity in previously stable lesions. We will then assess the association of this newly created variable ("biomarker event") with SH rate treated as continuous (using two sample t-test or Wilcoxon rank sum test) and binary (using Chi-square or Fisher's exact test) outcomes of interest. Finally, we shall compare the sensitivity/specificity of changes in mRS, QOL, and NIHSS scores, and lesional QSM and K_i in relation to SH during the same epochs, using McNemar's test with SH (yes/no binary) as the reference standard. All tests will be 2-sided and p-values <0.05 considered statistically significant.

9.2 SAMPLE SIZE DETERMINATION

Screening and Clinical Assessment (SCA) Arm: We calculated the width of the exact 95% CI for detecting CASH cases, varying the prevalence from 10% to 25% based on the range in preliminary data, and total sample sizes screened from 500 to 1,500. Based on these sample size models, we propose recruiting 200 CASH cases for the SCA arm of this project, to be enrolled during years 2-5, an average of 50 cases/year at all sites, and less than one case/site/month. Assuming a 15% prevalence of CASH cases (the average in three ongoing registries), a screening sample size of 1,333 would be required over a 4-year period (333 cases to be screened/year) to detect 200 CASH cases ± 2% (i.e., 13% to 17%). Even if the true prevalence is lower (e.g. 10%) or higher (25%), we will have excellent precision to within ± 1.5% to 2.5%, respectively, corresponding to 134 - 334 CASH cases for the same screening sample size. These CASH sample sizes will also allow flexibility in describing the proportion of important subgroups (i.e. sex, lesion location, genotype), and provide realistic estimates of recruitment at SCA sites (screened/enrolled ratio).

The 7 main sites are all high-volume CA clinical centers, with demonstrated ability to screen the requisite number of cases**.** Their recent clinical activity is demonstrated by the number of CA cases (n) seen over a 12-month period with diagnosis ICD9 228.02 on initial or follow-up visits at each of the institutions: 1) University of Chicago (n=106), 2) Mayo Clinic-Rochester (n=70), 3) University of New Mexico (n=80), 4) University of Utah (n=40), and 5) Barrow Neurological Institute, Phoenix (n=200); TOTAL (n=496). We would need to screen 1,333 CA cases over a 4-year period at the 5 sites (333 CAs screened each year)**,** in order to identify and enroll 200 CASH cases, based on the estimated prevalence of 15% CASH cases among overall CA cases**.** This is a very realistic target, with 496 CAs actually evaluated per year at the 5 sites for the SCA arm. To help meet the target enrollment, The University of California- San

Francisco (n=70) was added as a recruitment site in February 2019 and Johns Hopkins University (n=150) will be added in 2020. If we do not meet our target enrollment of CASH cases, we may add additional, yet to be decided on, sites.

Follow-up and Biomarker Validation (FUBV) Sites: University of Chicago, University of New Mexico, Mayo, University of California San Francisco, and Johns Hopkins were chosen because of additional established infrastructure for advanced imaging, including identified MRI physicists, neuroradiologists and site engineers who will work with the Biomarker Imaging Core (BIC) on implementing QSM and DCEQP protocols. A subset of approximately 120 CASH cases will be enrolled at FUBV sites to perform imaging biomarker validation studies (Specific Aim 2) and follow-up of CASH cases annually for up to two years (Specific Aim 3) to evaluate changes in outcomes. This subset of CASH cases will undergo a research MRI scan at baseline and at 1 and 2-year follow-up visits and undergo modified Rankin Scale (mRS) score and EQ-5D, PROMIS 29, and NIHSS assessments. A target recruitment of 120 CASH cases over 3-4 years at the sites conducting the FUBV arm is amply justified, with demonstrated 256 CA cases recently evaluated per year at those sites, expecting to identify 38 CASH cases each year (15% prevalence). Utah and Barrow may also serve as alternate FUBV arm sites if needed, with large demonstrated CA clinical activity. The University of California San Francisco and Johns Hopkins are now part of the FUBV arm .

Assuming a sample size of 120 CASH cases, and allowing 30% dropouts or missing biomarker or other data, we would have 84 evaluable patients (168 patient-years). We project 10%-20% re-bleed rate/year, supported by population studies and meta-analyses of CASH[18, 19], with the higher estimate particularly applying to brainstem cases. We would hence expect 17-34 SHs. Based on this, for continuous outcomes we will have 80% power at an alpha level of 0.05, to detect a difference between the means of patients with and without re-bleeding of at least 0.63-0.77 standard deviation. For categorical outcomes (i.e. presence or absence of a risk factor) we will be able to detect a difference of 32-40% between these two groups. This allows testing of questions regarding the rate of SH, and the prevalence of other outcomes in relation to SH during follow-up (Specific Aim 3).

