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# Framework for Clinical Trials in Cerebral Small Vessel Disease (FINESSE)

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## Abstract

**IMPORTANCE—**Cerebral small vessel disease (SVD) causes a quarter of strokes and is the most common pathology underlying vascular cognitive impairment and dementia. An important step to developing new treatments is better trial methodology. Disease mechanisms in SVD differ from other stroke etiologies; therefore, treatments need to be evaluated in cohorts in which SVD has been well characterized. Furthermore, SVD itself can be caused by a number of different pathologies, the most common of which are arteriosclerosis and cerebral amyloid angiopathy. To date, there have been few sufficiently powered high-quality randomized clinical trials in SVD, and inconsistent trial methodology has made interpretation of some findings difficult.

**OBSERVATIONS—**To address these issues and develop guidelines for optimizing design of clinical trials in SVD, the Framework for Clinical Trials in Cerebral Small Vessel Disease (FINESSE) was created under the auspices of the International Society of Vascular Behavioral and Cognitive Disorders. Experts in relevant aspects of SVD trial methodology were convened, and a structured Delphi consensus process was used to develop recommendations. Areas in which recommendations were developed included optimal choice of study populations, choice of clinical end points, use of brain imaging as a surrogate outcome measure, use of circulating biomarkers for participant selection and as surrogate markers, novel trial designs, and prioritization of therapeutic agents using genetic data via Mendelian randomization.

**CONCLUSIONS AND RELEVANCE—**The FINESSE provides recommendations for trial design in SVD for which there are currently few effective treatments. However, new insights into understanding disease pathogenesis, particularly from recent genetic studies, provide novel pathways that could be therapeutically targeted. In addition, whether other currently available cardiovascular interventions are specifically effective in SVD, as opposed to other subtypes of stroke, remains uncertain. FINESSE provides a framework for design of trials examining such therapeutic approaches.

Cerebral small vessel disease (SVD) causes about a quarter of all ischemic strokes, the majority of intracerebral hemorrhages, and is the most common pathology underlying vascular cognitive impairment and dementia, thereby causing enormous disability worldwide.[1] Despite its importance, there are few treatments with proven efficacy, particularly for individuals with symptomatic disease.[2] An important step to developing new treatment approaches is better trial methodology. Disease mechanisms in SVD differ from other stroke etiologies, and therefore treatments need to be examined in cohorts in which SVD has been well specified. While some risk factors such as hypertension and diabetes increase risk of all stroke subtypes, SVD has many risk factors unique to this stroke subtype.[3] Even within SVD itself, there are different underlying pathologies that can introduce heterogeneity in clinical trial populations. Broadly, there are 2 main pathologies.[1] First, the more common form of sporadic SVD is strongly related to hypertension and therefore often referred to as *hypertensive arteriopathy*. This nonamyloid, degenerative arterial disease has been variously termed *arteriolosclerosis, age-related, or vascular risk-factor-related SVD* or *degenerative microangiopathy* in the literature with pathological appearances described as arteriolosclerosis and lipohyalinosis.[1] The second is sporadic cerebral amyloid angiopathy, a chronic degenerative disease characterized by progressive deposition of amyloid-β in the media and adventitia of small arteries, arterioles, and sometimes capillaries in the cerebral cortex.[1] Aside from these major 2 pathologies, there are less frequent specific pathologies as seen, for instance, in hereditary types of SVD.

Previous trials have used variable inclusion criteria and end points, thus limiting options for meta-analyses and the development of treatment guidelines. Studies using clinical end points of incident or recurrent stroke or cognitive decline and dementia require large sample sizes, and many investigators advocate using surrogate end points in smaller phase 2 trials to facilitate identification of the most promising treatments that are then taken forward to larger definitive phase 3 studies. Potential novel targets are being identified by genetic and other approaches,[2] but an improved clinical trial methodology is required if potential therapies are to be rapidly and effectively assessed in patients.

To address these issues and develop guidelines for the design of clinical trials in SVD, we established the Framework For Clinical Trials in Cerebral Small Vessel Disease (FINESSE).

## Procedure and Methods

This initiative was established following informal discussions by experts in the area. Experts in all aspects of SVD trial methodology were identified by searching the literature, while also accounting for geographical and gender diversity and inclusion of early career

researchers. Experts were allocated to 1 of 7 work packages: study populations, inclusion and exclusion criteria; clinical end points; cognitive testing; imaging markers; circulating biomarkers (cerebrospinal fluid and blood); and novel trial designs including Mendelian randomization. At a first workshop on September 9, 2020, each work package group presented aims, which were subsequently discussed with all members. Work package groups then met independently, reviewed the literature in their area, produced first drafts of a review of current knowledge in their area, and suggested recommendations that were further refined within the whole group, circulated to all members, and voted on anonymously prior to a second workshop on April 14, 2021. At the second workshop, recommendations were reviewed and amended and subsequently voted on anonymously by all members as agree or disagree. A final document was drafted and circulated to all members for review. The percentage of experts voting for each recommendation is presented.

