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Trial Readiness in Cavernous Angiomas With Symptomatic Hemorrhage (CASH)

BACKGROUND: Brain cavernous angiomas with symptomatic hemorrhage (CASH) are uncommon but exact a heavy burden of neurological disability from recurrent bleeding, for which there is no proven therapy. Candidate drugs to stabilize the CASH lesion and prevent rebleeding will ultimately require testing of safety and efficacy in multisite clinical trials. Much progress has been made in understanding the epidemiology of CASH, and novel biomarkers have been linked to the biological mechanisms and clinical activity in lesions. Yet, the ability to enroll and risk-stratify CASH subjects has never been assessed prospectively at multiple sites. Biomarkers and other outcomes have not been evaluated for their sensitivity and reliability, nor have they been harmonized across sites.

OBJECTIVE: To address knowledge gaps and establish a research network as infrastructure for future clinical trials, through the Trial Readiness grant mechanism, funded by National Institute of Neurological Disorders and Stroke/National Institutes of Health.

METHODS: This project includes an observational cohort study to assess (1) the feasibility of screening, enrollment rates, baseline disease categorization, and follow-up of CASH using common data elements at multiple sites, (2) the reliability of imaging biomarkers including quantitative susceptibility mapping and permeability measures that have been shown to correlate with lesion activity, and (3) the rates of recurrent hemorrhage and change in functional status and biomarker measurements during prospective follow-up.

EXPECTED OUTCOMES: We propose a harmonized multisite assessment of enrollment rates of CASH, baseline features relevant to stratification in clinical trials, and follow-up assessments of functional outcomes in relation to clinical bleeds. We introduce novel biomarkers of vascular leak and hemorrhage, with firm mechanistic foundations, which 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 rebleeds, hence their fitness as outcome instruments in clinical trials.

DISCUSSION: The timing cannot be more opportune, with therapeutic targets identified, exceptional collaboration among researchers and the patient community, along with several drugs ready to benefit from development of a path to clinical testing using this network in the next 5 years.

KEY WORDS: Trial readiness, Cavernous angioma, Cerebral cavernous malformation (CCM), Symptomatic hemorrhage, Drug development, Biomarkers

GENERAL INFORMATION

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% to 30% of cases manifesting as multiple lesions that develop over time throughout the brain.[3] Magnetic resonance imaging (MRI) is the hallmark diagnostic modality for these lesions, revealing chronic and acute hemorrhage and tiny occult lesions (Figure 1). CAs are histologically identical in familial and sporadic cases, and harbor similar somatic mutations.[4-6]

CAs are often detected incidentally, or in association with seizures or nonspecific symptoms.[7-9] The natural history of such lesions is exceedingly benign, with <0.5% annual risk of clinically significant hemorrhage, and there is a consensus about these cases not needing interventions beyond symptom management and surveillance.[10] 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 neurological deficit within 5 years.[10-12] Cavernous Angiomas with Symptomatic Hemorrhage (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[13] requires diagnostic evidence of new lesional bleeding or hemorrhagic growth, in association with directly attributable symptoms (Figure 2).

Lesions in the brainstem and deep brain locations are more likely than other CAs to bleed,[14] rebleed,[11] and cause severe disability.[12,15] It is unclear if this greater propensity of 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 1 or more hemorrhagic strokes) particularly in deep or brainstem locations,[10,16] with significant public health impact and cost of care.[17]

While brain surgery for lesion excision may benefit some patients, it can be associated with significant cost.[18] Additionally, concerning are complications and morbidity with CA surgical excision of brainstem lesions, including a particularly alarming rate of surgical adverse events.[16] In a nonrandomized population-based cohort study, lesion excision was associated with significantly worse functional outcomes and greater complications compared to conservative management.[16] Stereotactic radiosurgery has been proposed, but there is controversy about its effectiveness and concern about complications and radiation-induced genesis of new CAs.[19,20]

