Title

Central vein sign: A diagnostic biomarker in multiple sclerosis (CAVS-MS) study protocol for a prospective multicenter trial

Authors

Ontaneda, D
Sati, P
Raza, P
et al.

Publication Date

2021

DOI

10.1016/j.nicl.2021.102834

Peer reviewed

NeuroImage: Clinical 32 (2021) 102834

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Central vein sign: A diagnostic biomarker in multiple sclerosis (CAVS-MS) study protocol for a prospective multicenter trial

D. Ontaneda [a,*], P. Sati [b,c], P. Raza [a], M. Kilbane [a], E. Gombos [b], E. Alvarez [d], C. Azevedo [e], P. Calabresi [f], J.A. Cohen [a], L. Freeman [g], R.G. Henry [h], E.E. Longbrake [i], N. Mitra [j], N. Illenberger [j], M. Schindler [j], D. Moreno-Dominguez [k], M. Ramos [k], E. Mowry [f], J. Oh [l], P. Rodrigues [k], S. Chahin [m], M. Kaisey [b], E. Waubant [h], G. Cutter [n], R. Shinohara [j], D.S. Reich [c], A. Solomon [o], N.L. Sicotte [b], North American Imaging in MS Cooperative

[a] *Cleveland Clinic Foundation, Cleveland, OH, United States*
[b] *Cedars Sinai, Los Angeles, CA, United States*
[c] *NINDS, NIH, Bethesda, MD, United States*
[d] *Neurology, U of Colorado, Denver, CO, United States*
[e] *USC, Los Angeles, CA, United States*
[f] *Neurology, Johns Hopkins, Baltimore, MD, United States*
[g] *Dell Medical School, The University of Texas at Austin, Austin, TX, United States*
[h] *University of California San Francisco, San Francisco, CA, United States*
[i] *Yale University, North Haven, CT, United States*
[j] *University of Pennsylvania, Philadelphia, PA, United States*
[k] *QMENTA Inc, Boston, MA, United States*
[l] *University of Toronto, Toronto, ON, Canada*
[m] *Washington University, St. Louis, MO, United States*
[n] *UAB School of Public Health, Birmingham, AL, United States*
[o] *The University of Vermont, Burlington, VT, United States*

ARTICLE INFO

Keywords:
Multiple sclerosis
MRI
Biomarker
Diagnosis
Central vein
Demyelinating disease
Susceptibility-weighted imaging
T2*-weighted imaging

ABSTRACT

The specificity and implementation of current MRI-based diagnostic criteria for multiple sclerosis (MS) are imperfect. Approximately 1 in 5 of individuals diagnosed with MS are eventually determined not to have the disease, with overreliance on MRI findings a major cause of MS misdiagnosis. The central vein sign (CVS), a proposed MRI biomarker for MS lesions, has been extensively studied in numerous cross sectional studies and may increase diagnostic specificity for MS. CVS has desirable analytical, measurement, and scalability properties. "Central Vein Sign: A Diagnostic Biomarker in Multiple Sclerosis (CAVS-MS)" is an NIH-supported, 2-year, prospective, international, multicenter study conducted by the North American Imaging in MS Cooperative (NAIMS) to evaluate CVS as a diagnostic biomarker for immediate translation into clinical care. Study objectives include determining the concordance of CVS and McDonald Criteria to diagnose MS, the sensitivity of CVS to detect MS in those with typical presentations, and the specificity of CVS among those with atypical presentations. The study will recruit a total of 400 participants (200 with typical and 200 with atypical presentations) across 11 sites. T2*-weighted, high-isotropic-resolution, segmented echo-planar MRI will be acquired at baseline and 24 months on 3-tesla scanners, and FLAIR* images (combination of FLAIR and T2*) will be generated for evaluating CVS. Data will be processed on a cloud-based platform that contains clinical and CVS rating modules. Imaging quality control will be conducted by automated methods and neuroradiologist review. CVS will be determined by Select6* and Select3* lesion methods following published criteria at each site and by central readers, including neurologists and neuroradiologists. Automated CVS detection and algorithms for incorporation of CVS into McDonald Criteria will be tested. Diagnosis will be adjudicated by three neurologists who served on the 2017 International Panel on the Diagnosis of MS. The

* Corresponding author at: 9500 Euclid Avenue, Cleveland, OH 44195, United States.
E-mail address: ontaned@ccf.org (D. Ontaneda).

https://doi.org/10.1016/j.nicl.2021.102834
Received 19 May 2021; Received in revised form 16 September 2021; Accepted 19 September 2021
Available online 23 September 2021

CAVS-MS study aims to definitively establish CVS as a diagnostic biomarker that can be applied broadly to individuals presenting for evaluation of the diagnosis of MS.

1. Introduction

The diagnosis of multiple sclerosis (MS) is currently based on criteria that incorporate clinical, MRI, and laboratory features (Thompson et al., 2018). Current diagnostic criteria for MS were designed and tested in patients with typical presentations (episodes of neurological dysfunction typical of MS, such as optic neuritis and partial myelopathy), and they have a high degree of sensitivity in making an MS diagnosis in these patients. However, when widely used in more heterogeneous real-world populations where many patients present with clinical symptoms atypical for MS (onset with symptoms outside of typical episodes of neurological dysfunction, such as encephalopathy or headache, or absence of symptoms), improper use of the MS diagnostic criteria can contribute to MS misdiagnosis. Improper use of the criteria may occur when applying