## Choosing the Right Study Population

The term *SVD* describes avariety of abnormalities related to the small perforating blood vessels in the brain. Radiological manifestations of SVD, best seen on magnetic resonance imaging (MRI) and shown in Figure 1, include lacunes, white matter hyperintensities (WMH), cerebral microbleeds (CMB), enlarged perivascular spaces, and brain atrophy.[4] The clinical manifestations of SVD are diverse and can include stroke, depression, apathy, cognitive decline and dementia, neuropsychiatric symptoms, and alterations in movement and gait.[1] Depending on their symptomatology, patients with SVD may be diagnosed in stroke services, cognitive neurology and memory clinics, geriatric services, or movement disorder clinics. SVD is often clinically covert, being detected coincidentally when brain imaging is performed for another reason. This heterogeneity must be accounted for in trial design.

A number of key aspects should be considered and clearly defined before selecting the target populations for a trial.

1. What type of SVD? The vascular pathology underlying SVD is heterogeneous. Major subtypes include arteriolosclerosis (usually associated with hypertension) and cerebral amyloid angiopathy. These may respond differently to therapies. Reducing heterogeneity of the underlying pathology may allow sample sizes to be reduced. Clinical imaging may assist in defining specific subtypes; for example, the distribution of CMB, and whether they are restricted to the cortex or primarily at the cortical-subcortical junction, can be used to identify a group enriched for cerebral amyloid angiopathy.

2. Which disease stage, including whether it is symptomatic or asymptomatic and identified only on brain imaging? The presence or extent of lesions on MRI are indicators of an increased risk of clinical events (stroke, dementia) even in asymptomatic individuals[5] and may be considered for targeting an asymptomatic or mildly symptomatic population at higher risk. Disease-modifying treatments may be more useful in earlier disease stages when the disease may be potentially modifiable.

3. Which target of treatment? If the objective is to relieve a particular clinical manifestation, eg, apathy, patients should present with the corresponding manifestation. If the objective is prevention through targeting risk factors, participants should have these risk factors, eg, hypertension.

4. Which phase of development of the intervention? Target populations may differ depending on whether it is intended to demonstrate a biological effect of the drug in early phase 2 studies or a clinical benefit in a larger phase 3 study.

It is essential that appropriately phenotyped patients with SVD are included to ensure that patients in SVD trials do have SVD as the underlying pathology. Neuroimaging confirmation is critical and should preferably include MRI for diagnostic confirmation. A typical MRI examination should include sequences to identify WMH (T2 and/or fluid-attenuated inversion recovery), lacunes (T1 and/or fluid-attenuated inversion recovery), recent infarcts (diffusion-weighted imaging, brain volume [T1], and CMB [Gradient echo or susceptibility weighted imaging]) (Figure 1). Studies using clinical syndromic classification or relying on computed tomography (CT) imaging, which may often be normal in lacunar stroke, have been shown to have only low to moderate specificity for diagnosis of lacunar stroke due to SVD.[6] Incorporation of other clinical parameters may increase the specificity of CT for SVD and this may be particularly relevant for trials where resources are more scarce, for example in low- and middle-income countries.[7]

Some studies will determine the effect of therapies on the cognitive impairment associated with SVD. The typical cognitive profile of SVD includes early involvement of executive function and information processing speed and later involvement of episodic memory.[8] Tests to identify patients with SVD who have cognitive impairment need to be sensitive to this pattern. Such tests for SVD have been developed and are shown to have higher sensitivity and specificity to SVD-related cognitive deficits than Alzheimer disease– based tests.[9,10] They can be used to select a study population who have evidence of cognitive impairment related to SVD and might allow a population with a higher risk of future dementia to be selected. Here, we offer 3 recommendations.

1. Brain imaging, preferably MRI, should be used to confirm the presence of SVD for inclusion in a trial (100% expert agreement).

2. Inclusion criteria should identify the appropriate type of SVD, disease stage, and clinical profile to match the hypothesized mechanism of intervention (93.8% expert agreement).

3. Cognitive tests used to screen for cognitive impairment for participant inclusion in SVD trials need to be sensitive to the characteristic pattern of cognitive impairment seen in the disease (93.8% expert agreement).

## Enriching the Population to Reduce Sample Size

The use of brain imaging, preferably MRI, and possibly CT, to pre-select patients with SVD who have a higher rate of progression to clinical end points, has been proposed as an approach to reduce sample size.[11] The presence of confluent WMH,[12] or leukoaraiosis on

CT,[13] has been shown to identify a subgroup with more rapid disease progression. Summary SVD scores that incorporate the presence of WMH, lacunes, CMB, and perivascular spaces captures multiple different radiological aspects of the disease.[14] These summary scores have been demonstrated to improve prediction of dementia compared with a clinical score (area under the curve increasing from 0.76 to 0.85).[15] The inclusion of perivascular spaces had little effect on improving prediction, but all other parameters were associated with increased risk. Power calculations demonstrated that selecting a group with a higher SVD score would reduce sample sizes for a clinical trial with dementia as the end point by 40% to 66%.[15] Similar scores for CT scans (which exclude CMB and perivascular spaces that are not visible on CT) have also been proposed[16] but are less sensitive to early changes. Potential disadvantages of such selection are that patients with more severe disease may be less responsive to interventions and that studying a subgroup of the disease limits external validity. A recommendation is that brain imaging can be used to identify a group with increased probability of clinical end points and therefore potentially reduce sample size (100% expert agreement).

