ARIC Manuscript Proposal #4211

PC Reviewed: 3/14/23 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Using retinal imaging to improve MRI screening for the study of small vessel disease: A theoretical recruitment proposal

b. Abbreviated Title (Length 26 characters):

2. Writing Group:
Writing group members:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __ME___ **[please confirm with your initials electronically or in writing]**

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3. Timeline:
Manuscript prepared and submitted in ~5-6 months.

4. Rationale:

White matter hyperintensity (WMH) is detected as bilateral hyper-intense regions on a T2 or FLAIR MRI scan and primarily located in the periventricular and deep WM regions. It is believed to be caused by chronic diffuse injury in the form of ischemic demyelination and axonal degeneration and is a common radiological feature in age-related sporadic cerebral small vessel disease (cSVD)[1]. Estimates on the prevalence of WMH in individuals above age 65 have varied depending on the methodology and the clinical characteristics of the selected sample, ranging between 27% to 87% [2, 3]. Recent evidence has however also shown that significant WMH lesions already occur at an earlier age in some people, and that their presence has been associated with higher blood pressure, impaired cognitive function and even significant cognitive decline [4-6]. Thus, clinical trials aimed at slowing down WMH lesion growth and associated clinical progression as early as possible are of interest, given the sequelae of these lesions and their progression.

One significant challenge in setting up such a clinical trial in individuals at risk for WMH presence and progression is to recruit the right population with significant WMH burden already in mid-to late life who are likely to progress without having to spend large financial resources during the screening process. As brain imaging is an expensive modality to screen for WMH lesions, more cost-effective pre-screening approaches might be used which could reliably filter out a significant proportion of cases without the required radiological manifestations. One approach is to recruit individuals based solely on their clinical history. However, this is problematic. Although CVD, recent infarct and hypertension are important risk factors for cSVD, evidence has shown that they alone explain little variance in the presence of graded WMH lesions (around 2%) [7-10].

Retinal microvascular imaging is a promising pre-screening tool available at a relatively low cost. Previous evidence in the ARIC Brain MRI cohort has shown that, cross-sectionally, individuals with retinopathy in late midlife were more likely to have WMH lesions than those without retinopathy (22.9% vs. 9.9%; odds ratio (95% *CI*)= 2.5 (1.5-4.0), adjusted for age, sex, race, and vascular risk factors) [11]. Two ARIC-MRI studies also examined the longitudinal association between retinal microvascular abnormalities and WMH progression. In the first study, WMH progression was defined as an increase in the Cardiovascular Health Study (CHS) grade of 2 or

more points, between visit 3 and follow-up MRI assessment 10 years later [12]. WMH lesion progression was only associated with earlier retinal arteriovenous nicking but not with retinopathy or any other retinal microvascular abnormality. In a subsequent study, where WMH lesion progression was treated as a continuous volumetric outcome measure, prior AV nicking and retinopathy were significantly associated with WMH progression, emphasizing the utility of having higher sensitivity to detect WMH progression when using a volumetric measure [13].

The retinal measures' great potential as a pre-screening modality as part of a 2-stage screening process has been recently demonstrated [14, 15]. A fully automatic imaging machine-learning algorithm relying on a combination of fractal, high order spectra, and statistical texture analyses predicted a high WMH burden in stroke-free and dementia-free healthy individuals with high accuracy (sensitivity= 0.929, specificity= 0.984) [14]. Demographic or clinical measures were not part of the unsupervised image analysis. There was also a strong correlation between the algorithm's predicted and the observed WMH load (r= 0.897). While these findings are very interesting and encouraging, it remains to be shown how easily applicable the AI-based algorithm with its high accuracy rate is in routine clinical settings and whether an single obtainable retinal score or combined with clinical features may be more suitable when designing a 2-stage retinal-MRI recruitment procedure for a clinical trial in cSVD. The trade-off between high accuracy rate versus the benefit of a more feasible clinical implementation requires further investigation.