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,[10] with clinical equipoise for testing novel therapies aimed at preventing rebleeding. It would be desirable to develop a drug that stabilizes CASH and prevent recurrent bleeding. This would mitigate neurological sequelae of rebleeds 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 rebleed) would be greatest within 2 to 3 years after a SH.[10-12]
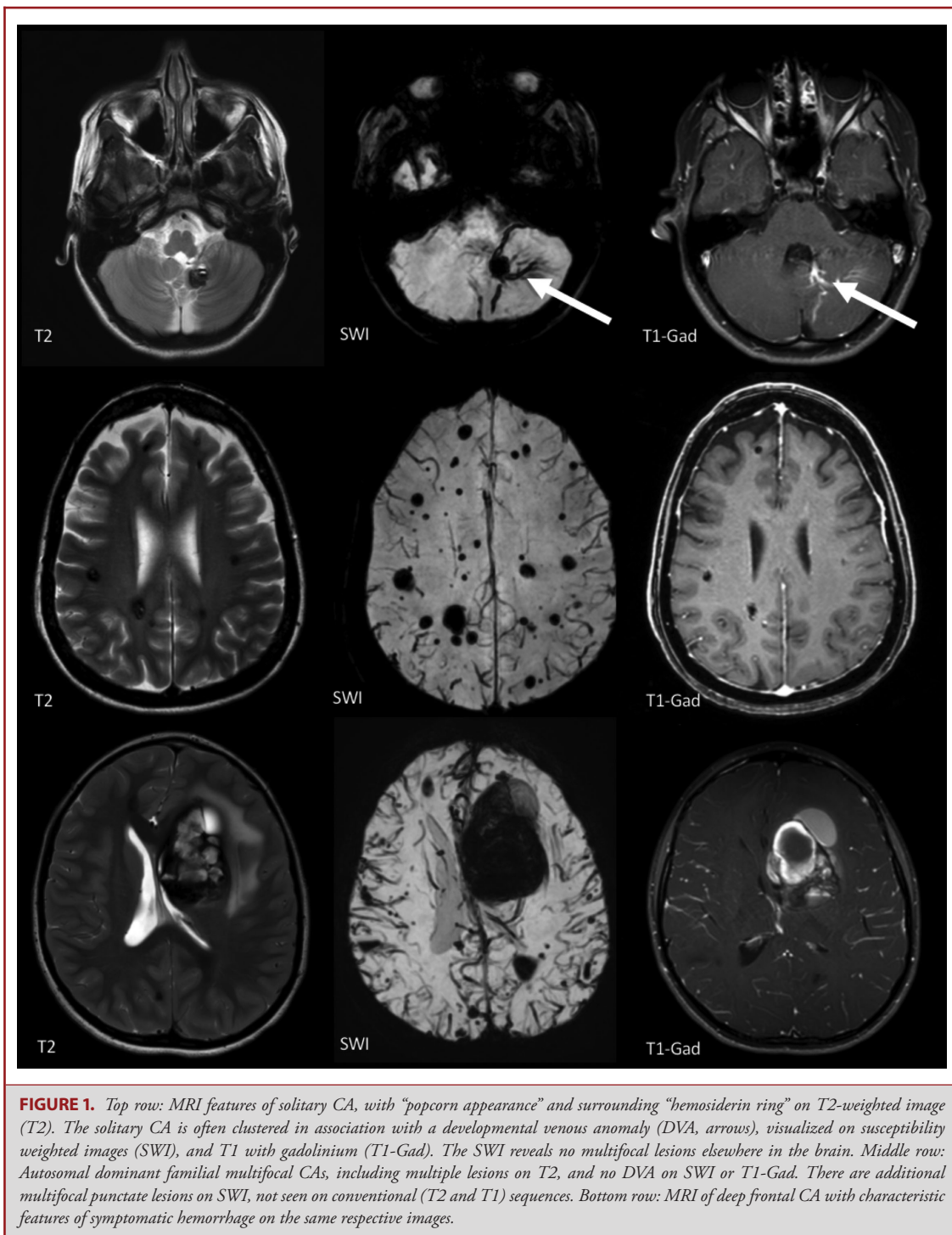
RATIONALE AND BACKGROUND INFORMATION

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 National Institute of Neurological Disorders and Stroke (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 multisite clinical trials (Table 1).