## Selecting the Optimal Clinical End Point

Given the diversity of clinical manifestations of SVD, trialists need to choose which end points to capture, keeping costs and participant burden in mind. A primary end point or set of end points should be specified in advance. Ideal end points have the following characteristics: they are a valid measure of functional ability or survival, can be accurately and reliably assessed, are sensitive to clinically meaningful change over time, have low cost, impose a low burden on participants, and crucially, matter to patients. End points that are reliably captured in routine care or remotely can be especially efficient.

End points must be chosen to suit the study design and guided by the risks of the intervention to ensure that important adverse events are captured. Because adverse events will depend on the type of intervention, they will vary across trials.

The choice of end points will vary by the phase of the trial. Phase 2 trials will likely include end points that are surrogate or monitoring biomarkers of treatment response (discussed further in the sections on cognitive testing and neuroimaging biomarkers) but should nonetheless collect key clinical outcomes, even if secondary. Phase 3 trials should include primary outcomes that are of direct clinical relevance.

## Clinical End Points and Their Assessment

Potential end points to consider, along with suitable validated assessment methods, are provided in Table 1.[17–27]

### Stroke

Stroke events should be identified and whether they are ischemic stroke or intracerebral hemorrhage. If possible, ischemic stroke subtype information should be collected as a secondary end point.

## Dementia

Dementia is defined by cognitive impairment that results in impairment of activities of daily living. The criteria used to specify dementia should be defined in advance. We suggest using the criteria for mild and major neurocognitive disorder in the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) or for mild neurocognitive disorder and dementia in *International Classification of Diseases, 11th Revision*, because both sets of criteria no longer require impairment in memory and thus are more sensitive to SVD-related vascular cognitive impairment, where memory may be less prominently affected in comparison with Alzheimer disease.[28] Dementia and mild cognitive impairment events can be reliably assessed algorithmically using assessment scales, as has been done in epidemiological studies.[29] We recommend that all-cause dementia, rather than vascular dementia is used as the primary dementia-related end point because the reliability of subtype-specific criteria is limited and, regardless of clinical classification, most cases of dementia have multiple pathologies.[30] It is recommended to capture vascular dementia incidence as a secondary end point, for which we recommend criteria from Vas-Cog[31] or the Vascular Impairment of Cognition Classification Consensus Study.[32]

The panel felt dementia was an important outcome because it is clinically meaningful and robust. Furthermore, longitudinal studies have shown that sufficient end points do occur for this to be used as an end point, eg, an approximately 20% 5-year dementia rate in a longitudinal follow-up of MRI-confirmed lacunar stroke.[33] However, follow-up durations as long as 5 years may be required for such studies depending on the sample size and effect size of any intervention.

## Other Outcome Measures

Neuropsychiatric symptoms particularly apathy and depression are prominent symptoms and assessing these symptoms at least as a secondary end point should be considered. Table 1 provides suitable scales and highlights other relevant end points including disability and gait.

## Recommendations

1. All-cause dementia should be used as the primary dementia-related end point and should be collected as an end point in all long-duration trials in SVD (100% expert agreement).
2. All-cause stroke should be used as the primary stroke-related end point and if possible, stroke subtype information should be collected (96.8% expert agreement).
3. For interventions that may influence SVD progression we recommend recording cognitive impairment, functional status, stroke, other cardiovascular events, and death (96.8% expert agreement).
4. Ascaleforneuropsychiatricsymptoms, includingapathyand depression, should be strongly considered (100% expert agreement).

## Cognitive Testing as an Outcome Measure

An ideal cognitive test for use as an outcome measure needs to be standardized, validated to detect a clinically meaningful change over the duration of the trial, and suitable for repeated assessment. Researchers must consider the cognitive test's demands on literacy, sensitivity to education, construct and psychometric equivalence across language and culture, and accessibility/validity for those with sensory or motor impairment since these are common in people with SVD. Some cognitive tests have proprietary status. Researchers must consider any requirements from regulatory and clinical organizations. Historically, the US Food and Drug Administration has required that dementia medications improve daily functioning, not just cognitive test scores so tests of function should be included.

While currently used cognitive tests are sensitive to the presence of vascular cognitive impairment in patients with SVD, they have low sensitivity to change over time in SVD.[8] Accordingly, longitudinal studies in SVD with follow-up durations from 2 to 3 years, the typical duration of a clinical trial, have found it difficult to detect change in cognition.[11,34] In the SPS3 trial in 3020 individuals with MRI-confirmed lacunar stroke, no change in cognition was detected over a 2- to 3-year period.[35] Using standard cognitive tests and follow-up durations of 2 to 3 years, sample sizes of thousands would be required for clinical trials in patients with symptomatic SVD unselected for the presence or absence of cognitive impairment, with dementia as the end point (Table 2).[34]

The reason for this low sensitivity may be multiple. Many studies have included patients predominantly with stroke and WMH who are not presenting with vascular cognitive impairment and therefore at low to moderate risk of dementia, whereas a higher-risk population might decline quicker; therefore, cognitive tests may be more sensitive to change in this population. Other possible factors may be practice effects due to repeated use of the same cognitive tests, natural variability in cognition over time, and psychometric properties of selected tests. More frequent web-based or computerized testing, using randomization of parallel versions of the same test, may have increased sensitivity but this requires validation. If more sensitive cognitive tests are to be developed, they need to tap into the pattern of cognitive impairment seen in the disease. This was demonstrated in a trial of donepezil in CADASIL (Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leucoencephalopathy)[36] in which the primary cognitive end point (Vascular Dementia Assessment Scale cognitive subscale) showed no change, but a secondary cognitive end point focusing on executive function showed significant differences between groups.