9.3 POPULATIONS FOR ANALYSES

Cavernous angiomas with symptomatic hemorrhage (CASH) are most likely to re-bleed and cause further neurologic sequelae. It would be desirable to develop a drug that stabilizes CASH, and prevent recurrent bleeding. CASH with recent bleed, where surgical resection is not undertaken, are the most likely cases to be followed expectantly per current evidence based guidelines, with clinical equipoise for testing novel therapies to prevent re-bleeding. They are the most likely cases to be targeted for clinical trials.

Appropriate and complete statistical modeling of data collected by the sites for both SCA/FUBV arms are imperative to the planning, development, and completion of a successful Phase III interventional trial. The most critical component is the accurate assessment of the enrollment rates of CASH across several sites, as well as the between-site variability in these estimates. Both within and between sites variability will be used to adequately power a Phase III trial, will be calculated by developing random-effect models along with using appropriate link functions quantifying the rates of CASH in these models.

As a follow-up step, in-depth data analyses will be performed using the demographic, imaging, clinical and biomarker data collected. These are applied to develop models assessing how predictive each of these factors is to the development of recurrent SH. Understanding which factors are most predictive of SH will be crucial in developing a covariate adaptive randomization scheme for the Phase III trial that insures proper balance in these prognostic factors between treatment arms. Finally, statistical assessments of changes in lesional iron content and permeability biomarkers, QOL, mRS, and NIHSS during follow-up of CASH patients will be performed. Understanding how these measures change over time will be an important step in the process of developing hypotheses on the effect of treatment on these as putative secondary or surrogate outcomes, or as potential composite outcomes.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Data collection. Key variables to be collected in this study will be decided on by all stakeholders in Year 1. At a minimum, these will include patient demographics, genotype, baseline MRI lesion features of the hemorrhagic CA (size, location), time from SH, prior bleeds/dates, and diagnosis date. Functional status will be measured using the modified Rankin Scale (mRS) score[57], Euro-QoL[53], PROMIS29[52], and NIH Stroke Scale. PROMIS 29 short forms are an assessment of anxiety, depression, and fatigue, and have been validated for use in several common neurological disorders. Presence of obstructive sleep apnea. Recent findings suggest that sleep apnea results in decreased blood flow to the brain. This transient ischemia may be implicated in CA hemorrhage. Sleep apnea questions will be included in the dataset and response analyses as described under the topic Predictors of SH.

Data harmonization. Common data elements from each site will be reviewed, updated, and harmonized using an iterative, stepwise process based on DataSHaPER (DataSchema and Harmonization Platform for Epidemiologic Research) recommendations[58-60]. Questionnaires, codebooks, and protocols, etc. at the 3 established CA databases (Table 2) will be compiled and distributed for review. A series of Executive Committee teleconference calls will be held in Year 1 to decide on a set of 'target' data elements for potential clinical trials, as has been similarly done with the consensus process for developing clinical guidelines paper[17]. The EDHC and DCC will then develop standardized electronic data entry forms and codebooks for data collection. Each site shall be trained in abstracting and entering data for their cases online. Data will be collected prospectively in Years 2-5. Analysis datasets will be generated quarterly by the DCC for quality control analysis by EDHC.

Event Rate: Time to recurrent SH will be analyzed using Kaplan Meier method and Cox proportional hazards regression approach. Rates of recurrent SH/patient/year from initial SH qualifying event, and SH/patient/year from enrollment (potentially more relevant for trial modeling) will be estimated along with 95% CIs.

Biomarker changes over 2 years: Changes in mRS, EQ-5D, PROMIS 29, and NIHSS scores, mean lesional QSM and K_i during 1 and 2-year epochs will be compared using paired t-test or Wilcoxon signed rank test to assess changes within patients over time, including 95% CIs.

