SUPPLEMENTAL MATERIAL

Expanded Materials and Methods

DICTIONARY OF DATA ELEMENTS

CAVERNOUS ANGIOMA WITH SYMPTOMATIC HEMORRHAGE TRIAL
READINESS (CASH TR) PROJECT

clinicaltrials.gov NCT03652181

V-7-19-20-R

Demographics:

- Age at registration: Patient's age at first research clinical encounter.
- Gender: Options listed. Socially constructed differences between men and women that give rise to masculinity and femininity.
- Ethnicity: Options listed. Imply one or more of the following: shared origins or social background; shared culture and traditions that are distinctive, maintained between generations, and lead to a sense of identity and group; and a common language or religious tradition.
- Race: Options listed. Reflect constructs of human variability based on perceived differences in biology, physical appearance, and behavior.

Genotype:

- Sporadic: Cavernous angioma (CA) occurring as a solitary hemorrhagic vascular lesion (no other lesions elsewhere in the brain on MRI susceptibility sequences) or as clustered lesions associated with a developmental venous anomaly.
- Developmental venous anomaly (DVA): Also known as venous angiomas, are composed of radially arranged venous complexes converging to a centrally located venous trunk, which drains the normal brain parenchyma. Characteristically, DVAs have numerous dilated deep medullary veins presenting in "caput medusae" configurations, which drain into a few dilated deep and/or superficial veins.
  - o Clustered lesions around DVA: Patient's cavernous angioma lesions are located and clustered around DVAs.
  - o Familial/Multifocal: Autosomal dominant familial form of CA, which is caused by a heterozygous germline loss-of-function mutation in one of three genes— *CCM1*/*KRIT1, CCM2*/*Malcavernin*, and *CCM3*/*PDCD10*—causing multifocal lesions throughout the brain and spinal cord.

- o CCM1, germline mutation at the gene locus proven by genetic testing of the patient or an index kindred
- o CCM2, germline mutation at the gene locus proven by genetic testing of the patient or an index kindred
- o CCM3, germline mutation at the gene locus proven by genetic testing of the patient or an index kindred
- o Multifocal unknown genotype: Non-genotyped cavernous angioma patients harboring multifocal lesions on MRI or familial disease, with no prior history of cranial irradiation, where genotyping was not performed or was negative for mutations in *CCM1/KRIT1, CCM2/Malcavernin*, and *CCM3/PDCD10.*
- Post-radiation: This category is endorsed whenever there has been a history of whole brain or large field irradiation (as for the treatment of prior malignancy). CA lesions with identical histology and MRI appearance arise in the brain following irradiation due to the propensity of radiation to induce somatic mutations. This category is not endorsed when there has been focused brain irradiation (radiosurgery) for a known CA.

Pregnancy:

- Pregnancy test: Assessment of pregnancy by measuring the level of human chorionic gonadotropin (hCG) in urine or blood.
- Assay methods
  - o Urine: Immunometric assay in which urine is used for quantitative measurement of hCG to detect pregnancy in the form of home pregnancy tests that are widely available.
  - o Serum: laboratory immunometric assay in which serum is used for quantitative measurement of hCG to detect pregnancy.

Eligibility: Meeting specific inclusion/exclusion criteria articulated in the CASH Trial Readiness project for baseline and follow-up cohorts.

- Screening and clinical assessment (SCA)
- Follow-up and biomarker validation (FUBV)

SCA trial readiness eligibility:

Inclusion criteria: the key features of the target population that the investigators will use to answer their research question.

- CA: Patient is confirmed to harbor 1 cavernous angioma lesion or more, which is defined as a lesion consisting of a clustered, giant, blood-filled capillary spaces "caverns", lined by endothelium, and separated by an amorphous matrix lacking mature vessel wall angioarchitecture. [10]
- Hemorrhagic CA[2]:
  - o Acute or subacute bleeding on CT or MRI,

- o New FLAIR signal on MRI, and/or
- o Lesion expansion in any diameter by ≥3 mm on comparable T1-weighted or T2-weighted sequences.
- SH: CA lesion that demonstrated new lesional bleeding or hemorrhagic growth on diagnostic studies and attributable new symptoms.[1]
- CASH: Cavernous angioma with symptomatic hemorrhage. Diagnostic evidence of new lesional bleeding or hemorrhagic growth, in association with directly attributable symptoms.[10]
- Informed consent: The process of agreeing to take part in a study based on access to all relevant and easily digestible information about what participation means, in particular, in terms of harms and benefits.