Opportunities in Clinical Research but Many Gaps in Trial Readiness

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 MRI techniques have applied dynamic contrast-enhanced quantitative perfusion (DCEQP)[21-23] and quantitative susceptibility mapping (QSM)[23-25] to measure vascular leak and lesional iron content in CAs (Figure 3), 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 (www.angioma.org).

However, 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

FIGURE 1. *Top row: MRI features of solitary CA, with "popcorn appearance" and surrounding "hemosiderin ring" on T2-weighted image (T2). The solitary CA is often clustered in association with a developmental venous anomaly (DVA, arrows), visualized on susceptibility weighted images (SWI), and T1 with gadolinium (T1-Gad). The SWI reveals no multifocal lesions elsewhere in the brain. Middle row: Autosomal dominant familial multifocal CAs, including multiple lesions on T2, and no DVA on SWI or T1-Gad. There are additional multifocal punctate lesions on SWI, not seen on conventional (T2 and T1) sequences. Bottom row: MRI of deep frontal CA with characteristic features of symptomatic hemorrhage on the same respective images.*

characteristics, including time from SH, hemorrhagic lesion location, disability status, and demographic features such as sex and age. 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

FIGURE 2. *Spectrum of manifestations of CAs. The SH is a singular clinical event with distinct clinical implications in terms of future risk and deploying clinical interventions. The definition of SH has been rigorously adjudicated. Reproduced with permission from* Stroke, *Al-Shahi Salman R, Berg MJ, Morrison L, Awad IA, Angioma Alliance Scientific Advisory B. Hemorrhage from cavernous malformations of the brain: definition and reporting standards. Angioma Alliance Scientific Advisory Board. Stroke. Dec 2008;39(12):3222-3230.*[13]

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 would likely fail.

STUDY GOALS AND OBJECTIVES

In response to these gaps in trial readiness, we proposed 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.

STUDY DESIGN

This is an observational cohort study of CASH cases with no intervention. Five high-volume CA sites have been identified for this project. We are activating sites and preparing data structure in year 1, then will prospectively screen and enroll 200 CASH cases in years 2 to 5 at the 5 sites. We shall collect harmonized baseline data and follow a subset of approximately 120 cases with imaging biomarker validation studies to assess and compare clinical outcomes, biomarker outcomes, and functional status and patient-reported QoL outcomes for potential use in future clinical trials.

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 on diagnostic studies AND attributable new symptoms)
(4) No prior treatment of the symptomatic lesion (after neurosurgical consultation).

Exclusion Criteria

(1) Spinal CA as source of SH
(2) Prior brain irradiation

TABLE 1. Candidate Therapeutics Implicated Mechanistically or Under Development for CAs.

Targeted pathway/function	Drug(s)	Testing/proof of concept status	Development status
RhoA/ROCK	Fasudil[26, 44]	Preclinical[a]	No current pathway for clinical development (side effects and expiration of patent)
	Statins[26]	Preclinical[a]	Ready for repurposing with IND exemption. Phase I-IIa proof of concept trial proposed
	ROCK-2 specific inhibitors (BA-1049)	Drug development stage (SBIR), preclinical[a] in progress	BioAxone committed to development for CASH indications in humans
Inflammation	Tempol[45]	Preclinical effect in acute models	Recursion Pharmaceuticals received Orphan Drug status, committed to development for CASH
	Immuno-modulators (B-cell depletion)[27,46]	Preclinical[a]	Potential repurposing of B-cell depletion biologics developed by several pharma companies for multiple sclerosis and other indications
	N-acetylcysteine[47]	Mechanistic Studies	
	Avenanthramide[48]	Mechanistic Studies	
	Platinum nanozymes[49]	Mechanistic Studies	
	Vitamin D3[45,50]	Cohort studies showing aggressive CA disease in Vit D deficient subjects[50]	Clinical trials not likely because of promiscuous use of Vit D in the population
Angiogenesis/VEGF	Propranolol[51,52]	Empiric case studies	Ready for repurposing with IND exemption. Plans for pragmatic exploratory trial
	VEGF receptor inhibitor (SU5416 semaxanib)[53]	Preclinical	Not likely to be pursued because of systemic side effects
Endothelial-mesenchymal transition/β-catenin	Inhibitors of TGF-β and β-catenin (ex: Sulindac metabolites)[54-56]	Preclinical	Sulindac proposal to the European Commission
Autophagy	mTOR inhibitors, autophagy inducers (ex: Torin 1, Rapamycin)[57]	Preclinical	
DELTA-NOTCH	Recombinant DLL4,[58] Sorafenib[59]	Preclinical	
MEKK/ERK/KLF	BIX02189 (anti-MEK5),[60] XMD17-109 (anti-ERK5)[60]	Preclinical	