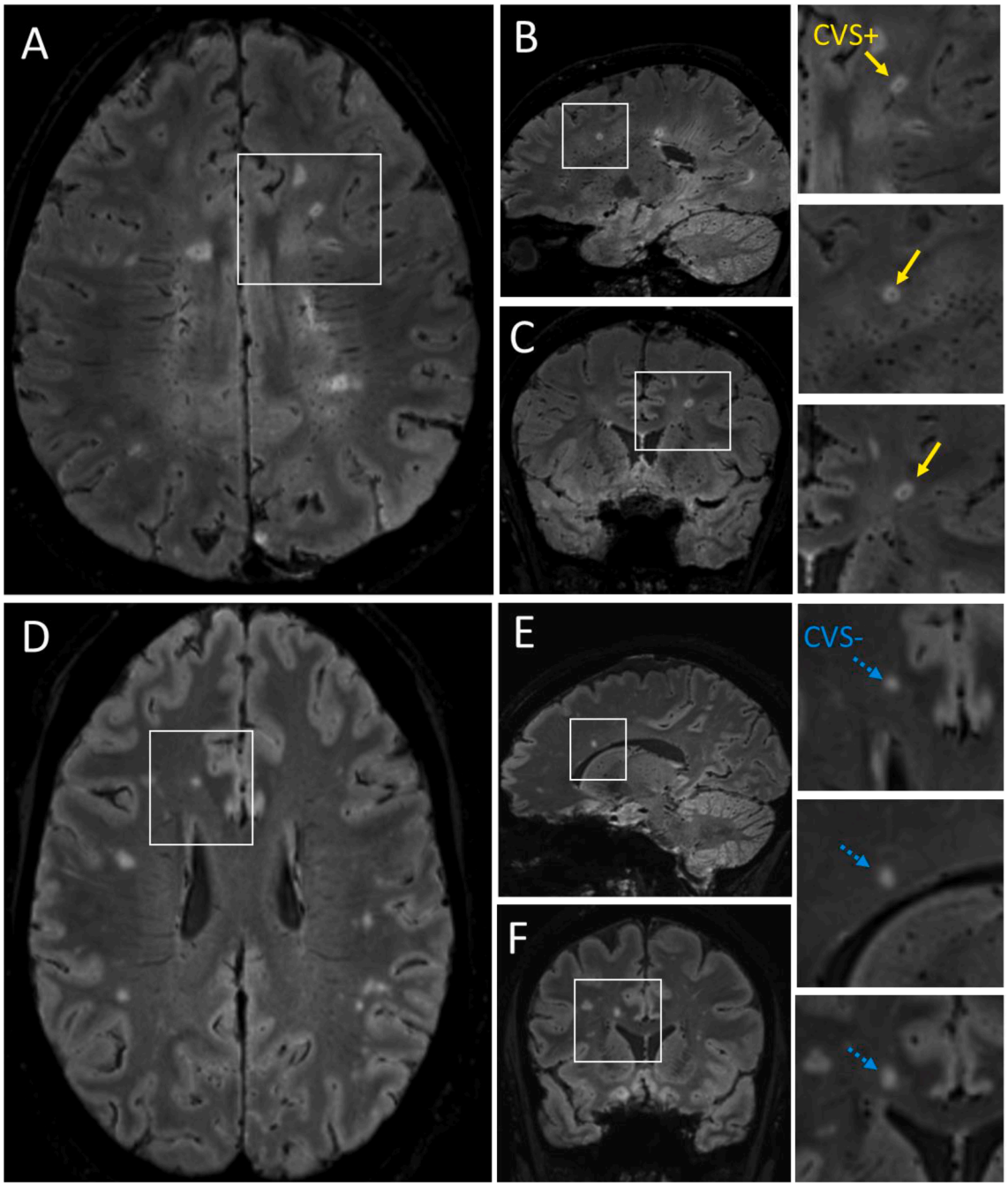

Fig. 1. Representative MRI of two patients evaluated for the "Central Vein Sign" with 3 T FLAIR*. Axial (A), sagittal (B), and coronal (C) FLAIR* reformatting shows high proportion of CVS positive (CVS +) lesions in a patient with MS. Same FLAIR* reformatting (D, E, F) shows a high proportion of CVS negative (CVS-) lesions in a patient with presumed small vessel ischemic disease without MS. Magnified views show examples of CVS+ (top) and CVS- (bottom) lesions, which can be identified in all three slice orientations due to the high-isotropic-resolution (650 μm) of 3 T FLAIR*.

the criteria outside a typical presentation, when the criteria for "no better explanation" of the presentation is not fully satisfied, and when using lesions that do not exhibit typical features (size and location) to satisfy dissemination in time and space. Identification of the appropriate clinical context is now emphasized in the 2017 criteria and has been highlighted as a step to reduce misdiagnosis (Solomon et al., 2019).

The problem of misdiagnosis is substantial, as roughly 20% of patients referred to an MS center with a previous diagnosis of MS have been found to be misdiagnosed (Kaisey et al., 2019). Approximately 2/3 of misdiagnosed patients are started on disease modifying therapy (DMT) for MS (Solomon et al., 2016). Consequences include substantial unnecessary costs (Gooch et al., 2017); psychological burden on misdiagnosed patients, potential false inflation of treatment success in clinical trials, and morbidity associated with adverse effects of some of the more potent DMT, which are increasingly used as first-line agents (Ontaneda et al., 2019; Midaglia et al., 2021). Overreliance on MRI is a major contributor to MS misdiagnosis, as many patients present with nonspecific white matter abnormalities on conventional MRI (Solomon et al., 2021). Thus, there is a great need for methods that improve the specificity of currently available MRI/clinical criteria to address this common clinical challenge.

One feature that may help differentiate MS lesions from other etiologies is identification of a central vein on MRI. MS lesions have been described histopathologically as occurring around central veins, and improvement in MR technology now permits their visualization (Sati et al., 2016). FLAIR*, a combination of T2-FLAIR and T2*-weighted segmented echo planar imaging (segEPI) (Sati et al., 2014; Sati et al., 2012), takes advantage of the high sensitivity of FLAIR to detect white matter lesions and that of T2*-weighted imaging to detect blood vessels, allowing the identification of white matter lesions and venous structures concomitantly (Fig. 1) (Sati et al., 2012). Using various susceptibility-based imaging techniques to visualize central veins at both 3 T and 7 T in multiple cohorts, the extensive literature on central vein imaging in MS suggests that CVS can be detected in $>$ 85% of white matter lesions in MS patients (Kilsdonk et al., 2014) and in the minority of white matter lesions found in other conditions, including small vessel ischemic disease (8%) (Mistry et al., 2016); migraine (34%) (Solomon et al., 2015); and other inflammatory or autoimmune diseases (14%) (Maggi et al., 2018). CVS is also prevalent in lesions in patients with the so-called "radiologically isolated syndrome" (RIS), in which findings highly suspicious for MS are discovered incidentally on brain MRI (Suthiphosuwan et al., 2019). The CVS is also scalable, as CVS can be assessed with readily available sequences on high-field MRI machines with feasible acquisition times. Both the European Magnetic Resonance Imaging in MS group (MAGNIMS) and the Consortium of Multiple Sclerosis Centers (CMSC) have highlighted the need for a prospective study examining CVS as a potential biomarker in MS (Filippi et al., 2016).

A peer-reviewed position statement from the North American Imaging in MS Cooperative (NAIMS) includes guidelines for a radiologic definition of CVS (Sati et al., 2016). A variety of criteria for defining central vein positivity on a given scan have been proposed, including a threshold of 40% of lesions with a visible central vein (Tallantyre et al., 2011); a combination of CVS positive (CVS $+$) lesion count and location (Kilsdonk et al., 2014); and counting central veins in a pre-defined subset of lesions (e.g. to identify at least 10 CVS $+$ lesions (Tallantyre et al., 2011). An alternative approach that has gained currency, Select6*, is to seek at least 6 CVS $+$ lesions; when $<$ 6 total lesions are present, a majority must contain a central vein (Mistry et al., 2016). An even more simplified version, Select3*, requires only 3 CVS $+$ lesions to be identified (Solomon et al., 2018). All of these CVS criteria are sensitive and specific markers of MS in cross-sectional studies (Sinnecker et al., 2019).

To date, CVS has mainly been applied in cross-sectional studies of patients who have met various iterations of the McDonald Criteria or have been confirmed to have other conditions that might mimic MS. The study presented here will evaluate CVS criteria prospectively in individuals with and without typical presentations of MS.

2. Material and methods

The protocol was developed by the study steering committee, comprised of 3 neurologists (DO, NS, AS), 2 statisticians (RS, GC), 1 MRI physicist (PS), and 1 double-trained neurologist/neuroradiologist (DSR). The design is based on preliminary data generated in the Central Vein in Multiple Sclerosis Pilot study, which was a cross-sectional study conducted by NAIMS at 10 North American sites, collecting data on 97 participants using T2*w segEPI/FLAIR* (Fig. 1). The current study, "Central Vein Sign: A Diagnostic Biomarker in Multiple Sclerosis (CAVS-MS)" is an NIH-supported (1U01NS116776-01), 2-year, prospective, international, multicenter study conducted by the North American Imaging in MS Cooperative (NAIMS) to evaluate CVS as an MRI-based diagnostic biomarker for immediate translation into clinical care (NCT04495556). CAVS-MS will be conducted by NAIMS with guidance by the NINDS Biomarker Program.

3. Results

3.1. Objectives

The study's primary objective is to determine whether CVS allows for an earlier, equally accurate diagnosis of MS in those presenting with typical first demyelinating events but not initially meeting McDonald Criteria. The three secondary objectives are: (1) to determine concordance of CVS and McDonald Criteria in those meeting McDonald Criteria at baseline; (2) to determine if CVS is specific for MS among individuals with atypical presentations over 24-month follow-up; and (3) to determine whether CVS predicts development of clinical MS in people with RIS. Exploratory objectives include: (1) to develop and test an optimal approach to integrating CVS into MS diagnostic criteria; (2) to calculate the overall healthcare cost savings associated with earlier diagnosis of MS using the CVS; and (3) to calculate cost savings from rejecting the diagnosis of MS in the atypical presentation group who do not have scan-level CVS at baseline and do not fulfil McDonald Criteria at 24-month follow-up.