In this study, our aim is to determine whether retinal features can be used as a promising pre-screening measure for a theoretical 2-stage retinal-MRI recruitment design, over and above or instead of clinical features, to inform potential future trials aimed at recruiting individuals at high risk for cSVD progression. In this theoretical recruitment design, recruited participants would be screened on the presence of retinal signs, clinical features, or their combination in a first stage, with confimatory MRI for inclusion/exclusion decisions in a second stage. Given specified minimum sample size for a phase-2 clinical trial, we will evaluate how different screening approaches impact the study's recruitment costs and ability to detect significant WMH progression over 10 years.

In case the retinal-WMH 2 stage recruitment process proves to be a valuable approach, an interactive web-based Shiny application could be designed to potentially incorporate into a clinical trial screening process, using the patient's retinal measure and clinical measures to determine whether the individual has an increased likelihood of WMH lesion and is at higher risk for WMH lesion progression and might thus be eligible for inclusion in a study.

5. Hypothesis/Study Questions:

1. To achieve the desired minimum sample size for a phase-2 clinical, a 2 stage retinal score pre-screening-WMH recruitment approach is associated with a significant reduction of financial costs than a WMH-alone recruitment process.
2. Participants selected through a pre-screening -WMH recruitment process show a significant WMH progression over 10 years. Only if a long-term WMH progression exists in the targeted sample, we can be certain that we selected the right population at risk for a clinical trial.
3. In a pre-screening-WMH recruitment design, a retinal pre-screening approach in combination with age and the clinical markers hypertension and diabetes at visit 3 is associated with lower financial costs than a pre-screening recruitment based on the 3 risk factors alone.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Design:

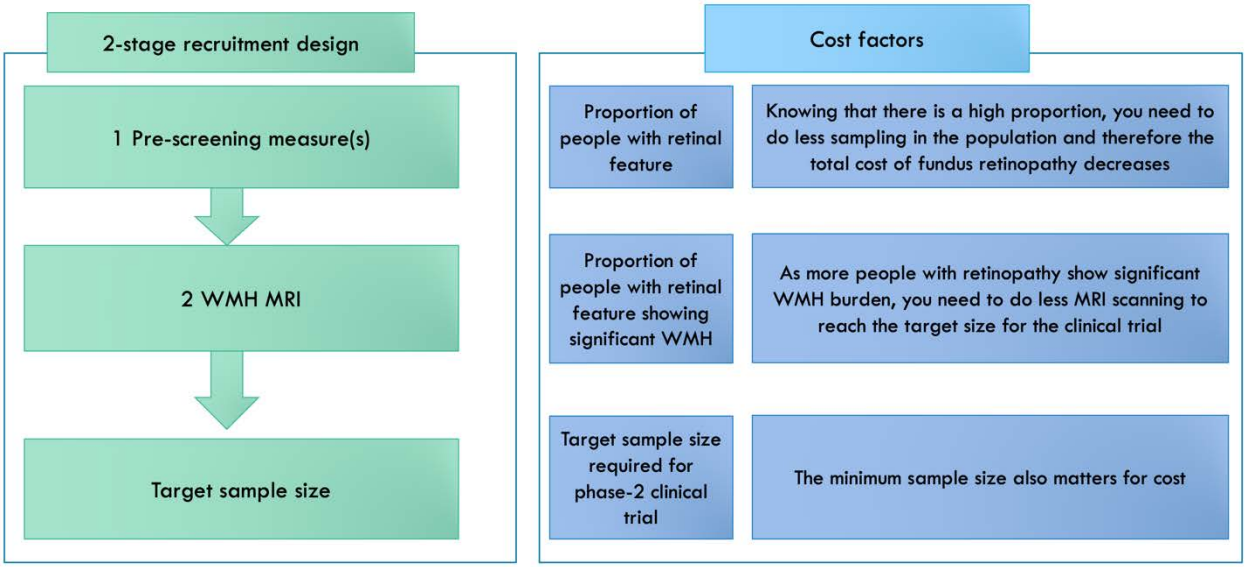
Participant inclusion:

