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MarkVCID Cerebral small vessel consortium: II. Neuroimaging protocols

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Conflicts of interest

Dr. Kashani is a consultant, recipient of honoraria and speaker for Carl Zeiss Meditec. Dr. Fischl has a financial interest in CorticoMetrics, a company whose medical pursuits focus on brain imaging and measurement technologies. BF's interests were reviewed and are managed by Massachusetts General Hospital and Partners HealthCare in accordance with their conflict of interest policies.

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EXECUTIVE SUMMARY

The MarkVCID consortium was formed under cooperative agreements with the National Institute of Neurologic Diseases and Stroke (NINDS) and National Institute on Aging (NIA) in 2016 with the goals of developing and validating biomarkers for the cerebral small vessel diseases associated with the vascular contributions to cognitive impairment and dementia (VCID). Rigorously validated biomarkers have consistently been identified as crucial for multicenter studies to identify effective strategies to prevent and treat VCID, specifically to detect increased VCID risk, diagnose the presence of small vessel disease and its subtypes, assess prognosis for disease progression or response to treatment, demonstrate target engagement or mechanism of action for candidate interventions, and monitor disease progression during treatment.

Keywords

Acquisition protocol; biomarker; magnetic resonance imaging; optical computed tomography angiography; quality assurance; small vessel disease; vascular contributions to cognitive impairment and dementia

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The seven project sites and central coordinating center comprising MarkVCID, working with NINDS and NIA, identified a panel of 11 candidate fluid- and neuroimaging-based biomarker kits and established harmonized multicenter study protocols (see companion paper “MarkVCID Cerebral small vessel consortium: I. Enrollment, clinical, fluid protocols” for full details). Here we describe the MarkVCID neuroimaging protocols with specific focus on validating their application to future multicenter trials. MarkVCID procedures for participant enrollment, clinical and cognitive evaluation, and collection, handling, and instrumental validation of fluid samples are described in detail in a companion paper.

Magnetic resonance imaging (MRI) has long served as the neuroimaging modality of choice for cerebral small vessel disease and VCID because of its sensitivity to a wide range of brain properties, including small structural lesions, connectivity, and cerebrovascular physiology. Despite MRI’s widespread use in the VCID field, there have been relatively scant data validating the repeatability and reproducibility of MRI-based biomarkers across raters, scanner types, and time intervals (collectively defined as instrumental validity). The MRI protocols described here address the core MRI sequences for assessing cerebral small vessel disease in future research studies, specific sequence parameters for use across various research scanner types, and rigorous procedures for determining instrumental validity.

Another candidate neuroimaging modality considered by MarkVCID is optical coherence tomography angiography (OCTA), a noninvasive technique for directly visualizing retinal capillaries as a marker of the cerebral capillaries. OCTA has theoretical promise as a unique opportunity to visualize small vessels derived from the cerebral circulation, but is

at a considerably earlier stage of development than MRI. The additional OCTA protocols described here address procedures for determining OCTA instrumental validity, evaluating sources of variability such as pupil dilation, and handling data to maintain participant privacy.

MRI Protocol and instrumental validation

- The core sequences selected for the MarkVCID MRI protocol are three-dimensional T1-weighted multi-echo magnetization-prepared rapid-acquisition-of-gradient-echo (ME-MPRAGE), three-dimensional T2-weighted fast spin echo fluid-attenuated-inversion-recovery (FLAIR), two-dimensional diffusion-weighted spin-echo echo-planar imaging (DWI), three-dimensional T2*-weighted multi-echo gradient echo (3D-GRE), three-dimensional T_2-weighted fast spin-echo imaging (T2w), and two-dimensional T2*-weighted gradient echo echo-planar blood-oxygenation-level-dependent imaging with brief periods of CO_2 inhalation (BOLD-CVR). Harmonized parameters for each of these core sequences were developed for four 3 Tesla MRI scanner models in widespread use at academic medical centers.
- MarkVCID project sites are trained and certified for their instantiation of the consortium MRI protocols. Sites are required to perform image quality checks every two months using the Alzheimer's Disease Neuroimaging Initiative phantom.
- Instrumental validation for MarkVCID MRI-based biomarkers is operationally defined as inter-rater reliability, test-retest repeatability, and inter-scanner reproducibility. Assessments of these instrumental properties is performed on individuals representing a range of cerebral small vessel disease from mild to severe.
- Inter-rater reliability is determined by distribution of an independent dataset of MRI scans to each analysis site. Test-retest repeatability is determined by repeat MRI scans performed on individual participants on a single MRI scanner after a short (1 to 14 day) interval. Inter-scanner reproducibility is determined by repeat MRI scans performed on individuals performed across four MRI scanner models.