3.2. Study design

CAVS-MS is a prospective, international, multicenter, longitudinal, observational study. The study will investigate CVS in a mixed population of participants referred for a diagnosis of MS with (n $=$ 200) and without (n $=$ 200) typical presentations, the latter including radiological presentations without neurological symptoms. The study will follow study participants for up to 24 months to determine the specificity and sensitivity of CVS for a diagnosis of MS using the 2017 McDonald Criteria as the criterion standard for diagnosis. Participants will be recruited from the patients presenting for a new evaluation of MS at 11 sites: Cleveland Clinic, Johns Hopkins University, Washington University in St. Louis, The University of Texas at Austin, University of Colorado Denver, University of Toronto (St. Michael's Hospital), University of Vermont, University of Pennsylvania, Cedars Sinai Medical Center, University of Southern California, and Yale University. Study investigators will confirm eligibility criteria, and participants will then be enrolled into the study. The study flow diagram is presented in Fig. 2.

3.3. Participants and recruitment

The study will recruit a total of 400 participants, 200 with typical presentations and 200 without typical presentations including radiological suspicion of MS. Inclusion criteria will include: (1) age 18–65 years; (2) referral to a study site for a clinical suspicion of MS; (3) onset with typical or atypical presentation (Appendix Table 1) Supplement Table 1. Detailed Inclusion/Exclusion Criteria; (4) ability to provide

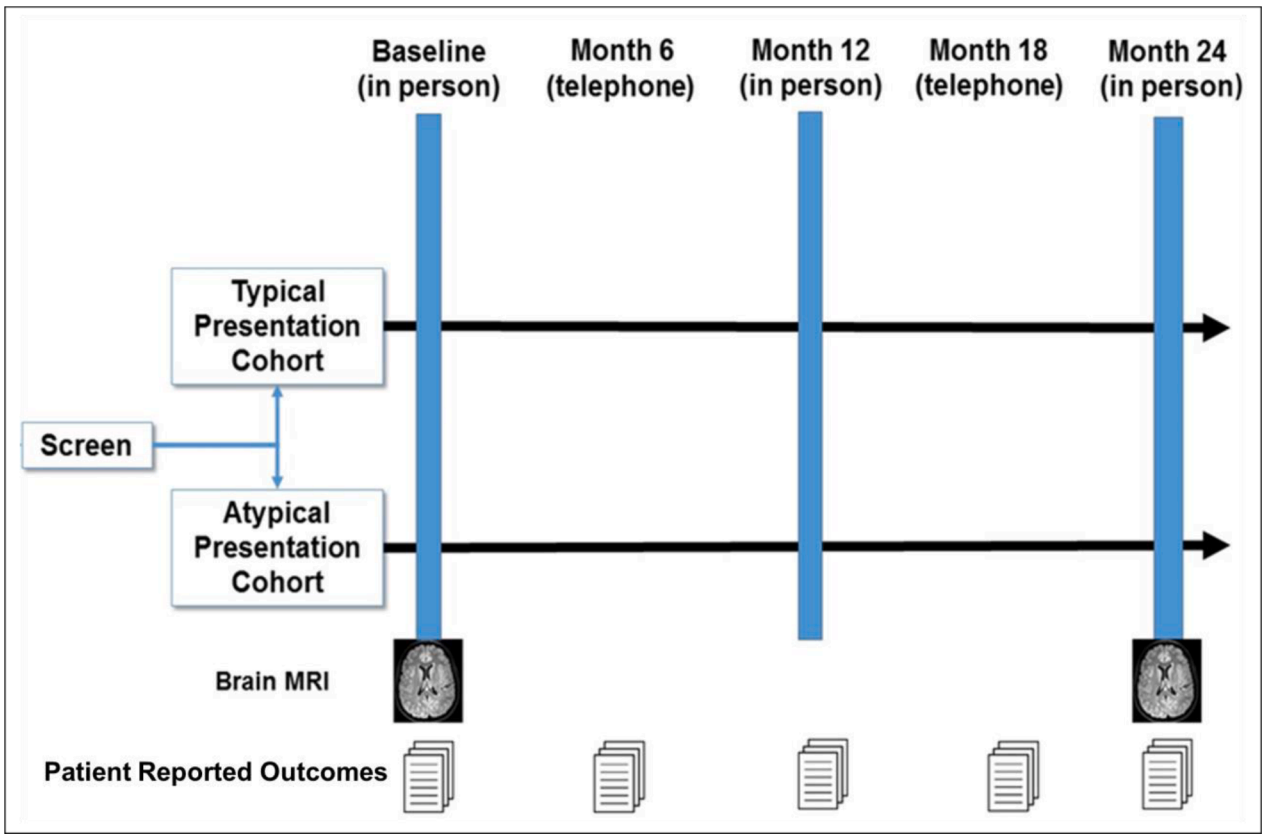

Fig. 2. Patients will be screened and adjudicated for typical or atypical presentations and followed with clinical visits and brain MRI at baseline and 24 months. Patient-reported outcomes will be collected every 6 months. The diagnosis of MS will be adjudicated using data collected at baseline, 12 months, and 24 months.

informed consent; (5) for participants referred for clinical suspicion of MS who had workup prior to referral or who are taking disease-modifying therapies for MS, digital availability of diagnostic cranial MRI with gadolinium within 3 months of initial symptoms (to retrospectively determine presence of CVS on lesions present on initial scans, based on the study FLAIR* scan), and (6) onset of typical or atypical symptoms within 10 years of screening. Exclusion criteria include: (1) contraindication to MRI studies; metal or metal implants incompatible with MRI; (2) inability to tolerate MRI due to claustrophobia or known excessive movement (e.g., tremor); (3) contraindication to use of gadolinium containing contrast agents (allergy or renal failure); and (4) treatment with systemic corticosteroids in the 4 weeks preceding enrollment. Participants will be recruited from the clinical population at the different sites. The sites represent major MS referral centers across the country and were selected to capture a distribution of sex, age, and race/ethnicity approximately representative of the general North American population.

3.4. Clinical study procedures

Prospective participants will be identified by site clinicians, pre-screened via chart review by site study coordinators, and scheduled for baseline visit. Enrollment will follow informed consent and confirmation of exclusion/inclusion criteria. Baseline procedures include collection of demographics, MS-related disease history, prior MRI studies, and cerebrospinal fluid results (if performed). Participants will undergo MRI of the brain before and after gadolinium, patient-reported outcomes (Patient-Determined Disease Steps, Quality of Life in Neurological Disorders [Neuro-QOL]), and clinical disability measures (Multiple Sclerosis Functional Composite). These same measures will be collected at months 12 and 24. Phone encounters will be conducted to collect interim data (patient reported outcomes, relapses, and diagnostic study results) at months 6 and 18. The study flowsheet, with detailed procedures, is presented in Table 2 of the Appendix. Presentation type (typical vs. atypical) will be noted by the site principal investigator (PI) and centrally adjudicated by 3 study neurologists. Clinical data, including relapses, MRI results, cerebrospinal fluid results and other *para*-clinical testing over the 24-month study period will be recorded by the local sites in the cloud database. MRI studies (brain, cervical cord, and thoracic cord) conducted during the study observation period, as part of clinical practice, will be rated for presence of new or enhancing lesions by the site investigators and results will be uploaded to the cloud. At all study visits, site PIs will note whether and when diagnostic criteria were met. When a diagnosis of MS is not made, the site-PI will indicate the most likely alternative diagnosis. The diagnosis of MS will also be adjudicated at baseline, 12 months, and 24 months by a group of 3 neurologists who previously served on the 2017 International Panel on the Diagnosis of MS. Serum, plasma, and buffy coat samples will be collected at baseline and stored for future studies.