Predictors of SH: Two sample t-test or Wilcoxon rank sum test will be used to compare such changes between patients with and without recurrent SH. Categorical variables such as proportions of patients with a drop in mRS score ≥ 1 point, between patients with and without recurrent SH will be compared using Chi-square or Fisher's exact test. Associations of baseline characteristics (sex, lesion locations, familial/sporadic) and recurrent SH as a binary outcome (yes/no) will be assessed using univariable and multivariable logistic regression and reported as odds ratios and 95% CIs. Depending on the number of recurrent SH over the 2-year period, we may analyze re-bleeds as a continuous outcome and the associations of baseline features or biomarkers assessed using linear regression. Performance of final model(s) will be assessed using r^2 in the case of linear regression, area under the curve (AUC) and Hosmer Lemeshow goodness of-fit test[55] in the case of logistic regression, or concordance index in the case of Cox proportional hazards regression. AUCs between various models (univariable) will be compared using the method proposed by DeLong et al[56]. For biomarkers, we will create a binary variable (yes/no) depending on whether the % change in mean lesional QSM or K_i during 1-year epochs exceed previously defined respective thresholds (+ 5.8% QSM and +39.6% for K_i) that were significantly associated with new clinical events at high sensitivity and specificity in previously stable lesions[33]. We will then assess the association of this newly created variable ("biomarker event") with SH rate treated as both continuous (using two sample t-test or Wilcoxon rank sum test) and binary (using Chi-square or Fisher's exact test) outcomes of interest. Finally, we shall compare the sensitivity/specificity of changes in mRS, QOL, and NIHSS scores, and lesional QSM and K_i in relation to SH during the same epochs, using McNemar's test with SH (yes/no binary) as the reference standard. All tests will be two-sided and p-values <0.05 considered statistically significant.

We will calculate the proportion and exact 95% confidence interval (CI) of CASH cases among all CA cases at each SCA site and overall. Baseline characteristics will be summarized using chi-square tests for categorical variables and t-tests for continuous variables. Baseline Euro-QoL and PROMIS29 measures will be validated for use in CAs. Euro-QoL and PROMIS29 measures are scored on the T-score metric, with a mean of 50 and standard deviation (SD) of 10 in a referent population (mild, moderate, and severe impairment is defined as 0.5-1.0 SD, 1.0-2.0 SD, or 2.0+ worse than the mean, respectively). Spearman correlation coefficients will be calculated between mRS and Euro-QoL and PROMIS29 scales, and mean scores of Euro-QoL and PROMIS29 will be stratified by mRS levels. This analysis will allow us to determine ceiling effects of scores and how well the Euro-QoL and PROMIS29 data are distributed in CASH cases.

Homogeneity of event rates, biomarker changes, and other endpoints in years 1 and 2. This will be assessed, as it impacts (1) sample size calculations for time averaged assessments of the impact therapies, and (2) whether future trials should be conducted for 1 or 2 years.

9.4.2 SUB-GROUP ANALYSES

All endpoints (rebleed rates, biomarker changes, functional status and QOL changes) shall be analyzed by pre-defined subgroups (sex, genotype and lesion location), information which may influence stratification or the need for adaptive randomization in clinical trials.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study procedures and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator or study team member will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the signed, informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the study files (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. Non-English speaking participants will not be targeted for enrollment. In the event of a participant who is eligible for enrollment but does not speak English, the institution's"short form" consent document may be given to the participant in their respective language. A "short form" consent document is defined as a document stating that the elements of the informed consent have been fully presented orally to the participant in the participants native language through the use of an interpreter.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

The study may be modified or discontinued at any time by the IRB, the NINDS, the PI, the OHRP, or other government agencies as part of their duties to ensure that research subjects are protected. Additionally, yearly go/no-go decision points have been built into the study, as described below.