OCTA Protocol and instrumental validation

- The MarkVCID OCTA protocol uses a commercially available, FDA-approved OCTA apparatus. Imaging is performed on one dilated and one undilated eye to assess the need for dilation. Scans are performed in quadruplicate. MarkVCID project sites participating in OCTA validation are trained and certified by this biomarker's lead investigator.
- Inter-rater reliability for OCTA is assessed by distribution of OCTA datasets to each analysis site. Test-retest repeatability is assessed by repeat OCTA imaging on individuals on the same day as their baseline OCTA and a different-day repeat session after a short (1 to 14 day) interval.

- Methods were developed to allow the OCTA data to be de-identified by the sites before transmission to the central data management system.

The MarkVCID neuroimaging protocols, like the other MarkVCID procedures, are designed to allow translation to multicenter trials and as a template for outside groups to generate directly comparable neuroimaging data. The MarkVCID neuroimaging protocols are available to the biomedical community and intended to be shared.

In addition to the instrumental validation procedures described here, each of the neuroimaging MarkVCID kits will undergo biological validation to determine its ability to measure important aspects of VCID such as cognitive function. The analytic methods for the neuroimaging-based kits and the results of these validation studies will be published separately. The results will ultimately determine the neuroimaging kits' potential usefulness for multicenter interventional trials in small vessel disease related VCID.

1. BACKGROUND

The US National Institutes of Health (NIH) created the MarkVCID consortium to develop and validate biomarkers for the small vessel diseases associated with vascular contributions to cognitive impairment and dementia (VCID). The rationale and overall structure of MarkVCID is described in a companion paper[1]. In brief, MarkVCID has developed a series of standardized protocols and selected a panel of biomarker kits for validation of instrumental properties (reliability across users, sites, and time points) and biological properties (association with clinically meaningful aspects of VCID such as cognitive and functional performance).

We describe here the MarkVCID protocols for multi-site acquisition and instrumental validation of neuroimaging data (Supplemental Figure A). Magnetic resonance imaging (MRI) has long been a mainstay for detecting SVD during life [2]. MarkVCID also selected optical coherence tomography angiography (OCTA) for validation because of this modality's ability to provide rapid, noninvasive, high-resolution imaging of capillaries in the retina [3].

2. METHODS

MarkVCID is comprised of seven project sites (Johns Hopkins University School of Medicine [JHU]; Rush Medical Center/Illinois Institute of Technology [Rush/IIT]; Universities of California San Francisco, Davis, and Los Angeles [UC]; University of Kentucky [UKy]; University of New Mexico Health Sciences Center [UNM]; University of Southern California [USC]; and the Cohorts for Heart and Aging Research in Genomic Epidemiology [CHARGE] consortium) and a central coordinating center (CC; Massachusetts General Hospital) working with the National Institute of Neurologic Diseases and Stroke and National Institute on Aging under cooperative agreements. Further organization structure is described in a companion paper[1].

Methods reported here for MarkVCID acquisition and processing of MRI and OCTA data and instrumental validation of candidate neuroimaging biomarkers were

devised by the Imaging-Based Biomarkers Subcommittee, consisting of investigators performing neuroimaging-based biomarker research. A full list of the membership of this subcommittees is provided in Supplemental Table 1. All procedures shown below were adopted by unanimous consensus of the proposing subcommittees and the full Steering Committee.