Traditionally, cognitive testing is administered at clinic visits by trained personnel. Most validated tests use this form of administration. However, it is costly, time consuming, and reduces accessibility. The COVID-19 pandemic impact has spurred massive growth in remotely delivered cognitive tests, with the adaptation of canonical psychometric tests delivered via video and telephone. Researchers use telephone-administered assessments to reduce study visits and participant burden for commonly administered tests, such as the Montreal Cognitive Assessment,[37,38] although their use in clinical trials needs further validation.

Web-based, self-administered computerized cognitive tests are becoming increasingly popular. However, variable levels of computer experience, attitudes to technology, and sensory and physical limitations might impact the feasibility and validity of results. Cognitive decline itself might impact on patient retention with computerized methods, resulting in systematic bias. Research is needed to identify which computerized tests, supervised and unsupervised, are the most suitable for stroke survivors and people with SVD-related cognitive impairment.

### Recommendations

1. The ability to detect a change in cognitive performance depends on the study population and the test used. This needs to be considered when selecting primary over secondary end points and the choice of cognitive tests (100% expert agreement).
2. Further work is required to further validate brief cognitive tests, ideally for remote use, that are sensitive to longitudinal change. These should be sensitive to the cognitive domains most affected in SVD (75% expert agreement).

## Brain Imaging as an Outcome Measure

Brain imaging is increasingly used in clinical trials of therapies for SVD both as a surrogate end point and to assess therapeutic efficacy and safety relating to specific aspects of the disease processes.

## Brain Imaging as a Surrogate End Point in Clinical Trials

Interventional trials in SVD using clinical end points such as dementia or recurrent stroke require very large sample sizes or long trial duration owing to the low incidence of clinical end points.[11,35] This has led to increasing interest in the use of surrogate end points such as neuroimaging biomarkers to evaluate therapies in phase 2 trials prior to larger phase 3 trials. Specific criteria such as those defined by Prentice[39] and the US Food and Drug Administration[40] have been developed to assess the suitability of markers as surrogate markers. These include sensitivity of the marker to change over time, correlation with clinical end points, and importantly that a treatment effect on the biomarker (eg, in a phase 2 trial) predicts a clinical benefit (eg, as assessed in a larger trial with clinical end points).

Proposed MRI markers of SVD[41] include WMH volume, lacunes (presence, number), CMB (number), brain volume, and white matter ultrastructure measured using diffusion tensor imaging (DTI). A summary of evidence evaluating how each of these markers both associates with, and predicts future risk, of clinical outcomes is shown in Table 2. WMH,[13,42] DTI,[33,34,43] and brain volume[44] have been shown to be sensitive to change during follow-up periods of 2 to 3 years. Power calculations suggest that their use, depending on the effect size of the intervention, could reduce sample sizes to less than 200 (Table 2).[11,13,34] Although the number of lacunes correlates strongly with cognitive impairment, owing to the low frequency of incident lacunes, they require much larger sample sizes than the other biomarkers.[11,34]

While there is strong evidence that WMH,[44] brain volume, and DTI markers[33] predict future dementia risk, there are limited data available from clinical trials demonstrating that an intervention has the same effect on the surrogate end point as on the clinical outcome. Most data are available for WMH: the recent SPRINT-MIND (Systolic Blood Pressure Intervention Trial–Memory and Cognition in Decreased Hypertension) study[45] demonstrated that intensive antihypertensive therapy reduced risk of the combined end point of dementia and mild cognitive impairment[45] and at the same time reduced WMH progression.[42]

An important consideration for multicenter studies is whether reliable data can be obtained across different centers and scanner types. WMH and brain volume appear the most robust markers although there has been little evidence obtained so far regarding between-center or between-scanner reproducibility for most SVD imaging markers.[46] The HARNESS (Harmonizing Brain Imaging Methods for Vascular Contributions to Neurodegeneration) initiative[47] has provided a framework for neuroimaging biomarker development with the goal of reducing the variability in measurements in MRI studies.[47] The MarkVCID MRI protocols suggest core MRI sequences for assessing cerebral SVD in future research studies, specific sequence parameters for use across various research scanner types, and rigorous procedures for determining instrumental validity.[48] Automated analysis techniques are important to increase speed and reproducibility of image analysis; such as peak width of skeletonized mean diffusivity for DTI analysis.[34] Although DTI has been used in multicenter studies[49] and excellent reproducibility across sites has been demonstrated for fully harmonized acquisition protocols,[50] more data are required on whether the use of different scanner types reduces power in multicenter studies.