3.5. Study MRI procedures and analysis

The study will include MRI at baseline and 24 months (final study visit). MRI at 24 months (end of study) will be used to assist in determination of McDonald Criteria and final review of CVS. A dedicated study MRI will not be conducted at month 12 due to budget constraints; however, clinical MRIs will be rated for new lesions across the entire 24 month study period. Scanning will be conducted in approximately 30-minute sessions and will be performed on both Siemens and Philips platforms at 3 T. Studies will be conducted with contrast (macrocyclic gadolinium chelates at a dose of 0.1 mmol/kg). Images will be acquired at each site according to the study imaging protocol (Table 1). T1 pre-contrast, T1 post-contrast, and T2-FLAIR images will be used for the determination of dissemination in space and time based on the 2017

Table 1
MRI sequence Details.

Image Type	Scan Time	Sequence Details	Voxel Size
T1-weighted MPRAGE	4 min 17 sec	3D, Sagittal	1 mm iso
T2-weighted FLAIR	6 min 53 sec	3D, Sagittal	1 mm iso
T2*-weighted segEPI	5 min 44 sec	3D, Sagittal	0.65 mm iso
T1-weighted GRE	3 min 34 sec	3D, Sagittal	1 mm iso
SWI-weighted GRE	4 min 20 sec	3D, Axial	0.65 mm × 0.65 mm x3 mm
Contrast Administration		*Single dose, 0.1 mmol/kg*	
T2*-weighted segEPI with contrast	5 min 44 sec	3D, Sagittal	0.65 mm iso
T1-weighted GRE with contrast	3 min 34 sec	3D, Sagittal	1 mm iso

McDonald MRI criteria (Thompson et al., 2018). 3D T2*-weighted segEPI, FLAIR*, and SWI (an additional and commonly available sequence for detection of CVS) will be used for rating of CVS. CVS will be rated on both the post-contrast (primary analysis) and pre-contrast FLAIR* images. We have previously demonstrated the increase in vein conspicuity when we acquired the segEPI sequence during or immediately after the injection of gadolinium-based contrast agent (Sati et al., 2014). This is due to the blood-pool susceptibility effects present within the first minutes of the circulation of paramagnetic contrast agent in the vascular system. Our preliminary data collected in the pilot CAVS-MS study, demonstrated increased conspicuity of the central vein with use of contrast (Daboul et al., 2020). SWI images will be obtained from the scanner using the manufacturer's standard processing methods (both Siemens and Philips provide similar susceptibility contrast enhanced with phase information). The SWI sequence uses the recommended echo time of ~ 20 ms at 3 T (Haacke et al., 2009); and the T2*-weighted segEPI uses an optimized echo time of ~ 30 ms at 3 T (Sati et al., 2014). Given that the T2*-weighted segEPI sequence uses a segmented (multishot) readout with an optimal EPI factor of 15 lines per shot, we anticipate minimal geometric distortions (only slight distortion in the frontal lobes), which will not affect the assessment of the CVS (Sati et al., 2014).

Images will be electronically uploaded to a cloud-based research/privacy-compliant database administered by a third-party contract research organization, QMENTA ®. Upload will occur on a web-based platform, which will be accessible to study investigators and which has already been tested in the CAVS-MS pilot study. The QMENTA pipeline (Fig. 3) includes 3 post-processing steps to generate FLAIR* images: (1) rigid registration of T2*w segEPI to T2 MNI template (2) rigid registration of T2-FLAIR to the aligned T2*w segEPI with upsampling of the registered T2-FLAIR to match the high spatial resolution of the T2*w segEPI; and (3) voxel-wise multiplication of the co-registered, interpolated T2-FLAIR by the T2*w segEPI with resultant FLAIR* (Sati et al., 2012). Image registration will be performed using the Advanced Normalization Tools (ANTs) and Insight ToolKit (ITK) (Avants et al., 2014).

The data flow and rating software were extensively tested and refined in the CAVS-MS pilot study. Uploaded images undergo an initial automated quality control check for presence of all required sequences on the cloud-based platform. The QMENTA platform described above is then initiated. A central image analyst individually checks all scans and feeds information back to sites regarding needed modifications or possible repeat scanning. Finally, five study neuroradiologists will perform quality control of the FLAIR* images.

The presence of central veins will be determined based on NAIMS guidelines (Sati et al., 2016). At the scan level, both Select6* and Select3* will be used. For Select6*, readers will rate a scan as CVS-positive if there are $\geq$ 6 morphologically characteristic lesions with central veins, or if there are $<$ 6 morphologically characteristic lesions, but CVS-positive lesions outnumber CVS-negative lesions. If neither condition is met, the scan will be rated as Select6* negative. Select3* defines a scan as CVS-positive if there are $\geq$ 3 candidate lesions that meet CVS criteria. MRIs with $<$ 3 candidate lesions are considered negative. For both Select6* and Select3*, the lesions evaluated for central vein must satisfy NAIMS criteria and are selected at the discretion of the local reader, as described (Solomon et al., 2018). Rating of Select 6* and Select 3* will be conducted locally by the site PI at each of the 11 participating clinical centers and centrally by neuroradiologists (5). Site PI raters will be blinded to patient data and will rate only the scans from their sites at the end of the enrollment period. The neuroradiologists will rate lesions centrally in batches of 20 cases. MRI images will be anonymized and raters blinded to the clinical characteristics of the participants.

An automated lesion detection algorithm will also be conducted as described (Dworkin et al., 2018). Briefly, the detection algorithm will use multiple MR contrasts, including T1w, T2-FLAIR, and T2*w. Vessels will first be segmented from the T2*w images using a Frangi filter. Vesselness maps will then be co-registered to T1 space. White matter

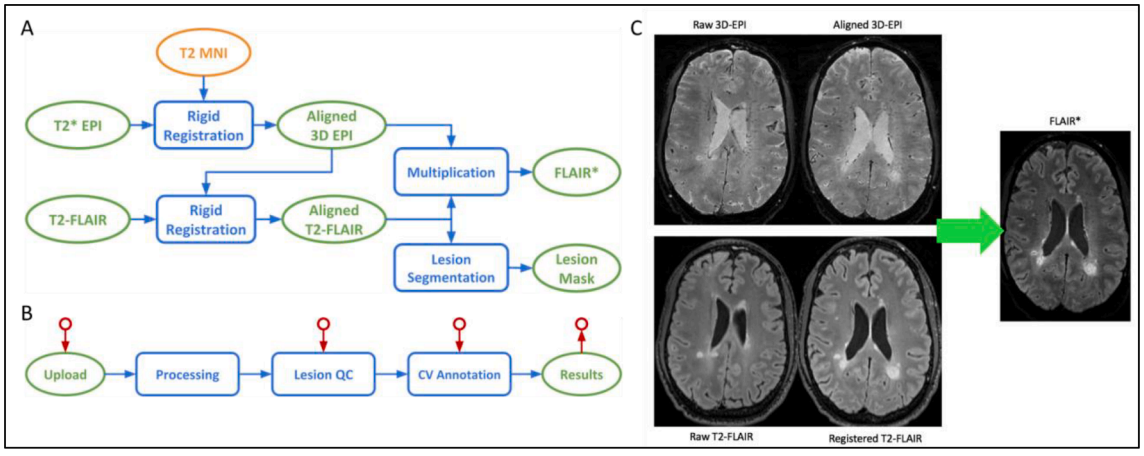

Fig. 3. Caption: Image processing. (A) Schematic of the processing pipeline to compute a FLAIR* image from raw T2* EPI and T2-FLAIR data, and a lesion mask overlay from the T2-FLAIR image. (B) Schematic of the custom-built workflow. User interaction in the workflow is represented by red circles and arrows. Automatic processing units are represented by blue rectangles and data input/output by green ovals. (C) Representative images: raw and aligned T2*-weighted 3D-EPI images (top row), raw and registered T2-FLAIR images (bottom row), and computed FLAIR* (right). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