The Imaging-Based Biomarkers Subcommittee process for reaching consensus on MarkVCID MRI image acquisition began with review of the sequences and data quality required for each proposed MRI-based biomarker kits. Based on this information, site representatives to the subcommittee, selected to represent each MRI vendor and model, volunteered to instantiate a draft MRI protocol at their site; this initial draft was then distributed to the full subcommittee. Representatives at the remaining sites then instantiated this draft protocol as closely as possible given limitations imposed by their site's hardware and software version, and issues that arose were brought back to the subcommittee. These limitations were discussed by the group and the protocol for each site iteratively modified until the MRI images were satisfactory at all participating sites. The final products of this process were MRI parameters optimized for each of the scanner types in use at participating MarkVCID sites: Siemens Trio and Prisma, Philips Achieva. To extend the generalizability of findings from inter-scanner instrumental validation testing, additional sequence parameters were developed for the General Electric (GE) 750W scanner type.

The MarkVCID OCTA image acquisition protocol was based on a pilot OCTA imaging protocol by the lead investigator for OCTA at USC. The pilot protocol was instantiated at the additional MarkVCID participating sites and issues that arose were addressed on a site-specific basis.

Prospective enrollment of participants and performance of new MRI scans occur at seven MarkVCID sites: JHU, UC (San Francisco and Davis), UKy, UNM, USC, and University of Texas Health Science Center San Antonio (UTHSCA, operating as part of the CHARGE site). Prospective enrollment of participants and performance of new OCTA scans occur at four MarkVCID sites: JHU, UC San Francisco, USC, and UTHSCA. Methods for MarkVCID participant enrollment, clinical evaluation, cognitive testing, and collection, processing, and instrumental validation of fluid-based biomarkers are described in a companion publication.

3. RESULTS

3.1 MRI Protocol

The key considerations in developing the MarkVCID MRI protocol were to acquire high quality MRI data that could be applied across sites in a future clinical trial, and to balance this goal against the need for a total scan duration tolerable to MarkVCID subjects. Based on the candidate MRI-based biomarker kits selected for MarkVCID validation and prior literature on imaging lesions associated with VCID, the following core sequences were selected for the MarkVCID MRI protocol: three-dimensional T1-weighted multi-echo magnetization-prepared rapid-acquisition-of-gradient-echo (ME-MPRAGE), three-dimensional T2-weighted fast spin echo fluid-attenuated-

inversion-recovery (FLAIR), two-dimensional diffusion-weighted spin-echo echo-planar imaging (DWI), three-dimensional T2*-weighted multi-echo gradient echo (3D-GRE), three-dimensional T_2-weighted fast spin-echo imaging (T2w), and two-dimensional T2*-weighted gradient echo echo-planar blood-oxygenation-level-dependent imaging with brief periods of CO_2 inhalation (BOLD-CVR). Imaging parameters for these sequences on different MRI models are provided in Table 1 and outlined below. Full protocols are also available online at https://markvcid.partners.org/consortium-protocols-resources (all MarkVCID web addresses accessible after site registration at markvcid.org).

ME-MPRAGE—An ME-MPRAGE [4, 5] sequence is included for anatomical reference, registration, normalization of images across individuals and modality, and estimation of brain volumes. ME-MPRAGE with a sagittal-plane acquisition, four echoes, and a voxel size of 1.0×1.0×1.0 mm^3 is used. An advantage of the ME-MRPAGE sequence is that the bandwidth of the sequence is higher than that of a typical single-echo, reducing image distortion in brain regions with large magnetic field inhomogeneity or poor shimming. The scan duration of the ME-MPRAGE sequence is approximately 6 minutes, modestly (10–20%) longer than a single-echo MPRAGE. (Exact durations for all sequences and vendors are provided in Table 1.)

FLAIR—FLAIR [6] MRI is included to evaluate white-matter-hyperintensities (WMH) of the brain. A high-resolution 3D FLAIR with a sagittal-plane acquisition and a voxel size of 1.0×1.0×1.0 mm^3 is used. The bandwidth of FLAIR MRI is matched as closely as possible to that of the ME-MPRAGE acquisition. By also matching read-out direction, the two sequences are constructed to have minimal differential distortion and can be brought into exact voxel register, maximizing their utility for extraction of biomarkers that require both T1 and T2/FLAIR information. The implementation of 3D FLAIR is different across MRI manufacturers. The inversion recovery and T_2-weighting components are combined in a T_2-preparation sequence module on the Philips system, for example, whereas they are separate modules on the Siemens systems. Furthermore, the fast-spin-echo acquisition modules also differ between the manufacturers. A neuroradiologist confirmed that the image quality of all FLAIR images from all vendors are sufficient for clinical reading. The approximate duration of the FLAIR scan is 6.5 min.