At the third ARIC visit, individuals age 55 or older at the sites Forsyth County, North Carolina and Jackson, Mississippi were invited to take part in the ARIC Brain MRI study. Of the 2891 individuals initially screened to participate, 1920 eligible participants underwent brain MRI and had sufficient image quality. 1684 of the participants had also undergone retinal examination at the third visit. 1031 individuals (61%) had repeated MRI examination at the fifth visit (median follow-up time 10.5 years) and will be included in this study [12].

Outcome:

The overall financial costs will be computed to determine which of the different recruitment designs should be best used for a future phase-2 clinical trial in cSVD. The financial costs is assumed to be impacted by (1) the proportion of people with a pre-screening feature, (2) the proportion of people with a pre-screening feature and with significant WMH burden, (3) the minimum sample size required to conduct the phase-2 clinical trial (**Figure 1**).

Figure 1. A flow chart showing the 2-stage recruitment design and the associated financial costs



Screening measures:

Retinal photographs collected for the first time in ARIC at Visit 3 (years 1993-1995) will be used in this study. Retinopathy, defined as present if any of the following lesions are detected: retinal micro- aneurysms, haemorrhages, soft exudates and other less common lesions (e.g. hard exudates, macular oedema, optic disc swelling) will be used as a measure. Three additional retinal features will also be included: arteriovenous nicking, focal arteriolar narrowing, and generalized arteriolar narrowing defined as the lowest central retinal artery equivalent quartile (CRAE). The demographic variable age as well as the vascular risk factors hypertension and diabetes will also be included in the analysis.

Cardiovascular Health Study (CHS) white matter hyperintensity grading scores will be used as a screening measure. The ordinal scale will be dichotomized into significant (CHS score 3-9) vs. no or little WMH burden (CHS score 0-2). WMH lesion progression will be assessed using a volumetric measure. Since WMH volume is not measured at visit 3, it will be imputed with a previously published prediction quadratic equation (R^2=. 80) [16, 17].

Other covariates

Age, diabetes (fasting glucose> 125, non-fasting >200, or self-report of DM or use of antidiabetic medication) and hypertension (measured systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg or use of antihypertensive medications) at visit 3 will be included in the study.

Data analysis:

The proportion of participants showing significant WMH burden (CHS > 2) will be estimated in the ancillary MRI study of the ARIC cohort at visit 3. The required minimum sample size estimate for a future phase-2 clinical trial in cSVD will be determined based on previous work by Egle and colleagues (2022) [18]. Based on their estimation for a hypothetical phase-2 clinical trial, 646 participants would need to be enrolled.

The computations of the various recruitment designs are illustrated in **Figure 2**. In the MRI-only recruitment design, the minimum sample size estimate will be divided by the proportion of participants with significant WMH burden (CHS > 2) to the estimate the number of participants required at the recruitment stage. The total MRI screening costs will be estimated by multiplying the number of participants at the recruitment stage with the research cost for a single MRI scan.