lesions will be segmented using T1w and T2-FLAIR images, and lesion centers created using an automated statistical technique (Dworkin et al., 2018). A permutation process will be implemented to determine the degree to which a vein appears to be present in the center of each lesion. Probabilities will then be averaged across lesions for each participant. Select3* and Select6* will be compared against total lesion threshold techniques at 40%, 50%, and 60%, which will be derived via the automated methods as described above. A variety of additional proportional thresholds and exploratory integration of CVS into 2017 McDonald Criteria will also be examined. Finally, central reading by four untrained neuroradiologists (selected to have no prior experience rating CVS) will be conducted on a subset of 100 patients for Select3*, Select 6*, and incorporation of CVS into diagnostic criteria, by requiring all or a variable number of lesions to be CVS-positive to be eligible for determination of dissemination in space and time. The reading will be performed on both FLAIR* and SWI images (coregistered to T2-FLAIR to enable identification of brain lesions) to compare diagnostic performance of the two image contrasts. Inter-rater reliability will be tested among the four neuroradiologists.

3.6. Statistical methods

The primary objective of the study is to determine whether CVS allows for an earlier diagnosis of MS in participants with typical presentations but not meeting McDonald Criteria at enrollment. This analysis will consist of two parts. First, CVS will be assessed for improved sensitivity at enrollment, based on the accuracy with which it predicts satisfaction of McDonald Criteria at end of study (24-month time point), using a one-sided McNemar's test. The sensitivity of both tests (CVS and McDonald Criteria at baseline), and their difference will be reported with appropriate confidence intervals. Second, the reduction in diagnostic delay will be calculated in people who do not meet McDonald Criteria at baseline, but who go on to meet criteria at subsequent study time points. Subjects who meet McDonald Criteria by the end of the study will be identified, and the proportion of subjects who meet scan-level CVS criteria (Select6* or Select3*) but not McDonald Criteria at baseline, with confidence interval, will be reported.

The first secondary objective is to determine concordance of scan-level CVS criteria and 2017 McDonald Criteria in those meeting McDonald Criteria at baseline, and will be analyzed by reporting point estimates and confidence intervals for the percentage agreement between the two tests, as well as the proportions of participants who test negative by CVS but meet McDonald Criteria, and vice versa. The second secondary objective is to determine if use of CVS yields improved specificity for MS among individuals with atypical presentations. To assess this, the proportion of people who do not have scan-level CVS criteria out of those who are determined not to have MS, as defined by absence of clinical relapses of MS and not meeting McDonald Criteria at 24 months, will be reported. The third secondary objective is to determine whether positive scan-level CVS predicts development of clinical MS in people with radiologically isolated syndrome. Individuals presenting with radiologically isolated syndrome will be followed over 24 months for development of MS based on diagnostic criteria. CVS will be assessed for improved sensitivity at baseline, based on the accuracy with which it predicts satisfaction of clinical and radiological elements of the McDonald Criteria at end of study (24-month time point). All MRI data and clinical data will be housed on the QMENTA ® platform and after completion of study analysis will be shared on the NAIMS repository platform for use by the scientific community.

The sample size was calculated based on the primary outcome. It was assumed that the sensitivity of baseline McDonald Criteria for determining MS at the end of the study is 70% (Kolčava et al., 2020). Given that $>$ 85% of MS lesions have a central vein on FLAIR* MRI, we estimate the sensitivity of CVS to be $>$ 80%, or approximately 12% improved sensitivity for MS. It was expected that the discordance rate between McDonald Criteria and CVS would be approximately 20%. Using a one-sided hypothesis test and assuming a type I error rate of 5% and a 20% dropout rate, with 200 patients with typical presentations we expect to have 88% power to detect a 12% improved sensitivity of CVS. Since 50% of participants are expected to have atypical presentations, the study will recruit approximately 400 participants in total. Sensitivity analysis with patients with low and high lesion load will be conducted.

4. Discussion

This study has been designed to address a major clinical challenge associated with current MS diagnostic criteria: the lack of a specific biomarker for diagnosing MS in all patients in whom MS is being considered. If successful, the results of this study will validate CVS as a diagnostic biomarker for MS, provide data about its optimal use, and justify its incorporation into the diagnostic criteria.

The study will establish the sensitivity of CVS in those with a typical first presentation. We have selected this as the primary outcome, as incorporation into the McDonald Criteria has historically relied on studies in those with typical presentations. At the same time, the study will address whether CVS can allow earlier diagnosis in patients in whom the McDonald Criteria are not yet met at baseline. The results will also address the utility of CVS as a specific test for MS in patients who have not had a typical presentation (clinical demyelinating event) — the substantial proportion of people assessed at MS centers(~50%) (Kelly et al., 2012) in whom the McDonald Criteria, as formulated, should not even be applied. This is a critical question, as the problem of misdiagnosis originates mainly from the improper application of the diagnostic criteria in this population (Solomon and Weinshenker, 2013). Thus, with the current study we will determine whether CVS is a sensitive, specific, and broadly applicable diagnostic biomarker for MS.

We will test the Select3* algorithm (Solomon et al., 2018) against the previously validated 6-lesion counting procedure (Select6*) (Mistry et al., 2016). These two approaches have similar performance characteristics in small cross sectional studies, but Select3* takes less time to compute. Rating of all brain lesions meeting NAIMS criteria will be used. We decided to include periventricular lesions and follow the methods used in the pilot study in which Select3* was modified to not exclude presence of periventricular lesions. This modification did not significantly affect sensitivity/specificity of the CVS for diagnosis of MS (Daboul et al., 2021). We also have decided to report scans with$<$3 total lesions as negative for CVS, rather than exclude them, given the goals of the study are to incorporate CVS into clinical practice, and want the results to be as widely applicable as possible. The ability to study several of the proposed criteria in the current study will allow us to select the optimal strategy for implementing CVS criteria in diagnostic algorithms.

Limitations of the current study include lack of dedicated cerebrospinal fluid (CSF) collection. We will partially mitigate the impact of this shortcoming by collecting CSF data obtained during routine clinical practice. In the pilot CAVS-MS study 57% of participants had CSF collection, we expect a similar proportion for the current study. Participation in a clinical study with the requirement for CSF collection as a study procedure was considered but would have a negative impact on enrollment. In addition CSF testing is itself not specific for MS, further highlighting the need for an accurate and non-invasive diagnostic biomarker. Some participants recruited to the study will have a small number of brain lesions or potentially no lesions (typical presentations with optic neuritis or partial myelopathy are key examples), which will limit a proportion-based model for CVS interpretation. Rather than exclude these patients, we have elected to include them, as we wish to test CVS in a population as close to a real-world settings as possible.

5. Conclusions

CAVS-MS is a 2-year, prospective, international, multicenter study to evaluate whether CVS is a MS diagnostic biomarker suitable for immediate translation into clinical care. We hypothesize that simple CVS

scoring will provide improved sensitivity and specificity relative to current approaches and replace the need for complicated or time-consuming clinical scoring methods. The ultimate ambition of the study is to collect data that will support incorporation of CVS into MS diagnostic criteria, routine use in clinical practice. The dataset, which will be made available to the research community through NAIMS, can be used for future validation of other MRI or blood diagnostic biomarkers to be developed from the collected data.

Funding

This work was supported by the National Institute of Neurological Disorder and Stroke (NINDS) 1U01NS116776-01 to DO and NS. DSR is supported by the Intramural Research Program of NINDS.