[a]Indicates that preclinical effects were shown (Fasudil, statins, B-cell depletion) or planned (BA-1049) in mouse models using contemporaneous randomized treatment assignment versus placebo, and blinded outcome assessment per NINDS guidelines.[44]

(3) Cases where verification of SH with clinical and imaging review cannot be accomplished
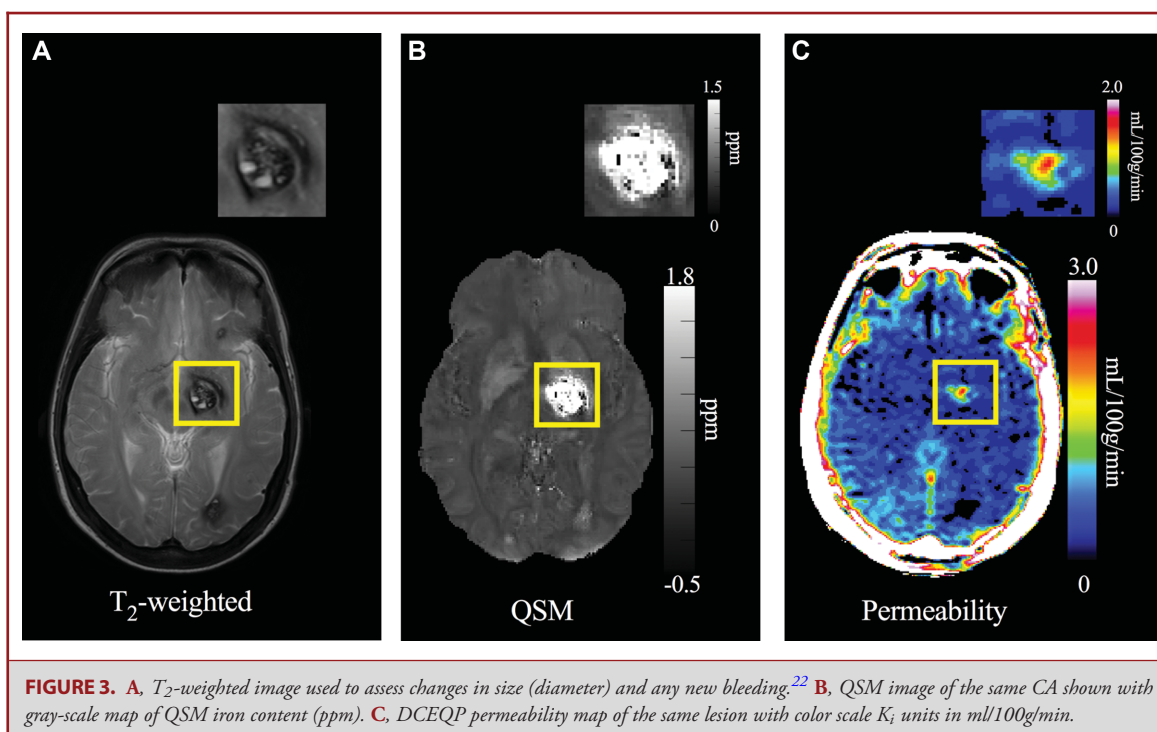
To be eligible for Aims 2 and 3, CASH cases enrolled in Aim 1 will be further excluded from follow-up and baseline validation (FUBV) for the following reasons:

(1) Contraindication for administration of contrast agent or otherwise unwilling or unable to undergo research MRI studies
(2) Pregnant or breastfeeding women
(3) Homeless or incarcerated persons, or other reason a subject will be unable/unlikely to return for follow-up visits