DWI—DWI can be used to evaluate microstructural properties of tissue relevant to SVD, using metrics such as mean diffusivity, fractional anisotropy, and free-water fraction (FW) [7] in the brain. To maintain consistency with legacy diffusion data and for ease of implementing the sequence at all sites, the MarkVCID protocol uses a single-shell (b=1000 s/mm^3), 40-direction diffusion sequence with a voxel size of 2.0×2.0×2.0 mm^3 and five b=0 (T_2-weighted volumes). Theoretically, FW calculation requires multiple b-values, but with suitable regularization can be accurately estimated from single-shell diffusion-weighted data[7]. An axial-plane acquisition is used with the fat chemical shift toward the posterior direction. An additional b=0 scan is performed in which the acquisition parameters are identical to the 40-direction diffusion sequence, but the fat chemical shift is reversed to be the anterior direction by changing the polarities of the phase-encoding gradients. The reverse

polarity data are used to estimate and correct image distortions in the DWI data. The total scan duration of both sequences is approximately 8.5 minutes.

3D-GRE—The 3D-GRE T_2*-weighted sequence is included for detection of microbleeds as well as quantitative susceptibility mapping. The sequence is performed in sagittal-plane orientation and acquires 6 or 8 echoes with TE ranging from approximately 3 to 21 ms. With a spatial resolution of 1.2×1.2×1.2 mm^3, the scan time is approximately 6 minutes. Both magnitude and phase images are collected and stored, so that they can be combined, using a common, non-vendor specific algorithm, to enhance visualization of microbleeds (i.e., susceptibility-weighted imaging [8]) or allow quantitative susceptibility mapping [9].

T2-weighted—A T2-weighted sequence is used to visualize enlarged perivascular spaces [10]. The sequence employs a 3D sagittal-plane acquisition with a spatial resolution of 1.0×1.0×1.0 mm^3. The scan is between 3 to 4 minutes in duration, depending on the scanner manufacturer.

BOLD-CVR—CVR[11] measures the brain's vasodilatory capacity in response to CO_2, which is primarily mediated through small resistance vessels in the brain. CVR is measured by collecting BOLD MRI images continuously while the subject breathes room air and then breathes a CO_2-enriched gas mixture in an interleaved fashion. The protocol uses a mildly hypercapnic gas of 5% CO_2 in room air and inhalation periods of 50 seconds. Three CO_2 periods are interleaved with four room air periods of 70 seconds each, resulting in a scan time of approximately 7 minutes. End-tidal CO_2 is recorded throughout the scan using a capnograph device (NMR3 monitor, Model 7900, Philips Respironics). The TE used for this scan (21 ms) is slightly lower than typical values (e.g. 30 ms) used in functional MRI studies at 3.0T to ensure that the signal change reflects blood oxygenation effects instead of cerebral blood volume effects [12, 13].

3.1.1 Site MRI Certification, quality assessment and data de-identification—

Each site is required to execute a series of steps to ensure that the instantiated protocol is correct, the data quality is acceptable, and site staff is trained on data de-identification, organization, and upload. Training documents (available at https://markvcid.partners.org/consortium-protocols-resources) cover procedures for subject and scan session registration, data anonymization, and data transfer. After site staff complete training on these procedures, they execute the following certification steps: 1) Download the protocol document for each scan type necessary for the site's biomarkers; 2) Instantiate the protocol on the site MRI scanner; 3) Send a copy of the instantiated protocol to the MarkVCID CC staff for review; 4) Upon approval, perform an MRI scan and send the data to the CC for review; 5) Incorporate any necessary protocol changes and repeat steps 3–5 as necessary until the site and CC are satisfied by the image quality.

To assess and maintain consistent image quality, each site is required to perform bimonthly MRI scans of the phantom [14] in use by the Alzheimer's Disease Neuroimaging Initiative (ADNI) [15]. Phantom scans are performed using modified versions of the ME-MPRAGE, diffusion-weighted, and CVR protocols used for patients, specifically use of a larger slice thickness (1.2 mm) for the ME-MPRAGE sequence to accommodate the phantom size and

a six-gradient-direction diffusion-weighted sequence with a single b=0 scan to calculate the apparent diffusion coefficient of the phantom's central sphere. The above five certification steps are also performed for the phantom protocol. The phantom protocols for each vendor and scanner model are also available at https://markvcid.partners.org/consortium-protocols-resources. The CC issues a certification letter upon successful completion of this process, which is also included in the site's annual progress report.