CRediT authorship contribution statement

D. Ontaneda: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Software, Supervision, Writing – original draft, Writing – review & editing. **P. Sati:** Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **P. Raza:** Project administration, Resources, Writing – original draft, Writing – review & editing. **M. Kilbane:** Project administration, Resources, Writing – original draft, Writing – review & editing. **E. Gombos:** Project administration, Resources, Software, Writing – original draft, Writing – review & editing. **E. Alvarez:** Funding acquisition, Project administration, Resources, Writing – review & editing. **C. Azevedo:** Funding acquisition, Project administration, Resources, Writing – review & editing. **P. Calabresi:** Funding acquisition, Project administration, Resources, Writing – review & editing. **J.A. Cohen:** Methodology, Writing – review & editing. **L. Freeman:** Funding acquisition, Project administration, Resources, Writing – review & editing. **R.G. Henry:** Funding acquisition, Project administration, Resources, Writing – review & editing. **E.E. Longbrake:** Funding acquisition, Project administration, Resources, Writing – review & editing. **N. Mitra:** Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing – original draft. **N. Illenberger:** Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing – original draft. **M. Schindler:** Funding acquisition, Project administration, Resources, Writing – review & editing. **D. Moreno-Dominguez:** Project administration, Resources, Software, Supervision, Writing – review & editing. **M. Ramos:** Project administration, Resources, Software, Supervision, Writing – review & editing. **E. Mowry:** Methodology, Writing – review & editing. **J. Oh:** Funding acquisition, Project administration, Resources, Writing – review & editing. **P. Rodrigues:** Project administration, Resources, Software, Supervision, Writing – review & editing. **S. Chahin:** Funding acquisition, Project administration, Resources, Writing – review & editing. **M. Kaisey:** Funding acquisition, Project administration, Resources, Writing – review & editing. **E. Waubant:** Methodology, Writing – review & editing. **G. Cutter:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing. **R. Shinohara:** Conceptualization, Funding acquisition, Methodology, Resources, Software, Supervision, Writing – original draft. **D.S. Reich:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Software, Supervision, Writing – original draft, Writing – review & editing. **A. Solomon:** Conceptualization, Funding acquisition, Methodology, Writing – original draft, Writing – review & editing. **N.L. Sicotte:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Software, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

DO: Research support from the National Institutes of Health, National Multiple Sclerosis Society, Patient Centered Outcomes Research Institute, Race to Erase MS Foundation, Genentech, Genzyme, and Novartis. Consulting fees from Biogen Idec, Genentech/Roche, Genzyme, Novartis, and Merck.

PS: Nothing to disclose.

PR: Nothing to disclose.

MK: Nothing to disclose.

EG: Nothing to disclose.

EA: Compensation for activities (advisory boards, lectures and consultancy) with the following companies and organizations: Actelion/ Janssen, Alexion, Bayer, Biogen, Celgene/BMS, EMD Serono/Merck, Genentech/Roche, Genzyme, Novartis, Sanofi, and TG Therapeutics and research support from: Biogen, Genentech/Roche, Novartis, TG Therapeutics, Patient-Centered Outcomes Research Initiative, National Multiple Sclerosis Society, National Institutes of Health, and Rocky Mountain MS Center.

CA: Receives research support from the National Multiple Sclerosis Society. Received consulting fees from Genentech, Biogen Idec, Novartis, Sanofi Genzyme, EMD Serono, and Alexion Pharmaceuticals, outside the submitted work.

PC: PI on a grant to JHU from Genentech. Consulting fees from Biogen, Disarm Therapeutics and NervGen.

JAC: Consulting fees from Adamas, Atara, Bristol-Myers Squibb, Convelo, MedDay, and Mylan; and serving as an Editor of Multiple Sclerosis Journal.

LF: PI on a grant to UT from Genentech. PI on a grant to UT from NIH/NINDS. Co-investigator on grant to UT from PCORI and NIH-NINDS. Consulting fees from Celgene/ Bristol Myers Squibb, Genentech, EMD Serono, Novartis and Biogen.

RGH: Consulting fees from Atara, Celgene/ Bristol- Myers Squibb, Genentech/Roche, MedDay, Neurona, EMD Serono, Novartis, Sanofi/ Genzyme, QIA and Biogen.

EEL: consulting for Genentech, Genzyme, Alexion, EMD Serono, Biogen.

NM: Nothing to disclose.

NI: Nothing to disclose.

MS: Nothing to disclose.

DMD: Former employee of QMENTA.

MR: Employee of QMENTA.

EMM: PI of grants to JHU as well as site PI of studies from Genentech, Biogen; free medication for a clinical trial of which I am PI from Teva; royalties for editorial duties for UpToDate. Research support from PCORI, National MS Society, Department of Defense, National Institutes of Health.

JO: Grants from MS Society of Canada, National MS Society, Brain Canada, Biogen-Idec, Roche, EMD-Serono, and consulting fees from Biogen-Idec, EMD-Serono, Novartis, Roche, Alexion, Sanofi-Genzyme.

PR: Employee of QMENTA.

SC: Research support from the Department of Defense (DOD) and The National Multiple Sclerosis Society. Consulting and/or speaking fees from Novartis, Genentech and Sanofi Genzyme, consulting fees from Biogen Idec.

MK: Grant from Race to Erase MS, site PI and coI of studies from Biogen, Genentech, PCORI, and honoraria for speaking engagements from Alexion, Biogen, Genentech, and Viela Bio.

EW: Grants from the National MS Society, Race to Erase MS, PCORI, NIH, CMSC, DoD. Site PI for ongoing trials with Roche, Alexion and Biogen, Advisory board of a Novartis trial (volunteer), Honoraria for pharma consulting: none, Honoraria for talks (AAN, ANA, The Corpus, MS@TheLimits, PRIME), Chair (volunteer), international Women in MS.

GC: Data and Safety Monitoring Boards: Astra-Zeneca, Avexis Pharmaceuticals, Biolinerx, Brainstorm Cell Therapeutics, Bristol Meyers Squibb/Celgene, CSL Behring, Galmed Pharmaceuticals, Green-Valley Pharma Ltd, Mapi Pharmaceuticals LTD, Merck, Merck/Pfizer, Opko Biologics, OncoImmune, Neurim, Novartis, Ophazyme, Sanofi-Aventis, Reata Pharmaceuticals, Teva pharmaceuticals, VielaBio Inc,

Vivus, NHLBI (Protocol Review Committee), NICHD (OPRU oversight committee). Consulting or Advisory Boards: Biodelivery Sciences International, Biogen, Click Therapeutics, Genzyme, Genentech, GW Pharmaceuticals, Immunic, Klein-Buendel Incorporated, Medimmune/Viela Bio, Medday, Merck/Serono, Neurogenesis LTD, Novartis, Osmotica Pharmaceuticals, Perception Neurosciences, Recursion/Cerexis Pharmaceuticals, Regeneron, Reckover Pharmaceuticals, Roche, SAB BIotherapeutics, TG Therapeutics.GC is employed by the University of Alabama at Birmingham and is President of Pythagoras, Inc. a private consulting company located in Birmingham AL.

RS: Personal compensation for reviewership duties for the American Medical Association and the Emerson Collective.

DSR: Supported by the Intramural Research Program of NINDS, NIH. Additional research support from Adelson Medical Research Foundation, National Multiple Sclerosis Society, Sanofi-Genzyme, and Vertex Pharmaceuticals.

AS: Consulting: EMD Serono, Genentech, Biogen, Alexion, Celgene, Greenwich Biosciences. Non-promotional speaking: EMD Serono and Biogen. Research funding: Biogen.