Exclusion criteria: Features of the potential study participants who meet the inclusion criteria but present with additional characteristics that could interfere with the success of the study or increase their risk for an unfavorable outcome.

- Symptomatic lesion located in spine: Intramedullary vascular lesions, most being located in the thoracic spine. Patients present with either acute neurologic deficit or gradual deterioration with weakness being the most common presenting symptom.
- Prior brain irradiation: A correlation between prior radiation and cavernous angioma is seen, particularly in children under 10 years of age at the time of radiation therapy. [28]

FUBV trial readiness eligibility:

- Contraindication for administration of contrast agent: The presence of any contraindication to the use of contrast agents, such as renal disease and allergic reactions.

Additional demographics:

- Date of birth.
- Age at First Symptom Onset Attributed to CA: Patient's chronological age when they had first symptom that is attributed to cavernous angioma disease. If patient was asymptomatic until recent symptomatic hemorrhage, then the date of the CASH event applies.

Clinical updates:

- Height: The distance from the bottom to the top of someone standing upright measured in inches.
- Weight: The amount that a person weighs measured in pounds.
- Blood pressure: Pressure that is exerted by the blood upon the walls of the blood vessels and especially arteries and that varies with the muscular efficiency of the heart, the blood

volume and viscosity, the age and health of the individual, and the state of the vascular wall. Blood pressure is measured in units of millimeters of mercury (mmHG).

- o Systolic: The highest arterial blood pressure of a cardiac cycle occurring immediately after systole of the left ventricle of the heart.
- o Diastolic: The lowest arterial blood pressure of a cardiac cycle occurring during diastole of the heart.

Current medications:

- Vitamin D: Fat-soluble vitamin that acts as a steroid hormone. The primary source of vitamin D is UVB-induced conversion of 7-dehydrocholesterol to vitamin D in the skin. Vitamin D influences the bones, intestines, immune and cardiovascular systems, pancreas, muscles, brain, and the control of cell cycles.
- Statins: Potent lipid lowering agents that inhibit HMG-CoA (critical enzyme for cholesterol synthesis). Beside its lipid lowering effect, it is well-known for its endothelial functional improvement by inhibiting RhoA kinase activity, and anti-inflammatory effects.
- Blood thinners: A wide range of medications with diverse mechanisms of actions used to prevent blood clotting in susceptible individuals, and patients with coagulopathies to lower the risk of thrombotic events, such as myocardial infarctions and strokes.
- Propranolol: A nonselective beta-blocker that blocks the action of catecholamines (adrenaline and noradrenaline) at both beta-1 and beta-2 adrenergic receptors. It is widely used in various cardiovascular diseases, including ischemic heart disease, arrhythmias and myocardial infarction. It has many other non-cardiovascular uses as well, such as essential tremors, anxiety, migraines and portal hypertension.
- Oral birth control pill: A contraceptive method based on the use of either one of the 2 hormone-based pills: combined estrogen-progesterone, or progesterone only pills for birth control.
- Estrogen: A steroid hormone associated with the female reproductive organs and is responsible for the development of female sexual characteristics, it is one of the components of the hormone replacement therapy used for the treatment of symptoms of menopause, and combined oral contraceptive pills.

Apnea:

- Sleep apnea: A disorder characterized by complete cessation of breathing (apnea) and abnormally shallow and slow breathing (hypopneas) of ≥ 10 seconds during sleep. It collectively describes both obstructive sleep apnea in which apneas and hypopneas are due to repetitive collapse of the upper airway, and central sleep apnea in which apneas and hypopneas occur in the absence of upper airway collapse.
- Sleep apnea treatment: Depending on the type of sleep apnea, management includes patient education and behavior modification, alleviation of airway obstruction, selection of the sleep apnea-specific therapy (i.e., positive airway pressure, oral appliance, surgery) and follow-up are important measures in the management.

<u>New symptoms associated with CASH lesions:</u>

- Seizure: A paroxysmal alteration of neurologic function caused by the excessive, hypersynchronous discharge of neurons in the brain.
- Focal neurological deficit: A set of symptoms or signs in which causation can be localized to an anatomic site in the central nervous system. The site of the pathologic abnormality is typically deduced through the history and physical examination before imaging.
- Headache: Pain or discomfort arising from pain-sensitive structures in the head. These include extracranial structures such as the skin, muscles, and blood vessels in the head and neck; mucosa of the sinuses and dental structures; and intracranial structures including the regions of the large arteries near the circle of Willis, the great intracranial venous sinuses, parts of the dura and dural arteries, and cranial nerves.
- Cranial nerve deficit: Dysfunction of any of the different cranial nerves caused by damage to that nerve, various clinical manifestations are observed depending on the nerve being affected.