Imaging data is de-identified using DicomBrowser [16] by the individual sites before transmission to the CC data management system. All Personal Health Information (PHI) is removed from the DICOM file headers. Any local identifier entered into the scanner at the time of data acquisition is replaced by the MarkVCID subject identifier and age at the time of scanning (rounded to the first decimal to maintain de-identification).

3.1.2 Instrumental validation for MRI-based biomarkers—Instrumental validation consists of assessment of measurement reliability determined by a biomarker's repeatability (variability of multiple measurements under identical conditions) and reproducibility (variability of multiple measurements under differing conditions[17]). For the purposes of MarkVCID MRI-based biomarkers, instrumental validation is operationally defined as: 1) inter-rater reliability (differences between values obtained for MRI biomarkers by raters at different sites analyzing the same MRI data), 2) test-retest repeatability (differences between results for MRI biomarkers obtained using scans of the same individual obtained on the same MRI scanner but on different days separated by a short time interval), and 3) inter-scanner reproducibility (differences between results for candidate MRI-based biomarkers using scans of the same individual obtained on different MRI scanners).

MarkVCID developed common approaches to assessing these instrumental parameters across all MRI-based biomarker kits (Table 2). The MRI-based biomarkers selected by MarkVCID for full validation consist of kits measuring WMH Volume, WMH Growth/Regression, Peak Skeletonized Mean Diffusivity, Arteriolosclerosis, MRI Free Water, and CVR. Each of the candidate MRI-based biomarker kits was proposed by one of the MarkVCID sites, which serves as lead site for that kit. Detailed descriptions of the selection and analytic methods for each MarkVCID MRI-based biomarker kit will be published separately.

To establish inter-rater reliability, test data sets from 20 MRI scans, selected from the inter-scanner reproducibility study (see below) data, will be distributed to each site for analysis. The selected scans will be stratified to cover the full range of SVD severities as measured by WMH volume. Each participating site will designate staff who will use the processing tool developed and distributed by the lead site to analyze the data sets. The outcome measures obtained from different sites will be visualized using a Bland-Altman [18] plot and the reliability of these measurements estimated using intraclass correlation coefficients (ICC).

To assess test-retest repeatability each actively enrolling site will recruit a subset of 6 enrolled individuals to return for repeat MRI using the same scanner and protocol, 1 to 14 days after their initial MRI. The total number of individuals available for test-retest analysis will range from 30 to 36 depending on the number of prospectively enrolling MarkVCID

sites executing each MRI-based biomarker kit. The metrics for each MRI-based biomarker will be calculated by the lead site for each candidate MRI-based biomarker and the results again visualized using a Bland-Altman plot and assessed for variability by ICC.

Inter-scanner reproducibility will be assessed by a series of cross-model MRI scans acquired on 20 individuals, stratified to include 10 with no-to-low SVD burden and 10 with moderate-to-high SVD assessed by Fazekas Scale [19] scores on previously obtained MRI scans. Participants for this reproducibility study will be recruited by the CC under an IRB-approved study protocol from individuals enrolled in other research studies, self-referral through an online research portal, or screening of patients presenting to stroke or memory clinics. Each participant will be scanned on four MRI scanners, including two Siemens system (TIM Trio and Prisma), one Philips system (Achieva), and one GE system (750W). Scans will consist of the full MarkVCID MRI protocol without BOLD-CVR and will be completed at all sites within 15 weeks of each other. Data from the inter-site reproducibility scans will be transferred to the lead site for each biomarker kit, where they will be processed and analyzed again by Bland-Altman plot and ICC.

3.2 OCTA Protocol

An OCTA protocol was developed to assess an OCTA-based biomarker of retinal microvascular density (vessel skeleton density, VSD) in the central macula. Detailed description of the analytic method for this candidate biomarker will be published separately.