Timeline/Milestones		Go/ No-Go Decision Points
	▪ IRB approval for sites, DCC and Cores	
Year 1	▪ Site activation, training and regulatory compliance certification of personnel. ▪ Finalize electronic data forms, data entry protocols for SCA and FUBV sites. ▪ Screen at least 10 cases and enroll 1 CASH case at each SCA/FUBV site. ▪ Feasibility and phantom validations of QSM and DCEQP measurements at FUBV sites.	▪ *Activate alternate sites as needed (per site activation milestones).* ▪ *Reject QSM or DCEQP if they fail validation test thresholds at FUBV sites (adjust budget if imaging biomarkers are rejected).*
Year 2	▪ Screen at least 50 cases and enroll of 10 CASH cases at each SCA/FUBV site, with successful completion of initial clinical, functional status and imaging assessments. ▪ Quality certification of clinical data acquisition, and validation of biomarker assessments by the BIC on enrolled cases.	▪ *Activate alternate sites as needed (per site performance or recruitment rates).* ▪ *Optimize baseline and outcomes collection instruments per problems with each.* ▪ *Reject QSM or DCEQP if they fail ongoing quality assurance threshold at interim midterm review (adjust project budget)* ▪ *Change follow-up to 6 & 18 months. (instead of 12 & 24) per timing/rate of recurrent SH at midterm review.*
Years 3-4	• Publish guidelines paper on reporting Terminology in CAs by the end of year 3. ▪ Screen at least 50 cases/year, enroll 10 CASH cases/year at each SCA/FUBV site. ▪ Log follow-up at least 40 cases/year for sites participating in the FUBV arm by the end of year 3 and 60 cases by the end of year 4 with clinical and biomarker data. ▪ Confirm quality and consistency of harmonized data acquisitions across sites at the end of years 3 and 4. ▪ Complete lagging enrollments and follow-ups.	▪ *Decision regarding certifiable outcomes based on interim and/or final analyses of trial readiness aims (SH alone, versus QOL and biomarkers); application to FDA.* ▪ *Decision regarding # of subjects (and # of sites) needed for clinical trials, including stratification and outcome parameters.* ▪ *Decisions regarding multi-site trial models per results of readiness aims. Pharma, StrokeNet and NCATS consultations.*
Year 5 (6)	▪ Test hypotheses regarding relative value/sensitivity of outcomes instruments. ▪ Apply for certification of 1 or more outcomes instruments by the FDA. ▪ Formulate trial hypotheses.	

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators and their staff. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, the Clinical Coordinating Center (CCC), the Data Coordinating Center (DCC), other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB) or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored by Prelude Dynamics. Research data will be synchronized to our internet-accessible clinical trials management software platform (VISION™ by Prelude Dynamics, Austin, TX). This system is used by the Data Coordinating Center (BIOS) for rapid and efficient protocol management in large, multicenter, acute stroke trials. Prelude Dynamics and Johns Hopkins Health Systems Corporation and The Johns Hopkins University have an executed Business Associate Agreement in place. Study participant data will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Prelude Dynamics research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived by Prelude Dynamics with BIOS at Johns Hopkins.

10.1.4 FUTURE USE OF STORED DATA

Firsts in this Disease: Harmonization of Baseline Characteristics and Outcomes Assessments. We propose for the first time a harmonized multi-site assessment of enrollment rates of CASH, baseline features relevant to stratification in clinical trials, and follow-up assessments of functional outcomes and QOL in relation to clinical bleeds. Without this information, clinical trials could use false assumptions and likely fail. We introduce novel biomarkers of vascular leak and hemorrhage, with firm mechanistic foundations, that have been linked to clinical disease activity. We shall test their reliability and validity at multiple sites, and assess their changes over time, with and without clinical re-bleeds, hence their fitness as outcomes instruments in clinical trials. Such a comprehensive project has never been undertaken previously in this disease. The recent James Lind Alliance priority setting partnership conducted by Cavernoma Alliance U.K. identified among the top priorities for research several aims of this trial readiness proposal (http://www.jla.nihr.ac.uk/priority-settingpartnerships/cavernoma/).

Scientific Rigor and Translation to Trial Modeling. Teams at UCSF and Mayo Clinic include investigators and statisticians, with respective experience in disease characteristics and data harmonization, and in prospective follow-up and natural history. The Chicago team contributes engineers

and physicists with demonstrated expertise with the proposed biomarkers, and a statistician with the greatest experience in the analysis of QSM and DCEQP data. The team at Johns Hopkins contributes a solid record in data structure, safety and integrity, trial modeling (including highly successful CLEAR and MISTIE trials, and recent planning of AT-CCM POC), and a longstanding proven collaboration with Awad's Chicago team. The senior statistician at Johns Hopkins and statisticians from the various Cores will cross-critique statistical plans proposed in each of the aims, and refine them during year 1, adding another level of peer-input and diversity of opinions, and optimizing data format for future analyses. Later in the project, they will construct workable models for multi-site trials based on emerging results. This will insure the most stringent rigor in trial assumptions, including validated estimates and confidence intervals of detection rates and baseline features of eligible subjects. They will endorse or reject outcome instruments or biomarkers based on empiric observations, hypothesizing a clinically meaningful impact of putative therapies. And they will propose the most optimal sample size, length of follow-up, and number of sites needed to test trial hypotheses. Our Advisory Committee will provide guidance and prioritization of workable trials to be conducted by industry or academia.