METHODOLOGY

Knowledge Gaps Regarding the Prevalence of CASH and Baseline Characteristics

For planning and executing multisite clinical trials, it is unclear what fraction of CA patients would meet the likely trial eligibility criteria of SH within the prior year and an unresected lesion. That prevalence varied between 10% and 25% in the three largest ongoing CA research databases at US institutions, with different referral patterns and enrollment criteria (Table 2). This might vary further at other institutions, and when utilizing 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

FIGURE 3. **A**, T_2-weighted image used to assess changes in size (diameter) and any new bleeding.[22] **B**, QSM image of the same CA shown with gray-scale map of QSM iron content (ppm). **C**, DCEQP permeability map of the same lesion with color scale K_i units in ml/100g/min.

sites needed. It is also unclear how CASH cases might vary by age, sex, familial vs 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 US more importantly; the assessment of these features at multiple sites has never been harmonized or adjudicated. Further, it is unclear if functional status and QoL instruments 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 Aim 1.

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 nonheme iron (including hemosiderin). Preclinical studies demonstrated rescue of vascular permeability and decreased lesional iron deposition with Rho-Associated Coiled-Coil Kinase (ROCK) inhibitors and statins,[26] and B-cell depletion therapy[27] in murine CA models recapitulating the human disease. The University of Chicago Neurovascular Program has implemented a novel MRI application of assessing iron deposition in human CAs using QSM.[22-25] Mean lesional QSM was shown to reflect actual iron concentrations assessed by mass spectroscopy in resected human CA specimens.[25] Researchers in Chicago and New Mexico optimized a second technique, DCEQP measure on

MRI in human subjects, reflecting mechanistically postulated vascular hyperpermeability.[21-23,28,29] The University of Chicago Neurovascular team used both QSM and DCEQP successfully in over 200 CA subjects and showed strong interobserver agreement in QSM and DCEQP measurements, stability of both measurements in clinically stable lesions, and reproducibility across MRI instrument platforms at the Chicago site.[21,24] As predicted by the conservation of mass hypothesis, CA lesions with greater permeability (K_i) had higher lesional iron content (QSM),[24] and lesional iron content was greater in older patients and in CAs with prior SH.[24] 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.[23] There were tight, sensitive and specific thresholds of QSM and DCEQP increases in association with clinical events.[23] 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 2 sites using slightly different protocols. The Food and Drug Administration (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

TABLE 2. Variable Baseline CA Characteristics in the 3 Largest Ongoing Research Databases.

Baseline characteristics	U Chicago[a]	Mayo Rochester[b]	BVMC[c]
Number of cerebral angioma (CA) cases	245	115	322
Age at first encounter (range)	41.1 (0.13-93.5)	45.5 (18.2-77.1)	39.3 (0.4-84.9)
Sex M/F (ratio)	76/169 (1/2.2)	70/45 (1.6/1)	118/199 (1/1.7)
Genotype sporadic/familial (ratio)	151/94 (1.6/1)	82/33 (2.5/1)	0/322 (0/1)
Age at diagnosis (range)	37.1 (0.3-93)	43.4	31.9 (0.3-83.8)
Number of patients with past SH	113	62	97
Number of SHs(range)	0.61 (0-14)		0.3 (0-6)
Number of CASH, SH within prior year, lesion unresected, age > 17 (% CA cases)	42 (17)	29 (25)	31 (9.6)
Age at diagnosis of CASH (range)	42.5 (21.3-71.3)	45.1 (18.1-61.6)	50.9 (19.7-84.9)
Sex M/F (ratio)	16/26 (1/1.6)	19/10 (1.9/1)	13/18 (1/1.4)
Genotype sporadic/familial (ratio)	28/14 (2/1)	21/8 (2.65/1)	0/31 (0/1)
Age at CA diagnosis (range)	38.5 (7-72)	46 (18.4-70.4)	40.6 (12.2-83.8)
CASH lesion location (% of CASH cases)			Not collected
Brainstem	23 (55)	17 (58)	
Cerebellar	2 (5)	0	
Deep supratentorial	6 (14)	4 (14)	
Lobar	11 (26)	7 (24)	
Associated venous anomaly (% of CASH cases)	22 (52)	11 (38)	0
CASH cases with mRS > 1 (%)	11 (26%)	19 (65%)	17 (57%)