The MarkVCID OCTA protocol specifies use of the commercially available, FDA-approved spectral domain Cirrus AngioPlex 5000 from Carl Zeiss Meditec (Dublin, CA). Before OCTA imaging the right eye of each subject is anesthetized using 1 drop of topical 1% Proparacaine (Sandoz AG, Basel, Switzerland) then dilated using one or more drops of 2.5% Phenylephrine and 1% Tropicamide. Imaging of first the untreated left eye and then the dilated right eye is performed at least 10-minute after instillation of the last dilation drop. The rationale for performing OCTA on one dilated and one undilated eye in each participant is to assess whether dilation is necessary for potential application of this method to future clinical trials. Individuals are excluded from OCTA for history of vision-threatening ocular disease (e.g. advanced neovascular or non-neovascular macular degeneration, glaucoma, or diabetic retinopathy), concurrent prescription eye drop use, history of intravitreal injections or non-cosmetic ocular surgery, or history of adverse reactions to pupillary dilation. OCTA exclusion criteria and ophthalmic history are assessed by screening questionnaire provided prior to the study and, when available, clinical records from the most recent ophthalmic/optometric assessment.

Imaging is performed in a darkened room without ambient lighting other than the OCTA device-technician interface. Both the dilated and undilated eye of each subject are imaged using a commercially available $3\times3mm^2$ raster scan pattern (“Angiography 3×3mm”) centered on the fovea and a similar pattern centered on the optic nerve (“Optic Disc Cube 200×200”). All scans are repeated in quadruplicate and assessed by study personnel at the time of acquisition. Suboptimal scans are discarded and repeated based on prespecified protocol criteria. Scan quality is assessed objectively by a “signal strength” metric provided by the manufacturer and deemed unacceptable for signal strength of 7 or less. Imaging

technicians are also trained to discard scans for significant media opacity obscuring retinal vessels or motion artifact. OCTA data are archived in the native vendor format (DICOM) and exported as a set of bitmap images to be used in further analysis.

3.2.1 Site OCTA training, certification, and data de-identification—Imaging technicians at all sites are trained to perform OCTA assuming no prior training or knowledge for ophthalmic imaging. Site training certification is monitored by the CC and includes 1) review of the MarkVCID OCTA imaging protocol, acquisition instructions, screening worksheet, and case report forms, 2) video training modules on dilation, scanning procedures, and data management 3) a live training teleconference or recorded webinar with the OCTA lead site, 4) online assessment based on the training materials, and 5) submission of complete data set from one volunteer using the protocol's data registration, anonymization, and upload procedures. To assist sites with training and for quality control, the lead investigator reviews a sample of OCTA data from each site to provide real-time feedback and conducts a visit to each site in the first year of recruitment.

OCTA data is de-identified by the individual sites using the built-in function on the Zeiss system before transmission to the CC data management system. Exported bitmap- and TIFF-formatted files, used in the OCTA biomarker processing, are renamed to remove any remaining PHI from the filename before the data is sent to the CC.

3.2.2 Instrumental validation for OCTA—Inter-rater reliability for OCTA-derived VSD will be assessed by independent raters from each participating site applying the OCTA-VSD processing tool[3] to baseline OCTA scans from 30 participants stratified to represent a range of SVD severities. Test-retest repeatability will be assessed by repeated OCTA imaging on 6 individuals at each participating site total of 24 individuals) on the same day as their baseline OCTA and on a different day 1–14 days after their baseline study. All instrumental validation analyses will be performed separately on the dilated and undilated eyes to determine the impact of dilation on instrumental reliability of OCTA-VSD. The above inter-rater and test-retest measures will be visualized using Bland-Altman plots and the reliability estimated by ICC.

4. DISCUSSION

The MarkVCID consortium was formed to develop and validate fluid- and imaging-based biomarkers for the small vessel diseases associated with VCID. We describe here the MarkVCID protocols for MRI and OCTA image acquisition and instrumental validation. These protocols serve as the basis for validating the set of imaging-based biomarker kits selected by MarkVCID and ultimately for applying them to multi-site studies or interventional trials.