Ultimately, the data collected in this trial will help shape future trials in this disease by informing enrollment possibilities, disease progression, numbers of subjects available, feasibility of enrolling at multiple centers, etc. The data collected during this study will be analyzed to better understand this population and will be used to prepare grants for future trials, including drug treatment trials.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Scientific Cores: There are three scientific cores that include Epidemiology and Data Core (EDHC), Biomarker Imaging Core (BIC) and Follow-up and Clinical Hypotheses Core (FCHC).

Executive Committee (EC): Project PI, co-chairs, Core leaders and other site PIs shall form the project's Executive Committee. The EC shall teleconference monthly regarding trial progress and review interim analyses yearly and at midterm in each specific aim. The NINDS Program Officer shall attend all EC meetings and teleconferences.

Advisory Committee (AC): will meet with the EC each fall in conjunction with the Angioma Alliance Investigators Workshop and by teleconference each spring. A progress report shall be presented by the EC and the AC shall help resolve emerging problems, propose alternative approaches, or identify unique opportunities. The AC will make specific suggestions about each aim, propose revisions, and ultimately approve the emerging study protocols. In years 2-4, the AC shall review project progress, and in Years 3-5 emerging data (interim reports) and all go/no-go decisions. In Years 4-5, the AC shall be expanded to include representative of StrokeNet and NCASTS, agencies who might sponsor Phase III trials. The AC may also be called upon for *ad hoc* advice regarding problems and opportunities as they arise.

Central Institutional Review Board (cIRB): The Johns Hopkins University School of Medicine will be utilized for this trial readiness project.

10.1.6 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control. After agreement on key variables to be collected in this study, we will generate 10 case summaries for training, meant to illustrate the variability in identifying CASH cases and will discover any uncertainties in target variable definitions that require clarification before sites commence data collection. For outcome measures that are more subjective (e.g. verification of SH, mRS, lesion size/location), a second clinical assessor with CA experience (Awad, Flemming or Morrison) will review the anonymized raw data on the case and assess the parameters independently. We will calculate the interrater reliability for the 10 training cases to determine the percent agreement (kappa).

The DCC will review the online case forms for completeness, logic, and consistency, then verify the entered data against the uploaded source records/data collection worksheets in a random 5% sample of cases. Routine queries identified in this process will be entered into the EDC system (triggering an automated notice to the site). The monitors will then work with the site personnel to obtain correction of all data errors and resolution of the corresponding queries.

10.1.7 DATA HANDLING AND RECORD KEEPING

10.1.7.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data will be entered into the Vision database, a 21 CFR Part 11-compliant data capture system provided by Prelude Dynamics. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.7.2 STUDY RECORDS RETENTION

Participation in this study requires that original study documents be retained for a minimum of 2 years following the end of the trial. This standard complies with U.S. FDA regulations (21 cfr §312.62[c]).

Records must not be destroyed without first contacting the study investigator to ensure that the time limits defined in the regulations have been met.

> For the purposes of this section, "original study documents" are defined as:
> Subject records created at or available to the study center during the subject's participation in the trial, or any other document that supports entries in the EDC system and represents the original source of that information, including but not limited to applicable sections of medical charts, patient correspondence, laboratory data, pharmacy logs and drug accountability forms, as well as any forms or documents used to compile or maintain original subject data or study procedural information.

All Essential Regulatory Documents [as defined under Good Clinical Practice (GCP) Regulations] including: all material communications with the IRB; all communications that are related to study subjects or which otherwise document material study-related procedures or safety issues. All study documents should be uploaded to the source documents section of the database. The database will be used as the master repository for all site and Sponsor regulatory documents.

10.1.8 PROTOCOL DEVIATIONS

Protocol Compliance: Procedures will be implemented to maximize adherence to the protocol. Early review of data is made possible by real-time entry of data into a database with validations and real-time monitoring. Minor or administrative deviations will be reported to the JH IRB at the time of continuing review. Examples of minor administrative deviations include: follow up visits and/or study tasks occurring outside the protocol required time frame because of the subject's schedule.