## Brain Imaging to Assess Therapeutic Efficacy and Safety

Brain imaging techniques provide insights into a number of pathophysiological processes presumed to be important in SVD pathogenesis, which can be used to provide evidence of therapeutic efficacy and safety. These can be divided into techniques to study the vasculature and blood flow and techniques studying parenchymal damage. Because hypoperfusion is believed to play an important role in SVD, trials have used cerebral blood flow imaging, which can be assessed by arterial spin labeling MRI to assess the effects of therapies.[51] Cerebrovascular reactivity and autoregulation are impaired in SVD, and trials have used vascular reactivity imaging most often with transcranial Doppler or MRI combined with a vasodilatory stimulus such as carbon dioxide.[52] Dynamic contrast-enhanced MRI has been used to demonstrate blood-brain barrier leakage in SVD,[53] which is thought to be an important factor mediating both arterial and parenchymal damage. This technique is being used to study interventions that may reduce blood-brain barrier leakage. Microglial activation has been demonstrated in SVD using [$^{11}$C](R)-PK11195 positron emission tomography imaging.[54] We do not yet know whether inhibiting inflammation reduces manifestations of SVD, but trials of anti-inflammatory approaches are using this imaging modality to assess efficacy.

Imaging may also be useful in phase 2 studies to assess safety. For example, CMB, which has been shown to predict future bleeding risk,[55] may provide a surrogate marker to assess

whether interventions that have vasodilator or antiplatelet effects are likely to increase bleeding risk.

### Recommendation

We recommend that MRI markers of SVD can be used to assess treatment efficacy and allow for smaller sample sizes in phase 2 trials. For ischemic SVD, there is most evidence for the use of WMH, and DTI shows promise (100% expert agreement).

## Circulating Biomarkers

Blood-based biomarkers hold the potential to advance clinical trials in SVD both by serving as surrogate markers of outcome and by assisting in screening of target populations. Collection of peripheral blood can easily be implemented in trials as part of routine diagnostics, and in contrast to MRI, at low cost. Samples can be stored for central analysis on trial completion, thus greatly reducing intersite variability in multicenter trials.

Circulating biomarkers may be useful in selecting a specific patient group for a trial, screening patients to exclude comorbidities, and quantifying copathologies that might modify the effect of the intervention. For example coexistent Alzheimer disease pathology could be excluded or quantified by novel, highly sensitive blood assays, which are much more scalable and affordable than cerebrospinal fluid analysis or positron emission tomography imaging.[56] A potential application for circulating biomarkers is their use as surrogate end points to evaluate therapeutic efficacy in phase 2 trials. The same criteria listed under the imaging section must be applied to evaluate such a marker.

A multitude of circulating biomarkers has already been identified in SVD, mostly in studies comparing patients with SVD with healthy control individuals, or in studies assessing associations with SVD-typical clinical deficits.[57] These include markers of endothelial dysfunction, neuronal injury, and blood-brain barrier dysfunction. However, many of the identified candidates await replication in independent studies and to our knowledge, none has been proven to meet the Prentice criteria[39] for surrogate markers in SVD trials. Further research targeted at specific use cases and covering both technical and clinical validations is needed. One notable effort is the National Institutes of Health–sponsored MarkVCID consortium, which has identified biomarker development as a key step toward translating scientific advances in VCID (Vascular Contributions to Cognitive Impairment and Dementia) into effective prevention and treatment strategies and has developed standard protocols forevaluating the use of validating blood cerebrospinal fluid and blood biomarkers for the SVD.[58] Clinical validation heavily depends on the intended use case. Importantly, validation studies need to be conducted in patient groups representative of a trial population.

As an illustration, one promising candidate biomarker is serum neurofilament light chain (NfL), a marker of neuroaxonal injury. Serum NfL levels have been shown in multiple studies to be higher in patients with SVD compared with controls and to be associated with lacunes and DTI markers of white matter damage in cross-sectional analyses.[59] However while NfLlevels predicted future dementia risk, there was no change in levels over a 3-year period in 90 patients with moderate to severe SVD.[60] Further longitudinal studies

are required to assess whether NfL levels are only useful for selecting a high-risk group or also for assessing therapeutic efficacy. The lack of specificity of NfL, levels of which are raised in other dementias and neurological diseases, is also a potential limitation to consider, especially in the context of competing etiologies of dementia in the memory clinic. Although several circulating biomarker candidates have been identified, to date none has been systematically validated or is close to implementation in trials. To expedite this process, we recommend sampling of serum or plasma in future SVD trials using standardized procedures for sampling, processing, and storage.

### Recommendations

1. No circulating blood biomarker has yet been demonstrated to be avalid outcome measure for clinical trials (100% expert agreement).
2. SVD trials should consider collecting blood samples for future biomarker evaluation (96.7% expert agreement).

## Novel Trial Designs

Novel trial designs may improve efficiency without compromising practicality, accuracy, or internal and external validity. Efficient trial designs are currently being used in limited crossover (TREAT-SVDs [NCT03082014], OxHARP [NCT03855332]) or factorial (LACI [NCT03451591]) phase 2 studies, concurrently assessing multiple interventions. Master protocol or platform designs[61] have been used successfully in other disease, for example COVID-19, to enhance trial efficiency by assessing multiple treatments without the need for repeated trial setup, by reducing sample sizes through common control groups, and by using adaptive randomization strategies to more rapidly exclude unpromising candidates.[62] They have not yet been widely explored in SVD.

For phase 3 trials, large numbers are required to offset the low acute event rate and slow evolution of chronic disability. Stepped-wedge designs[63] can be used by randomizing at the center level to optimized clinical interventions, such as remote blood pressure monitoring. Very long-term outcomes can be assessed by nesting trials within longitudinal cohorts or by pragmatic linkage to routine health care data.