<u>Previous seizures:</u> Signs and/or symptoms due to abnormal excessive or synchronous neuronal activity of the brain.

- Controlled on medication (drug-responsive epilepsy): Patient receiving the current anti-epileptic drug regimen has been seizure-free for a minimum of three times the longest preintervention seizure interval or 12 months, whichever is longer.
- Intractable on medication (drug-resistant epilepsy): failure of adequate trials of two tolerated, appropriately chosen and administered anti-seizure drugs (whether as monotherapy or in combination) to achieve seizure freedom.

<u>Characteristics of Lesion(s) with Symptomatic Hemorrhage that Occurred more than a year ago:</u>

- Cavernous angioma on MRI: Lesion with typical "popcorn appearance", mixed signals of blood at different stages of organization and calcifications, and surrounding hemosiderin ring. [29]
- Type of Hemorrhage of Previous Bleed
  - Hemorrhage into CA (intralesional hemorrhage): Hyperintense signal in a CA, observable on T_1- and/or T_2-weighted MRI sequences, that does not cross the outer hemosiderin ring.
  - Small hemorrhage outside of hemosiderin ring into surrounding tissue (extralesional hemorrhage): Hyperintense signal in a CA, observable on T_1- and/or T_2-weighted MRI sequences, that crosses the outer hemosiderin ring extending onto the surrounding brain parenchyma.
  - Subarachnoid hemorrhage: Extravasation of blood into the subarachnoid space.
  - Large intraparenchymal hemorrhage related to CA: Hemorrhage of CA origin that extends into surrounding brain parenchyma causing significant mass effect evidenced by CT or MRI.

- Location of Lesion of Previous Bleed
  - Cerebellum: Located posterior to the brainstem and 4th ventricle. Is separated from the cerebrum by the tentorium cerebelli. Consist of two hemispheres and a narrow midline zone (vermis).
  - Thalamus: Nuclear complex located in the diencephalon, located above the midbrain and bellow the lateral ventricles and corpus callosum.
  - Brainstem: Structure that connects cerebral hemispheres with cerebellum and medulla. Composed of midbrain, pons, and medulla oblongata.
  - Temporal lobe: Located inferior to the frontal lobe, anterior to the occipital lobe, and inferior to the parietal lobe. Separated from the frontal and parietal lobe by the Sylvian fissure.
  - Parietal lobe: Located above the temporal lobe and behind the frontal lobe separated by the central fissure.
  - Occipital lobe: Inferior to the parietal and temporal lobe. Separated from the cerebellum by the tentorium cerebelli.
  - Frontal lobe: Largest of four major lobes. Located in front of the parietal lobe, separated by the central sulcus, and the temporal lobe, separated by the Sylvian fissure.

Medical condition:

- Hypertension: Systolic blood pressure of ≥ 130 mmHg or a diastolic blood pressure of ≥ 80 mmHg on ≥ 2 reading in ≥ 2 occasions.
- Diabetes: Fasting plasma glucose ≥ 126 mg/dL (7 mmol/L), 2-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test, A1C $\geq 6.5\%$ (48 mmol/mol), or a patient with classic symptoms of hyperglycemia or hyperglycemic crisis and a random plasma glucose ≥ 200 mg/dL (11.1 mmol/mol).
- CA presenting during pregnancy: Female patient diagnosed with CA during pregnancy.