NLS: Research support from the National Institutes of Health, National Multiple Sclerosis Society, Patient Centered Outcomes Research Institute, Race to Erase MS Foundation, Biogen, Genentech.

Acknowledgments

We would like to acknowledge Cassandra Kendeigh for assistance in grant development, and also the site coordinators and participants of the CAVS-MS pilot study. Funding This work was supported by the National Institute of Neurological Disorder and Stroke (NINDS) 1U01NS116776-01 to DO and NS. DSR is supported by the Intramural Research Program of NINDS.

Appendix

Table 1. Detailed Inclusion/Exclusion Criteria

Inclusion criteria for participants with **typical presentations**:

1. Age 18 to 65 inclusive
2. Referral to a study academic site for a clinical suspicion of MS
3. Onset with typical symptom onset including: acute unilateral optic neuritis, double vision due to an internuclear ophthalmoplegia or sixth nerve palsy, facial sensory loss or trigeminal neuralgia in a young adult (<40 years of age), cerebellar ataxia and nystagmus, partial myelopathy, sensory symptoms in a CNS pattern, Lhermitte's symptom, asymmetric limb weakness, urge incontinence or erectile dysfunction, or other neurological presentation considered to be typical by the site investigator.
4. Able to provide written informed consent to participate in the study
5. For participants referred for clinical suspicion of multiple sclerosis who had workup prior to referral or who are taking disease-modifying therapies for MS, digital availability of diagnostic cranial MRI with gadolinium within 3 months of initial symptoms

Onset of typical neurological symptoms within 10 years of screening.

Inclusion criteria for participants with **atypical presentations**:

1. Age 18 to 65 inclusive
2. Referral to a study academic site for a suspicion of MS
3. Onset with atypical onset including: bilateral optic neuritis or unilateral optic neuritis with a poor visual recovery, complete gaze palsy or fluctuating ophthalmoparesis, intractable nausea, vomiting, or hiccups, complete transverse myelopathy with bilateral motor and sensory involvement, encephalopathy, subacute cognitive decline, headache or meningismus, isolated fatigue or asthenia, constitutional symptoms, other clinical presentations considered atypical by the site investigator (examples include: vague or patchy sensory symptoms, pain, short lasting bilateral blurred vision, etc.), or absence of clinical symptoms with MRI features suggestive of MS
4. Able to provide written informed consent to participate in the study
5. For participants referred for clinical suspicion of multiple sclerosis who had workup prior to referral or who are taking disease-modifying therapies for MS, digital availability of diagnostic cranial MRI with gadolinium within 3 months of initial symptoms

Onset of atypical neurological symptoms within 10 years of screening.

Exclusion criteria for **both typical and atypical presentation populations**:

1. Contraindication to MRI studies; metal or metal implants incompatible with MRI
2. Inability to tolerate MRI due to claustrophobia or known excessive movement (e.g. tremor)
3. Contraindication to use of gadolinium containing contrast agents (allergy or renal failure)
4. Treatment with systemic corticosteroids in the 4 weeks preceding enrollment.

Table 2. Appendix

Study Flowsheet

Procedures	Visit 1 BL	Visits 2 & 4 Telephone(Months 6 and 18)	Visit 3 Office visit (Month 12)	Visit 5 Office visit (Month 24)	Early Withdrawal
Informed consent	X				
Screening	X				
Clinical characteristics	X				
Medical history	X				
Demographics	X				
Interval history		X	X	X	X

(*continued on next page*)

(*continued*)

Study Flowsheet					
	Visit 1	**Visits 2 & 4**	**Visit 3**	**Visit 5**	
Diagnosis review	X	X	X	X	X
DMT review		X	X	X	X
MRI review	X	X	X	X	X
Relapse review		X	X	X	X
PDDS	X	X	X	X	X
Adjudication of presentation type*	X				
Adjudication of MS diagnosis*	X		X	X	X
Neuro-QoL	X		X	X	X
HRU survey**	X	X	X	X	X
Brain MRI	X			X	X
Lab/CSF testing review***	X	X	X	X	X
Blood draw****	X				

*Conducted off-site by central adjudication committee; **health resource utilization (HRU) forms used for economic survey; ***May include recording of: cerebrospinal fluid testing (CSF), baseline (BL), neuromyelitis optica antibodies (NMO), and myelin oligodendrocyte glycoprotein (MOG) testing; ****serum, plasma, and buffy coat. DMT: disease modifying therapy, PDDS: patient determined disease steps, Neuro-QoL: Neurological quality of life scale.

References

Thompson, A.J., Banwell, B.L., Barkhof, F., Carroll, W.M., Coetzee, T., Comi, G., Correale, J., Fazekas, F., Filippi, M., Freedman, M.S., Fujihara, K., Galetta, S.L., Hartung, H.P., Kappos, L., Lublin, F.D., Marrie, R.A., Miller, A.E., Miller, D.H., Montalban, X., Mowry, E.M., Sorensen, P.S., Tintoré, M., Traboulsee, A.L., Trojano, M., Uitdehaag, B.M.J., Vukusic, S., Waubant, E., Weinshenker, B.G., Reingold, S.C., Cohen, J.A., 2018. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. The LancetNeurology 17 (2), 162–173.

Solomon, A.J., Naismith, R.T., Cross, A.H., 2019. Misdiagnosis of multiple sclerosis: Impact of the 2017 McDonald criteria on clinical practice. Neurology 92 (1), 26–33.

Kaisey, M., Solomon, A.J., Luu, M., Giesser, B.S., Sicotte, N.L., 2019. Incidence of multiple sclerosis misdiagnosis in referrals to two academic centers. Mult. Scler. Relat. Disord. 30, 51–56.

Solomon, A.J., Bourdette, D.N., Cross, A.H., Applebee, A., Skidd, P.M., Howard, D.B., Spain, R.I., Cameron, M.H., Kim, E., Mass, M.K., Yadav, V., Whitham, R.H., Longbrake, E.E., Naismith, R.T., Wu, G.F., Parks, B.J., Wingerchuk, D.M., Rabin, B. L., Toledano, M., Tobin, W.O., Kantarci, O.H., Carter, J.L., Keegan, B.M., Weinshenker, B.G., 2016. The contemporary spectrum of multiple sclerosis misdiagnosis: A multicenter study. Neurology 87 (13), 1393–1399.

Gooch, C.L., Pracht, E., Borenstein, A.R., 2017. The burden of neurological disease in the United States: A summary report and call to action. Ann. Neurol. 81 (4), 479–484.

Ontaneda, D., Tallantyre, E., Kalincik, T., Planchon, S.M., Evangelou, N., 2019. Early highly effective versus escalation treatment approaches in relapsing multiple sclerosis. Lancet Neurol. 18 (10), 973–980. https://doi.org/10.1016/S1474-4422(19)30151-6.

Midaglia, L., Sastre-Garriga, J., Pappolla, A., Quibus, L., Carvajal, R., Vidal-Jordana, A., Arrambide, G., Río, J., Comabella, M., Nos, C., Castilló, J., Galan, I., Rodríguez-Acevedo, B., Auger, C., Tintoré, M., Montalban, X., Rovira, À., 2021. The frequency and characteristics of MS misdiagnosis in patients referred to the multiple sclerosis centre of Catalonia. Mult. Scler. J 27 (6), 913–921.

Solomon, A.J., Pettigrew, R., Naismith, R.T., Chahin, S., Krieger, S., Weinshenker, B., 2021. Challenges in multiple sclerosis diagnosis: Misunderstanding and misapplication of the McDonald criteria. Mult. Scler. J. 27 (2), 250–258.