[a]Subjects enrolled in biomarker studies 2013 to 2016, do not include other CA patients evaluated clinically without research enrollment.
[b]Prospective Cohort study beginning in January 2015 where patients with CA identified clinically must consent to ongoing follow up.
[c]Brain Vascular Malformation Consortium (BVMC): Familial CA cases recruited in 2 phases: BVMC1 cases all had the same gene mutation in CCM1 (Q455X, aka "Common Hispanic Mutation") and were recruited between 2009 and 2014; BVMC2 cases were recruited based on known genetic mutation in *CCM1, CCM2,* or *CCM3* or having multifocal lesions, or family history, between 2014 and 2019.

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 plan a rigorous approach to address these gaps in Aim 2.

DISCUSSION

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 neurological 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 a lesion is not undertaken, with the aim of preventing recurrent bleeding within 2 to 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 multisite 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 this current clinical readiness project (Figure 5). The timing cannot be more opportune, with therapeutic targets identified, and several drugs ready to benefit from a track to clinical testing in about 5 years.

We propose for the first time a harmonized multisite 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, which 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 rebleeds, hence their fitness as outcomes instruments in clinical trials. Such a comprehensive project has never been undertaken previously in this disease and will facilitate the design of clinical trials for emerging therapies. This project is a model of trial readiness that may be applied in other neurological diseases.

TRIAL STATUS

This trial readiness project is underway as of December 2017 and funded by the NINDS/National Institutes of Health (NIH) U01 NS104157 for 5 years (2017-2022).

TABLE 3. Power Calculation Models for Numbers of Patients Needed in Prospective Trials, Based on Different Rebleed Rates and Effect Size Assumptions, Assuming 1.5 years of Treatment/Follow-up.