Coexisting risk factors:

- Risk factor: Something that increases the chance of developing a disease.
- Smoking status:
  - Current smoker: Currently smokes or smoking at the time of the ictus. Has smoked ≥ 100 cigarettes during their lifetime and were smoking every day or some days at the time of interview.
  - Quit (former smoker): Stopped smoking >6 months ago or >6 months before ictus. Has reported having smoked ≥ 100 cigarettes during their lifetime but were not smoking at the time of interview.
  - Nonsmoker: Has never smoked.
  - Recreational drugs (drugs of abuse/drug misuse): Substances used for a purpose not consistent with legal or medical guidelines.
  - Types of recreational drugs:
    - Narcotics: Fentanyl, heroin, hydromorphone, methadone, morphine, opium, oxycodone

- Stimulants: Amphetamines, cocaine, khat, methamphetamine
- Depressants: Barbiturates, benzodiazepines, GHB, rohypnol
- Hallucinogens: Ecstasy/MDMA, ketamine, LSD, peyote & mescaline, psilocybin
- Marijuana/cannabis
- Steroids
- Inhalants
- Drugs of concern: DXM, kratom, salvia divinorum.
- Designer drugs: Bath salts or designer cathinones, K2/spice, synthetic opioids
- Prior brain surgery for CA: Prior surgery for CA resection.

Family history:

- Relatives with CA: Blood relatives with diagnosed CA disease.
- No family history of documented CA: Blood relatives without CA disease.

Means of documentation (check all that apply):

- Magnetic Resonance Imaging: Procedure in which radio waves and a powerful magnet linked to a computer are used to create detailed pictures of areas inside the body. Also called MRI, NMRI, and nuclear magnetic resonance imaging.
- Genetic testing: Medical test that identifies changes in chromosomes, genes, or proteins linked to a disease or clinical condition.
- Surgery: Structurally altering the human body by incision or destruction of tissues and is part of the practice of medicine. Surgery also is the diagnostic or therapeutic treatment of conditions or disease processes by any instruments causing localized alteration or transportation of live human tissue.
- Autopsy: Post-mortem examination of the human body to reveal evidence of organic disease or to discover medical causes of death.

Other family history:

- Other type of intracranial vascular malformation: arteriovenous malformations (AVM), dural arteriovenous fistula (dAVF), developmental venous anomaly (DVA), telangiectasias, aneurysms, hemangiomas, Sturge Weber syndrome, among others.
- Intracranial hemorrhage from unknown source: ICH without a possible, probable or definite etiology.
- Ischemic stroke: episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction.
- Stroke of unknown type (cryptogenic stroke): symptomatic cerebral infarcts for which no probable cause is identified after adequate diagnostic evaluation.
- Intracranial aneurysm: abnormal dilatation on the arterial wall of the cerebral vessels.

MRI relevant to CASH:

- Date of Symptomatic Hemorrhage: Date of symptom onset attributed to hemorrhagic CA.
- Index Symptomatic Hemorrhage: Hemorrhagic CA of interest.
- MRI Field strength: The strength of the magnetic field is measured in gauss or tesla units (10,000 G = 1 T). In general, higher field strength improves the signal-to-noise ratio (SNR). SNR, contrast, and resolution increase almost linearly with field strength. The increases allow faster scanning and lower the incidence of motion artifacts.
    - 3T
    - 1.5T
- SWI: neuroimaging technique, which uses tissue magnetic susceptibility differences to generate a unique contrast.
    - SWI lesion count: Total number of lesions present on SWI scan.
    - New SWI lesions: New lesions on SWI compared to previous SWI scan of comparable field strength.
- T2
    - T2 Lesion Count (≥5mm maximum diameter): Lesions observable on T2 MRI sequence that measure ≥5mm.
    - Lesional growth on T2 (≥3mm): Increase in any lesion diameter of ≥3mm on comparable T2-weighted sequences.
    - New T2 lesion: New lesion of ≥5mm on comparable T2-weighted sequences.
- New hemorrhage: New bleeding on imaging studies.
    - Lesional: Hyperintense signal in a CA, observable on T_1- and/or T_2-weighted MRI sequences, that does not cross the outer hemosiderin ring.
    - Extralesional: Hyperintense signal in a CA, observable on T_1- and/or T_2-weighted MRI sequences, that crosses the outer hemosiderin ring extending onto the surrounding brain parenchyma.
- Rebleed in CASH lesion: New bleeding in a lesion with confirmed previous bleeding on MRI
- Type of Intracranial Hemorrhage
    - Hemorrhage into CA: Hyperintense signal in a CA, observable on T_1- and/or T_2-weighted MRI sequences, that does not cross the outer hemosiderin ring.
    - Hemorrhage into proximity of wall of CA: Hyperintense signal in a CA, observable on T_1- and/or T_2-weighted MRI sequences, in close proximity to defined CA wall.
    - Subarachnoid hemorrhage: Extravasation of blood into the subarachnoid space.
    - Large intraparenchymal hemorrhage related to CA: Hemorrhage of CA origin that extends into surrounding brain parenchyma causing significant mass effect evidenced by CT or MRI.
    - Intraparenchymal hemorrhage clearly unrelated to CA: Intracranial hemorrhage of known origin different from a CA causing significant mass effect evidenced by CT or MRI.
- Location of Lesion of Previous Bleed
    - Cerebellum: Located posterior to the brainstem and 4th ventricle. Is separated from the cerebrum by the tentorium cerebelli. Consist of two hemispheres and a narrow midline zone (vermis).