The challenges and potential approaches to harmonizing MRI-based VCID studies across multiple study sites were recently reviewed under the HARmoNizing Brain Imaging MEthodS for VaScular Contributions to Neurodegeneration (HARNESS) initiative [20]. Several prior studies have attempted to achieve harmonized multi-site MRI protocols. The ADNI study developed harmonized T1- and T_2-weighted sequences across MRI

manufacturers in ADNI-1 [15] and FLAIR and T_2* weighted sequences in subsequent phases (ADNI-GO, ADNI-2, and ADNI-3). [21, 22] ADNI-GO/2 also proposed diffusion, perfusion, and functional MRI sequences, although these sequences were each only developed on a single vendor platform (GE, Siemens, and Philips respectively).[21, 22] Compared to the ADNI protocol, the MarkVCID MRI protocol uses 3D acquisitions for all anatomical sequences, improving signal-to-noise ratio and spatial resolution in the slice direction and allowing collection of isotropic voxels and re-slicing and reorientation of the images in any direction. Another difference is that the MarkVCID diffusion and BOLD sequences are harmonized across three MRI vendors (and four models) instead of one. A third difference is that the MarkVCID T1-weighted sequence employs a multiple-echo version of the MPRAGE sequence with a high bandwidth, which reduces susceptibility-related image distortion. Finally, it should be noted that the bandwidths of the FLAIR and T1-weighted sequences are matched, so that the distortions in the two data sets will be similar and correlations between the observed positions of WMH and brain volumes/thicknesses, will be more accurate.

Another ongoing multi-site study that standardized a brain MRI protocol across manufacturers is the Adolescent Brain Cognitive Development (ABCD) study,[23] which recruits and follows approximately 10,000 adolescents over the ages of 10 to 20 years across the United States. The ABCD MRI protocol uses T_1- and T_2-weighted sequences that are similar to the MarkVCID sequences and does not include FLAIR or T_2* sequences because of the study population age. Another difference is that the ABCD study protocol was developed based on high-end MRI systems that are capable of multi-band echo-planar-imaging (MB-EPI). The UK Biobank project, a prospective epidemiological study with an MRI-based component, [24] performs its MRI acquisitions at three dedicated imaging facilities with identical dedicated MRI hardware and software and therefore does not require harmonized cross-scanner protocols.

Strengths of the MarkVCID protocols are the harmonization across multiple scanner types, systematic training of personnel and protocol implementation, and rigorous pre-specified plan for instrumental validation, including inter-rater reliability, test-retest repeatability, and inter-scanner reproducibility. There are also several limitations to the imaging-based protocols. The MRI protocols are limited to 3 Tesla (T) MRI systems; although this is the currently preferred field strength for clinical trial neuroimaging, the protocols do not provide guidance for studies using 1.5 or 7 T MRI. Another potential limitation to generalizability is that none of the consortium's prospective enrollment sites use a GE model MRI; we nonetheless included a GE scanner in the inter-scanner reproducibility analysis to enhance generalizability. Because of the consortium's panel of selected biomarkers and scan time constraints, the MarkVCID protocol does not include brain perfusion or functional MRI sequences that might also be useful in SVD. Finally, we note that there is considerably less experience instituting OCTA than MRI across multiple study sites. Because of OCTA's relatively recent introduction into clinical use, MarkVCID selected the device model with the earliest Food and Drug Administration clearance, the Cirrus Angioplex 5000, for use across participating sites.

The overarching goal of MarkVCID is to facilitate future multi-site observational studies and treatment trials for SVD-related VCID. The neuroimaging protocols described here as well as the results of the ongoing imaging-based biomarker kit instrumental and biological validation studies will be made available to the VCID community to serve as the basis for such trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in Context

Systematic review:

This manuscript reflects the consensus site-harmonized imaging protocol created by the Imaging Biomarker working group within the MarkVCID consortium. This protocol reflects the group's review of existing publicly available multi-site protocols and methodological papers, as well as consulting with external experts in the field. References to these sources are appropriately cited.

Interpretation:

The paper describes the protocols for the validation of imaging-based biomarkers used to investigate vascular contributions to cognitive impairment and dementia (VCID) and the instrumental validation plan for these biomarkers.

Future directions:

These protocols establish a standard for multi-site imaging-based studies which investigate VCID biomarkers and will provide the foundation for the validation of additional biomarker kits in this domain.