Sati, P., Oh, J., Constable, R.T., Evangelou, N., Guttmann, C.R.G., Henry, R.G., Klawiter, E.C., Mainero, C., Massacesi, L., McFarland, H., Nelson, F., Ontaneda, D., Rauscher, A., Rooney, W.D., Samaraweera, A.P.R., Shinohara, R.T., Sobel, R.A., Solomon, A.J., Treaba, C.A., Wuerfel, J., Zivadinov, R., Sicotte, N.L., Pelletier, D., Reich, D.S., 2016. The central vein sign and its clinical evaluation for the diagnosis of multiple sclerosis: a consensus statement from the North American Imaging in Multiple Sclerosis Cooperative. Nat. Rev. Neurol. 12 (12), 714–722.

Sati, P., Thomasson, D.M., Li, N., Pham, D.L., Biassou, N.M., Reich, D.S., Butman, J.A., 2014. Rapid, high-resolution, whole-brain, susceptibility-based MRI of multiple sclerosis. Mult. Scler. 20 (11), 1464–1470.

Sati, P., George, I.C., Shea, C.D., Gaitán, M.I., Reich, D.S., 2012. FLAIR*: a combined MR contrast technique for visualizing white matter lesions and parenchymal veins. Radiology 265 (3), 926–932.

Kilsdonk, I.D., Wattjes, M.P., Lopez-Soriano, A., Kuijer, J.P.A., de Jong, M.C., de Graaf, W.L., Conijn, M.M.A., Polman, C.H., Luijten, P.R., Geurts, J.J.G., Geerlings, M. I., Barkhof, F., 2014. Improved differentiation between MS and vascular brain lesions using FLAIR* at 7 Tesla. Eur. Radiol. 24 (4), 841–849.

Mistry, N., Abdel-Fahim, R., Samaraweera, A., Mougin, O., Tallantyre, E., Tench, C., Jaspan, T., Morris, P., Morgan, P.S., Evangelou, N., 2016. Imaging central veins in brain lesions with 3-T T2*-weighted magnetic resonance imaging differentiates multiple sclerosis from microangiopathic brain lesions. Mult. Scler. 22 (10), 1289–1296.

Solomon, A.J., Schindler, M.K., Howard, D.B., et al., 2015. 'Central vessel sign' on 3T FLAIR* MRI for the differentiation of multiple sclerosis from migraine. Ann. Clin. Transl. Neurol. 3, 82–87.

Maggi, P., Absinta, M., Grammatico, M., Vuolo, L., Emmi, G., Carlucci, G., Spagni, G., Barilaro, A., Repice, A.M., Emmi, L., Prisco, D., Martinelli, V., Scotti, R., Sadeghi, N., Perrotta, G., Sati, P., Dachy, B., Reich, D.S., Filippi, M., Massacesi, L., 2018. Central vein sign differentiates Multiple Sclerosis from central nervous system inflammatory vasculopathies. Ann. Neurol. 83 (2), 283–294.

Suthiphosuwan, S., Sati, P., Guenette, M., et al., 2019. The Central Vein Sign in Radiologically Isolated Syndrome. Am. J. Neuroradiol. 40, 776–783.

Filippi, M., Rocca, M.A., Ciccarelli, O., De Stefano, N., Evangelou, N., Kappos, L., Rovira, A., Sastre-Garriga, J., Tintorè, M., Frederiksen, J.L., Gasperini, C., Palace, J., Reich, D.S., Banwell, B., Montalban, X., Barkhof, F., 2016. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. The LancetNeurology 15 (3), 292–303.

Tallantyre, E.C., Dixon, J.E., Donaldson, I., Owens, T., Morgan, P.S., Morris, P.G., Evangelou, N., 2011. Ultra-high-field imaging distinguishes MS lesions from asymptomatic white matter lesions. Neurology 76 (6), 534–539.

Solomon, A.J., Watts, R., Ontaneda, D., Absinta, M., Sati, P., Reich, D.S., 2018. Diagnostic performance of central vein sign for multiple sclerosis with a simplified three-lesion algorithm. Mult. Scler. J. 24 (6), 750–757. https://doi.org/10.1177/1352458517726383.

Sinnecker, T., Clarke, M., Meier, D., Enzinger, C., Calabrese, M., De Stefano, N., Pitiot, A., Giorgio, A., Schoonheim, M.M., Paul, F., Pawlak, M., Kappos, L., Rovira, A., Evangelou, A., Wuerfe, J., 2019. Evaluation of the "Three Lesions with a Central Vein Sign" Criteria for the Differentiation between Multiple Sclerosis and its Imaging Mimics. Neurology.

Daboul, L., O'Donnell, C., Moreno-Dominguez, D., Rodrigues, P., Derbyshire, J., Azevedo, C., Bar-Or, A., Caverzasi, E., Calabresi, P., Cree, B., Freeman, L., Henry, R., Longbrake, E., Oh, J., Papinutto, N., Pelletier, D., Samudralwar, R., Schindler, M., Sotirchos, E., Sicotte, N., Ontaneda, D., 2020. Gadolinium improves detection of central vein lesions in MS using 3t flair*. MSVirtual 2020 – Poster Abstracts. Mult. Scler. J. 2020 (26), 118–659.

Haacke, E.M., Mittal, S., Wu, Z., Neelavalli, J., Cheng, Y.-C.-N., 2009. Susceptibility-Weighted Imaging: Technical Aspects and Clinical Applications, Part 1. Am. J. Neuroradiol. 30 (1), 19–30.

Avants, B.B., Tustison, N.J., Stauffer, M., Song, G., Wu, B., Gee, J.C., 2014. The Insight ToolKit image registration framework. Front. Neuroinform. 8, 44.

Dworkin, J.D., Sati, P., Solomon, A., Pham, D.L., Watts, R., Martin, M.L., Ontaneda, D., Schindler, M.K., Reich, D.S., Shinohara, R.T., 2018. Automated Integration of Multimodal MRI for the Probabilistic Detection of the Central Vein Sign in White Matter Lesions. Am. J. Neuroradiol. 39 (10), 1806–1813.

Dworkin, J.D., Linn, K.A., Oguz, I., et al., 2018. An Automated Statistical Technique for Counting Distinct Multiple Sclerosis Lesions. Am. J. Neuroradiol. 39, 626–633.

Kolčava, J., Kočica, J., Hulová, M., Dušek, L., Horáková, M., Keřkovský, M., Stulík, J., Dostál, M., Kuhn, M., Vlčková, E., Bednařík, J., Benešová, Y., 2020. Conversion of clinically isolated syndrome to multiple sclerosis: a prospective study. Mult. Scler. Relat. Disord. 44, 102262. https://doi.org/10.1016/j.msard.2020.102262.

Kelly, S.B., Chaila, E., Kinsella, K., Duggan, M., Walsh, C., Tubridy, N., Hutchinson, M., 2012. Using atypical symptoms and red flags to identify non-demyelinating disease. J. Neurol. Neurosurg. Psychiatry 83 (1), 44–48.

Solomon, A.J., Weinshenker, B.G., 2013. Misdiagnosis of multiple sclerosis: frequency, causes, effects, and prevention. Curr. Neurol. Neurosci. Rep. 13, 403-013-0403-y.

Daboul, L., O'Donnell, C.M., Moreno-Dominguez, D., Rodrigues, P., Derbyshire, J., Azevedo, C., Bar-Or, A., Caverzasi, E., Calabresi, P., Cree, B.A., Freeman, L., Henry, R.G., Longbrake, E.E., Oh, J., Papinutto, N., Pelletier, D., Samudralwar, R., Schindler, M.K., Sotirchos, E., Sicotte, N.L., Solomon, A.J., Shinohara, T., Reich, D.S., Sati, P., Ontaneda, D., 2021. A Multicenter Evaluation of the Diagnostic Performance of the Central Vein Sign Using Simplified Algorithms. ACTRIMS Forum 2021 – Poster Presentations. Mult. Scler. J. 2021 (27), 15–122.