The use of a composite brain health end point including multiple clinical end points such as both stroke and dementia, and/or multiple MRI end points has been suggested as a method to enhance the power of an interventional trial to detect a clinically meaningful benefit, and is currently being tested in some trials (eg, LACI-2 [Lacunar Intervention Trial-2]), although further assessment is required of its efficacy compared with single outcome end points in SVD trials.[64]

### Recommendations

1. Future SVD trials should combine optimized patient selection, efficient trial designs and analysis, and enhanced participant retention to maximize statistical power (87.5% expert agreement).

2. Development of a composite brain health end point including multiple outcomes should be considered (87.1% expert agreement).

## Prioritization of Therapeutic Targets

Prioritizing therapeutic strategies and specific drugs or drug classes for interventional trials in SVD remains challenging. Recent developments in Mendelian randomization genetic methods[65] have improved the ability to infer causal relationships between exposures and outcomes, better informing decisions on which drugs or drug classes to select for testing in a clinical trial. Indeed, drug targets supported by genetic data have been shown to be more likely to lead to the production of drugs reaching regulatory approval than those lacking such data.[66]

Mendelian randomization uses genetic variants that are associated with an exposure (risk factor) and determines their associations with an outcome such as stroke or WMH volume, thus enabling inferences on causal relationships between the exposure and the outcome. Because individual alleles are allocated randomly at conception, Mendelian randomization shares critical features with randomized clinical trials. For instance, an intronic variant (rs6511720) in the low-density lipoprotein receptor gene that associates with low-density lipoprotein cholesterol concentrations also associates with risk of myocardial infarction and genetically elevated low-density lipoprotein cholesterol concentrations associate with risk of coronary artery disease in a dose-dependent manner consistent with trials involving cholesterol-lowering interventions.[67]

By focusing on genetic variants that perturb a known drug target Mendelian randomization can be used to explore drug effects. It enables predicting the success or failure of a randomized clinical trial in silico, thus reducing risks for participants, cutting down on cost, and accelerating decisions on promising targets. Genetic variants acting in cis on druggable protein levels or gene expression that encode druggable proteins can inform on potential drug repurposing, as they mimic the on-target (beneficial or harmful) effects observed by pharmacological modification. Such Mendelian randomization analyses have been used to suggest repurposing opportunities for licensed drugs, such as suggesting high-density lipoprotein cholesterol raising strategies could be considered for testing in ischemic SVD.[68]

### Recommendation

Because Mendelian randomization techniques allow stronger inferences on causality than classical observational studies, it may be useful to select therapies to be evaluated in SVD trials (82.8% expert agreement).

## Conclusions

The FINESSE framework provides recommendations for aspects of trial design in patients with SVD developed by an international panel of experts (Figure 2). Despite the global importance of SVD, there are currently few effective treatments. However, new insights into understanding disease pathogenesis, particularly from recent genetic studies, provide novel pathways that could be therapeutically targeted.[3] In addition, whether many other

currently available cardiovascular interventions are specifically effective in SVD, as opposed to other subtypes of stroke, remains uncertain. Evaluating such treatments requires data from robust adequately powered randomized clinical trials, and we hope that the FINESSE recommendations will provide a useful framework for design of such trials.

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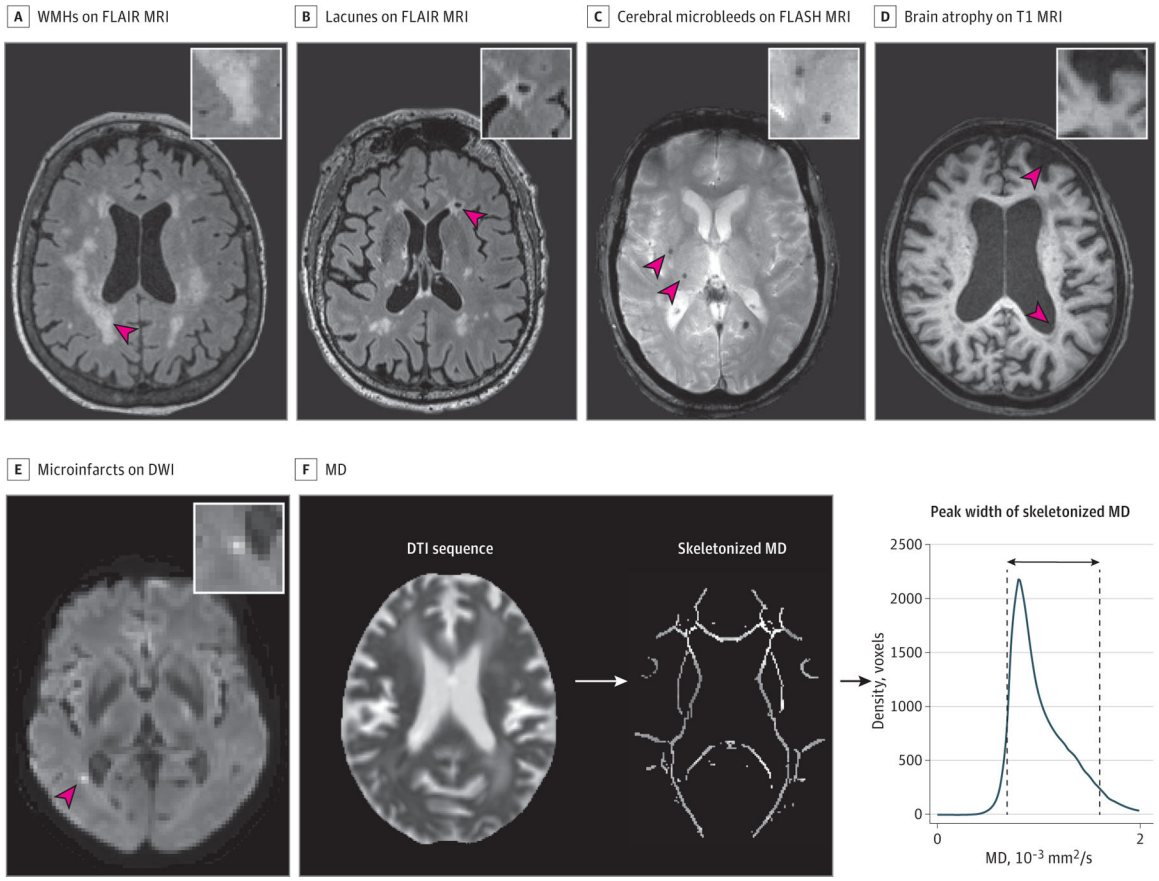