Table 1

MarkVCID Core MRI protocol

MRI imaging parameters listed by MRI manufacturer

Philips						
	ME-MPRAGE	**FLAIR**	**Diffusion**	**3D-GRE**	**T2w**	**CVR**
FOV (mm)	256×256	256×256	256×256	256×256	256×256	220×220
Δz (mm)	1	1	2	1.2	1	3.8
N_x×N_y	256×256	256×256	128×128	212×212	256×256	64×64
Nz	176	176	80	146	176	36
Plane	Sagittal	Sagittal	Axial	Sagittal	Sagittal	Axial
TR/TE/ΔTE (ms)	2530/1.66/1.9	4800/271	9245/76	27/2.4/2.3	2500/252	1500/21
Flip (deg)	7	40	90	15	90	90
BW (Hz/Px)	657	660	2096	786	775	2418
TI (ms)	1300	1650				
Echoes	4			8		
b (s/mm^2) (averages)			0 (5) and 1000 (1)			
Diff. directions			41			
Repetitions						281
Time (min:s)	5:26	5:55	7:15	5:24	3:10	7:13

Siemens						
	ME-MPRAGE	**FLAIR**	**Diffusion**	**3D-GRE**	**T2w**	**CVR**
FOV (mm)	256×256	256×256	256×256	[a]224×224 or 240×240	256×256	220×220
Δz (mm)	1	1	2	[a]1.2 or 1.3	1	3.8
N_x×N_y	256×256	256×256	128×128	212×212	256×256	64×64
Nz	176	176	80	[a]144 or 128	176	34
Plane	Sagittal	Sagittal	Axial	Sagittal	Sagittal	Axial
TR/TE/ΔTE (ms)	2530/1.64/1.86	[a]5000/388 or 6000/427	[a]8600/68 or 9800/84	[a]24/2.98/2.53 or 27/4.31/3.94	[a]2500/106 or 4000/427	1500/21
Flip (deg)	7	Varying	90	15 or 25	Varying	90
BW (Hz/Px)	650 or 651	651	1628	790	[a]781 or 651	2442
TI (ms)	[a]1100 or 1200	[a]1800 or 2000				
Echoes	4			[a]8 or 6		
b (s/mm^2) (averages)			0 (1) and 1000 (1)			
Diff. directions			45			
Repetitions						281
Time (min:s)	5:53~6:03	6:27~6:38	7:01~7:50	5:09~6:18	4:14~4:26	7:17

General Electric					
	BRAVO (T1WTD)	**FLAIR (3D)**	**Diffusion**	**SWAN 3D-GRE**	**CUBE T2w**
FOV (mm)	256×256	256×256	256×256	240×240	256×256

General Electric					
	BRAVO (T1WTD)	**FLAIR (3D)**	**Diffusion**	**SWAN 3D-GRE**	**CUBE T2w**
Slice Thickness (mm)	1	1	2	2	1.2
$N_x \times N_y$	256×256	256×256	128×128	320×288	288×288
Nz	176	176	80	50	176
Plane	Sagittal	Sagittal	Axial	Axial	Sagittal
TR/TE/ΔTE (ms)	9.5/3.7	6000/173	[a]8600/68 or 9800/84	43.4/23.4	3000/maximum
Flip Angle (deg)	10	90	90	10	90
BW (kHz)	25	25	1628	62.5	62.5
TI (ms)	600	1601			
Echoes/ETL	X	200		X	
b (s/mm^2) (averages)			0 (1) and 1000 (1)		
Diff. directions			5 b=0, 40 b≠0		
Repetitions					
Time (min:s)	5:19	4:52	9:27	3:53	3:40

[a]The first (second) parameter was used on Siemens Prisma (TrioTIM) system.

X denotes non-adjustable or non-viewable parameter

Table 2

Summary of MarkVCID MRI and OCTA instrumental validation process

	No. of subjects (MRI)	**Timepoints (MRI)**	**No. of subjects (OCTA)**	**Timepoints (OCTA)**
Inter-rater reliability	20	N/A	20	N/A
Test-retest repeatability	30–36 (6 per prospectively enrolling site performing each kit)	2 scans 1–14 days apart	24 (6 per participating site)	2 complete scans at baseline; one additional scan within 1–14 days of baseline
Inter-site reproducibility	20	4 scans on different scanner models within 15 weeks	N/A	N/A