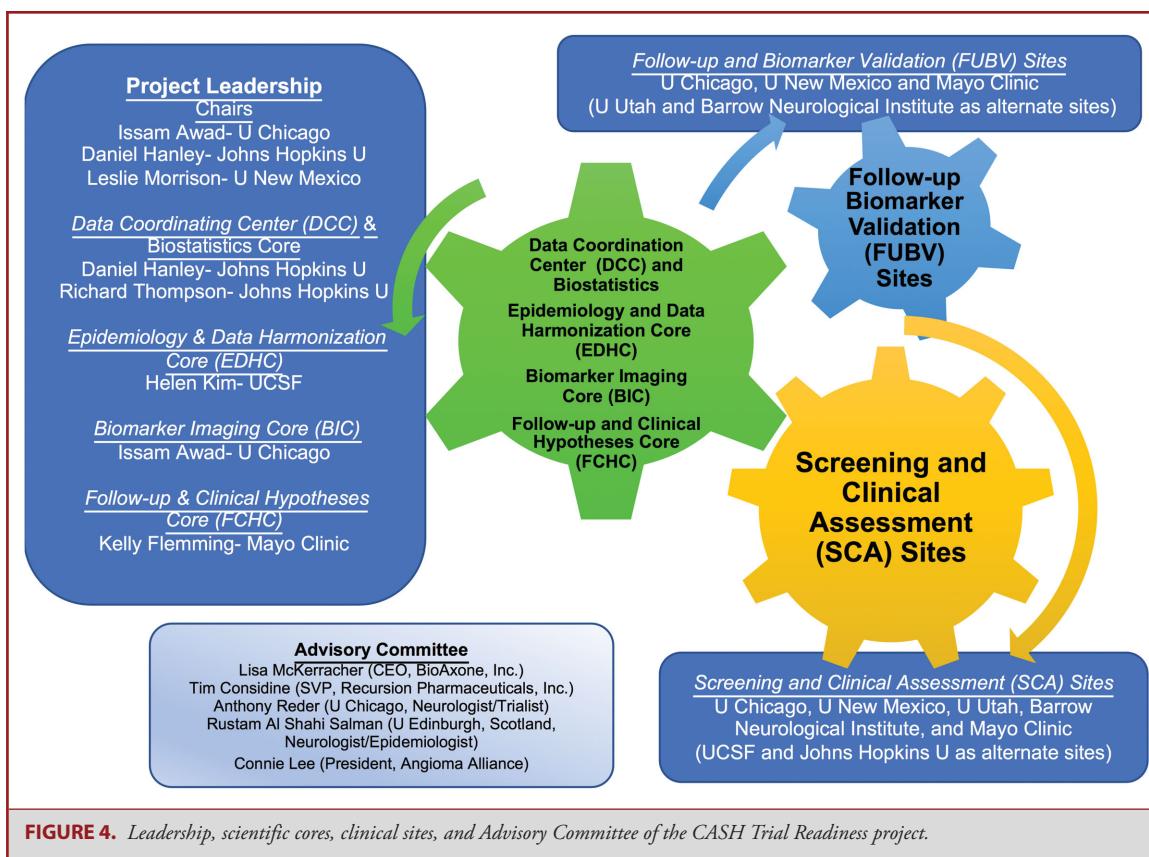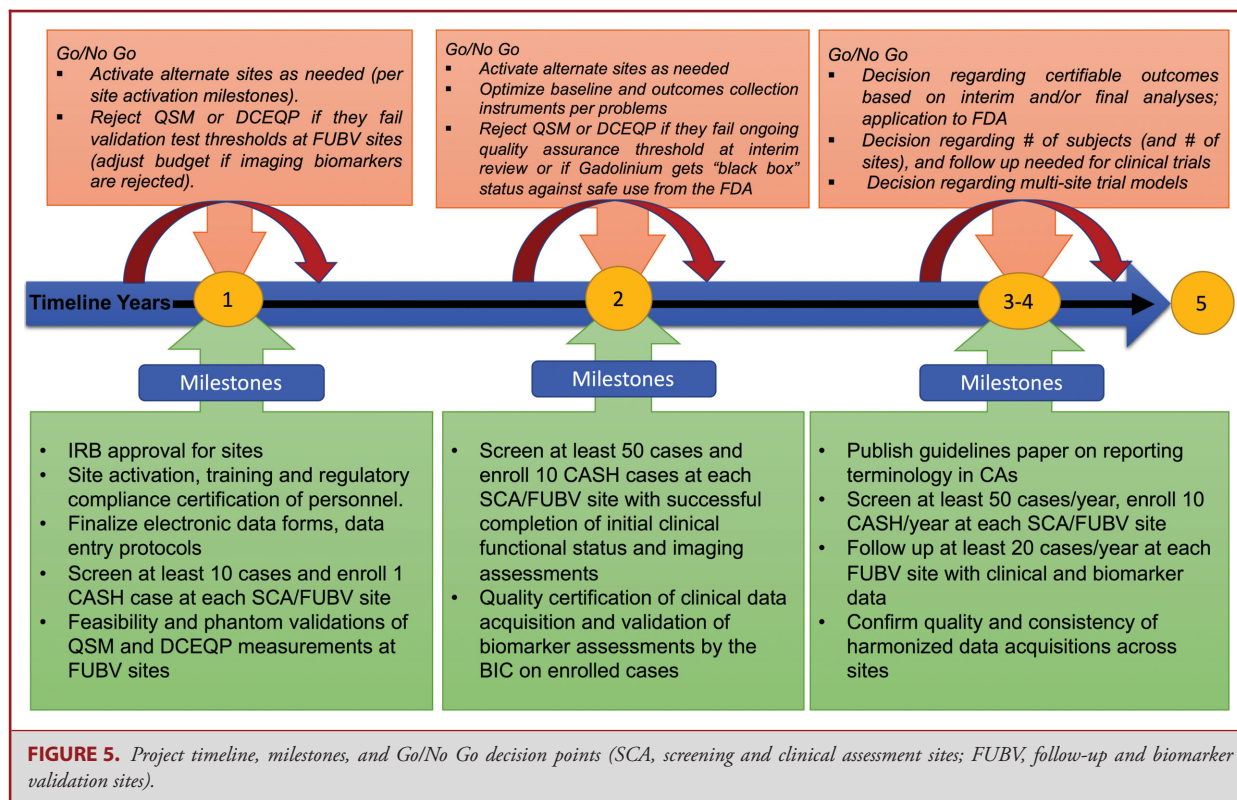| Calculated by Parexel, 90% power, 1-sided, Type 1 error 0.025, treatment allocation 1:1, dropout rate 10%			
Annual rate of recurrent SH in control	Follow-up period	Reduction in SH rate	Sample size/group
6%	1.5 yr	25%	3341
	1.5 yr	50%	720
15%	1.5 yr	25%	1161
	1.5 yr	50%	253
30%	1.5 yr	25%	435
	1.5 yr	50%	98