**Figure 1.**

Different Radiological Features of Small Vessel Disease Visible on Magnetic Resonance Imaging (MRI)

DTI indicates diffusion tensor imaging; DWI, diffusion-weighted image; FLAIR, fluid-attenuated inversion recovery; FLASH, fast low-angle shot; MD, mean diffusivity; WMH, white matter hyperintensities.

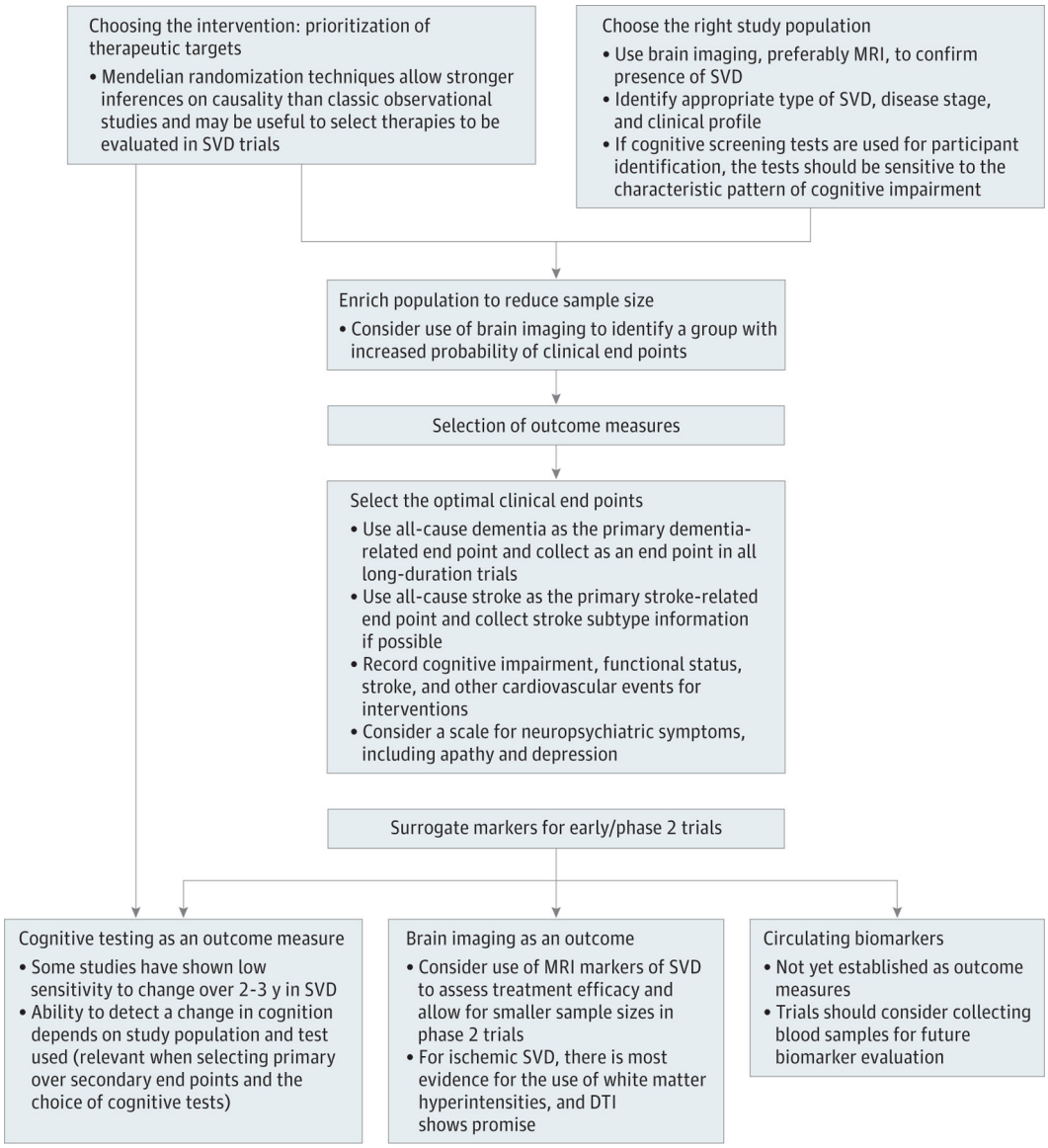


**Figure 2.**

Flowchart Highlighting Key Points in Design of Clinical Trials in Small Vessel Disease (SVD)

DTI indicates diffusion tensor imaging; MRI, magnetic resonance imaging.