FDA Guidance for Electronic Data Entry Compliance: The design and development of the electronic database system will reflect the FDA Guidance for Industry for Computerized Systems Used in Clinical Trials (April 1999) as well as the Electronic Records/Electronic Signatures rule (21 CFR part 11). A secure, computer generated, time- stamped electronic record will allow reconstruction of the course of events relating to the creation, modification, and deletion of an electronic record. Source documents will be retained to enable a reconstruction and evaluation of the trial. The system will ensure that all applicable regulatory requirements for record keeping and record retention in clinical trials are met with the same degree of confidence as are provided with paper systems. Clinical investigators will retain the original copy of all source documents uploaded onto the eCRF. Query resolution correspondence will be maintained and eCRF edits will be tracked by the system. Changes to a required record will not obscure the original information. The record will clearly indicate the time a change was made and clearly provide a means to locate and read the prior information through the audit trail. This audit trail will be in compliance with the 21 CFR 11.10(e). The record, along with supporting documentation, will also indicate who made the changes and when changes were made.

Security measures will be in place to prevent unauthorized access to the system and data. To ensure that individuals have the authority to proceed with data entry, the system will be designed to verify the electronic signature (user id and password) at the start of a user session. Each entry to an electronic record, including any change, will be made under the electronic signature of the individual making that entry. A separate electronic signature will not be required for each entry or change; a single electronic signature will cover multiple entries or changes. Individuals who maintain the electronic record systems as well as the audit trail will carry the responsibilities to protect authenticity, integrity, and confidentiality of electronic records. Audit trails will be available at the study site or any other location where associated electronic study records are maintained. The system will be designed to contain the prompts, lookup values, cross-field validations, flags, and on-line help to encourage consistent use of clinical terminology and to alert the user in case that data entered are out of acceptable range. External safeguards will be in place to ensure that access to the computerized system and to the data is restricted to authorize personnel. Servers will be stored in a physically secured, guarded data center.

10.1.9 PUBLICATION AND DATA SHARING POLICY

Trial readiness updates shall be presented annually at the Angioma Alliance Investigators Workshop. Relevant results shall be presented at a major scientific meeting and submitted for publication within one year of the respective interim or final analyses, including a guidelines paper on reporting terminology. A complete de-identified dataset containing all variables collected and a data dictionary will be submitted to NINDS for data sharing within a timeframe to be agreed upon with NINDS Program Officer. We shall discuss with NINDS the application of our data structure to vet and approve as "common data elements" to be applied in future research with this disease (www.commondataelements.ninds.nih.gov).

10.2 ABBREVIATIONS

AT-CCM POC	Atorvastatin in CCM Proof of Concept study
AUC	Area Under the Curve
BIC	Biomarker Imaging Core
BIOS	Brain Injury Outcomes
BVMC	Brain Vascular Malformation Consortium
CA	Cavernous Angioma
CASH	Cavernous Angioma with Symptomatic Hemorrhage
CCC	Clinical Coordinating Center
CCM	Cerebral Cavernous Malformations
CFR	Code of Federal Regulations
CI	Confidence Interval
CITI	Collaborative Institutional Training Initiative

CLEAR	Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage
CRF	Case Report Form
DataSHaPER	DataSchema and Harmonization Platform for Epidemiologic Research
DCC	Data Coordinating Center
DCEQP	Dynamic Contrast Enhanced Quantitative Perfusion
eCRF	Electronic Case Report Forms
EDC	Electronic Data Capture
EDHC	Epidemiology and Data Harmonization Core
EQ-5D	Euroquol-5D
FDA	Food and Drug Administration
FUBV	Follow-up and Biomarker Validation
GCP	Good Clinical Practice
IRB	Institutional Review Board
K_i	Permeability
MISTIE	Minimally Invasive Surgery Plus Rt-PA for Intracerebral Hemorrhage Evacuation
MOP	Manual of Procedures
MRI	Magnetic Resonance Imaging
mRS	modified Rankin Score
NIH	National Institutes of Health
NIHSS	NIH Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
PI	Principal Investigator
PROMIS	Patient-Reported Outcomes Measurement Information System
ROCK	Rho kinase
QA	Quality Assurance
QC	Quality Control
QSM	Quantitative Susceptibility Mapping
SAP	Statistical Analysis Plan
SCA	Screening and Clinical Assessment
SD	Standard Deviation
SH	Symptomatic Hemorrhage
SOA	Schedule of Activities
SOP	Standard Operating Procedure
US	United States

11 REFERENCES

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