- Thalamus: Nuclear complex located in the diencephalon, located above the midbrain and bellow the lateral ventricles and corpus callosum.
- Brainstem: Structure that connects cerebral hemispheres with cerebellum and medulla. Composed of midbrain, pons, and medulla oblongata.
- Temporal lobe: Located posterior to the frontal lobe, anterior to the occipital lobe, and inferior to the parietal lobe. Separated from the frontal and parietal lobe by the Sylvian fissure.
- Parietal lobe: Located above the temporal lobe and behind the frontal lobe separated by the central fissure.
- Occipital lobe: Posterior to the parietal and temporal lobe. Separated from the cerebellum by the tentorium cerebelli.
- Frontal lobe: Largest of four major lobes. Located in front of the parietal lobe, separated by the central sulcus, and the temporal lobe, separated by the Sylvian fissure.
- Deep: Bleed located basal nucleus (basal ganglia) of the brain.
- Superficial: Lobar bleed in close proximity to brain cortex.

Modified Rankin Scale (mRS): Measures the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability.[12]

EuroQoL (EQ)-5D Descriptive System: The EQ-5D descriptive system is a preference-based health-related quality of life measure with one question for each of the five dimensions that include mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[15]

EQ-Visual Analog Scale (VAS): The EQ-VAS is a vertical visual analog scale that takes values between 100 (best imaginable health) and 0 (worst imaginable health). Patients provide a single value that gives a global assessment of their overall health.[15]

National Institutes of Health Stroke Scale (NIHSS): The NIHSS is a systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficit.[30]

Patient-Reported Outcomes Measurement Information System (PROMIS)-29: The PROMIS-29 instrument (version 2.0) is a collection of twenty-nine items drawn from the seven primary PROMIS® domains (depression, anxiety, physical function, pain interference, fatigue, sleep disturbance, and satisfaction with participation in social roles). The instrument contains four items from each primary domain plus a single pain intensity rating.[31]

Biomarker: Measurable subjective criteria that are entirely devoid of the individual's personal feelings, functionality, and beliefs that accurately reflect the underlying state of health or disease in an individual.

Medication use: Substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.

- Drug category
    - Antipyretics
    - Analgesics
    - Antibiotics
    - Antiseptics
    - Psychiatric medications
    - Oral contraceptives
    - Hormones
    - Anticoagulants
    - Antihypertensives
    - Antidiabetic
    - Statins
- Drug status
    - Current: Currently uses medications
    - Past use, quit: Has used medication in the past

Subject status:

- Alive
- Dead

Final status:

- Completion/Removal Date
- Death
- Withdraw from study
- Lost to follow-up
- Terminated by sponsor
- CASH lesion excised: Cavernous angioma with symptomatic hemorrhage surgically removed.

Supplemental Table I. Characteristics of screened cavernous angioma cases by recruitment site and overall between August 2018 -

March 2020 for the CASH Trial Readiness project.

Characteristic*	BNI (N=144)	Mayo (N=235)	UNM (N=140)	Utah (N=68)	UCSF (N=73)	UoC (N=189)	Overall (N=849)
Age	49 ± 17	48 ± 17	40 ± 20	55 ± 18	46 ± 16	42 ± 17	46 ± 18
Female	79 (55%)	130 (55%)	81 (58%)	36 (53%)	45 (62%)	124 (66%)	495 (58%)
White	111/125 (89%)	223/232 (96%)	112/120 (93%)	57/64 (89%)	43/59 (73%)	159/183 (87%)	705/783 (90%)
Hispanic	25/118 (21%)	4/233 (2%)	72/96 (75%)	9/65 (14%)	16/71 (23%)	20/183 (11%)	146/766 (19%)
Familial	49 (34%)	44 (19%)	122 (87%)	26 (38%)	23/72 (32%)	77/188 (41%)	341/847 (40%)

*Values are presented as mean ± standard deviation, n (%), or n/total (%)