**Table 1.**

Clinical End Point Types and Potentially Suitable Validated Scales

| Domain | Type | Recommendation | Potentially suitable diagnostic criteria or scale[a] |
|---|---|---|---|
| Mortality | Death | Include in all trials | NA |
| Pathophysiological or physiological | Stroke | Include in all trials with stroke subtype when feasible | For stroke subtype, Trial of Org 10172 in Acute Stroke Treatment (TOAST)[17] |
| | Mild cognitive impairment | Include in trials of sufficient size and duration; aid with valid assessments of cognitive-related quality of life, cognition, and function | *DSM-5* criteria |
| | Dementia | Include in trials of sufficient size and duration; aid with valid assessments of cognitive-related quality of life, cognition, and function | *DSM-5* criteria[16] |
| | Gait | Recommend for interventions to improve mobility or prevent falls | Timed up & go test[18] |
| | Major adverse cardiovascular events | Consider as secondary end points for trials | NA |
| Quality of life | Patient-reported health-related quality of life | Suggest for trials; proxy questionnaires are available and may be necessary when there is aphasia or dementia | EQ-5D[19] |
| | | | PROMIS[20] |
| Psychosocial/behavioral including apathy and depression | Neuropsychiatric symptoms | Consider in all trials; use information from an informant when available | Neuropsychiatric Inventory, Mild Behavioral Impairment Checklist,[21] and/or specific scales for apathy[22] and depression[23,24] |
| Function | Global disability | Consider in all trials | Modified Rankin Scale[25] |
| | Basic and Instrumental ADL | Recommended to assess stroke-related dysfunction and for stage of cognitive dysfunction | Barthel Index (basic ADL only) |
| | | | Functional Assessment Questionnaire[26] |
| | Frailty | Emerging as a potentially useful end point | Clinical Frailty Scale[27] |
| Compliance with treatment | Patient-reported pill counts or other objective measures | Consider for interventions that may be difficult to adhere to | NA |
| | Withdrawal | | |
| Satisfaction | Reported by patient, caregiver, or health care professional | May be useful depending on intervention | NA |
| Resource use | Health care use and costs | Consider hospitalizations, long-term care, direct and indirect costs of care | NA |
| Adverse events | NA | Recommend to include | Depends on intervention type |

Abbreviations: ADL, Activities of Daily Living; *DSM-5*, *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition); EQ-5D, EuroQol 5-Dimension; NA, not applicable; PROMIS, Patient-Reported Outcomes Measurement Information System.

[a] Scales listed by name are examples only, and the list is not meant to be comprehensive. Actual choice of end point types and assessment scales will need to balance multiple factors including measurement properties (such as content validity, reliability, responsiveness, and measurement error) and feasibility (such as cost and participant burden). Cognitive and neuroimaging end points are covered in other sections.

**Table 2.**

Suitability of Magnetic Resonance Imaging Markers as Surrogate Markers in Clinical Trials

| | Evidence marker predicts clinical end points | | | Sample size required (range from 2 studies)[a] | |
|---|---|---|---|---|---|
| | | Longitudinal studies | | | |
| Characteristic | Cross-sectional studies | Baseline prediction | Change prediction | For treatment effect size of 20% | For treatment effect size of 30% |
| WMH | ++ | ++ | ++ | 279–280 | 124–129 |
| Lacunes | +++ | ++ | + | 1345–25 545 | 572–11 354 |
| DTI | +++ | ++ | ++ | 108–289 | 48–128 |
| Brain atrophy | ++ | ++ | ++ | 325–5075 | 145–2256 |
| CMB | + | + | ? | NA | NA |
| Cognition | | | | | |
| Executive function | +++ | ++ | +/− | 13 803 | 6135 |
| Processing speed | +++ | ++ | +/− | 6060–59 331 | 2694–26 369 |

Abbreviations: CMB, cerebral microbleeds; DTI, diffusion tensor imaging; NA, not assessed; WMH, white matter hyperintensities; +, limited evidence; ++, moderate evidence; +++, strong evidence; −, low evidence; ?, uncertain.

[a]Sample size estimates are provided for a putative clinical trial in small vessel disease with magnetic resonance imaging markers of small vessel disease as outcome measures. These are compared with those using cognitive tests as outcome measures. Numbers refer to the predicted minimum sample size per arm (power = 0.80 and type I error = 0.05) for a clinical trial of 3-year duration to test a hypothetical treatment effect of 20% and 30% in the intervention group. Values represent the range taken from 2 sources.[11,33] The latter values were calculated for a 1.5-year duration trial so sample sizes have been halved.