FOLLOW-UP

Knowledge Gaps Regarding Follow-up 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 neurological 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-years study and a significant number of patients (Table 3). The relative mix of lesions with different rebleed 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.[14] The rates of recurrent SH in

FIGURE 4. Leadership, scientific cores, clinical sites, and Advisory Committee of the CASH Trial Readiness project.

FIGURE 5. *Project timeline, milestones, and Go/No Go decision points (SCA, screening and clinical assessment sites; FUBV, follow-up and biomarker validation sites).*

CASH trial candidates have never been assessed prospectively at multiple sites.

Moderate to severe disability after SH has been reported in 11% to 22% of patients.[10,30-32] A CA rebleed causes significantly greater disability than initial SH.[15] The proportion of CASH cases with any functional disability varied between 26% and 65% at U Chicago, Mayo, and BVMC (Brain Vascular Malformation Consortium) cohorts. Only 2 studies assessed QoL in CAs, and both were limited to surgical patients. One study[33] used Karnofsky performance scale, Patzold Rating, and SF-36, and the second[34] used only SF-36. Newer QoL scores (eg, Neuro-QoL) have been validated and are more specific for stroke patients compared to SF-36,[35-42] and easier to obtain than the Patzold Rating.[43] No study to date has reported QoL measures or their changes over time in CASH patients observed without surgery. It will be useful to assess functional outcome and QoL measures at baseline and document their change over time with or without a symptomatic rebleed. 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 Aim 3.

STATISTICAL ANALYSIS

Trial Modeling and Planning

The statistical analyses plan and sample size calculations for each of the three Aims are presented in the **Supplemental Digital Content**. Appropriate and complete statistical modeling of data collected by the screening and clinical assessment (SCA) and FUBV sites is 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 the several sites, as well as the between-site variability in these estimates. Both within and between site variability, to 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.

PROJECT MANAGEMENT/DATA MANAGEMENT/QUALITY ASSURANCE

Leading CA research teams have been assembled (Figure 4) with expertise in the questions being tackled, including rigorous

imaging validation and statistical approaches, and a data coordinating center with a proven record in trial planning and execution, forming the foundation of the future CA clinical research network. The project shall be overseen by a Central Institutional Review Board and implement an electronic data capture system allowing de-identified data entry and tracking. It includes data quality checks that will be executed at the time of data entry at each site and deploys robust features for data monitoring and security. Liaison was established with the US FDA Biomarker Qualification Program. An Advisory Committee with broad expertise will make 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.

EXPECTED OUTCOMES OF THE STUDY

Understanding which factors are most predictive of recurrent SH will be crucial in developing a covariate adaptive randomization scheme for the phase III trial that ensures proper balance in these prognostic factors between treatment arms. Finally, statistical assessments of changes in lesional iron content and permeability biomarkers, QoL, and modified Rankin Scale (mRS) during follow-up of CASH patients will be performed. Understanding how these measures change during year 1 and 2 will help optimize the follow-up period in prospective trials, and develop hypotheses on how these measures are affected by treatment (as putative secondary or surrogate outcomes, or as potential composite outcomes).

DURATION OF THE PROJECT

We are activating sites and preparing data structure in year 1, then will prospectively screen and enroll 200 CASH cases in years 2 to 5 at the 5 sites.

ETHICS

All protocols will undergo Institutional Review Board review.

Disclosures

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