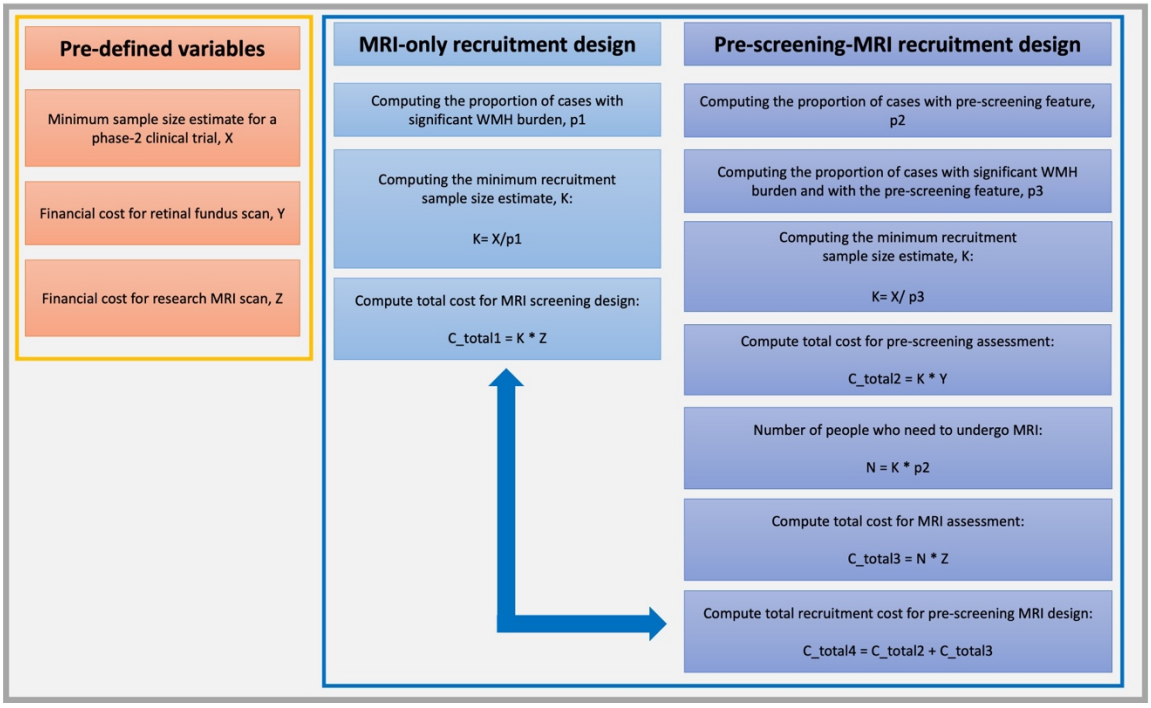
A retinal score will be created which ranges between 0-3 points and is the sum of 4 individual retinal signs: retinopathy, arteriovenous nicking, focal arteriolar narrowing, and generalized arteriolar narrowing. The value of the points depends on the abnormality of retinal severity. Whereas the presence of retinopathy will be given the maximum score of 3 points, only 1 point will be given for each of the other retinal signs. Summed scores of 4 or higher will be given the maximum score of 3. A clinical score will also be created ranging between 0-3 points and is the

sum of 3 demographic and clinical characteristics, i.e. age, hypertension and diabetes. For the presence of hypertension, diabetes and when being age 60 or older, one point will be given. A composite score will also be built that is composed of the retinal and clinical scores. This score therefore ranges between 0-6.

In the pre-screening-MRI recruitment design, different retinal cutoff scores (1-3), different clinical cutoff scores (0-3) and different composite cutoff scores (0-6) will be used to exclude participants at the pre-screening stage. The proportions of cases with the chosen pre-screening feature alone and of those additionally showing significant WMH burden (CHS >2) will be estimated. The minimum sample size estimate for a future phase-2 clinical trial will then be divided by the proportion of people with the pre-screening feature who also show significant WMH burden to determine the total number of people required to be recruited for the study. The total recruitment sample size will be multiplied by the financial cost of a single pre-screening assessment to estimate the overall pre-screening costs. To determine the number of participants who need to undergo MRI at the second screening stage, the proportion of participants with a chosen pre-screening score will be multiplied by the total recruitment sample size. The MRI cost of the 2 stage recruitment design will be estimated by multiplying the number of participants required to undergo MRI with the cost for a single MRI scan. The total cost of the pre-screening-MRI recruitment design will be computed by adding the pre-screening and the MRI screening costs together. The total costs associated with the various recruitment designs will be compared.

Using a Wilcoxon signed-rank test, it will also be tested whether the sample selected through the recruitment process shows significant WMH progression over a 10-year period.

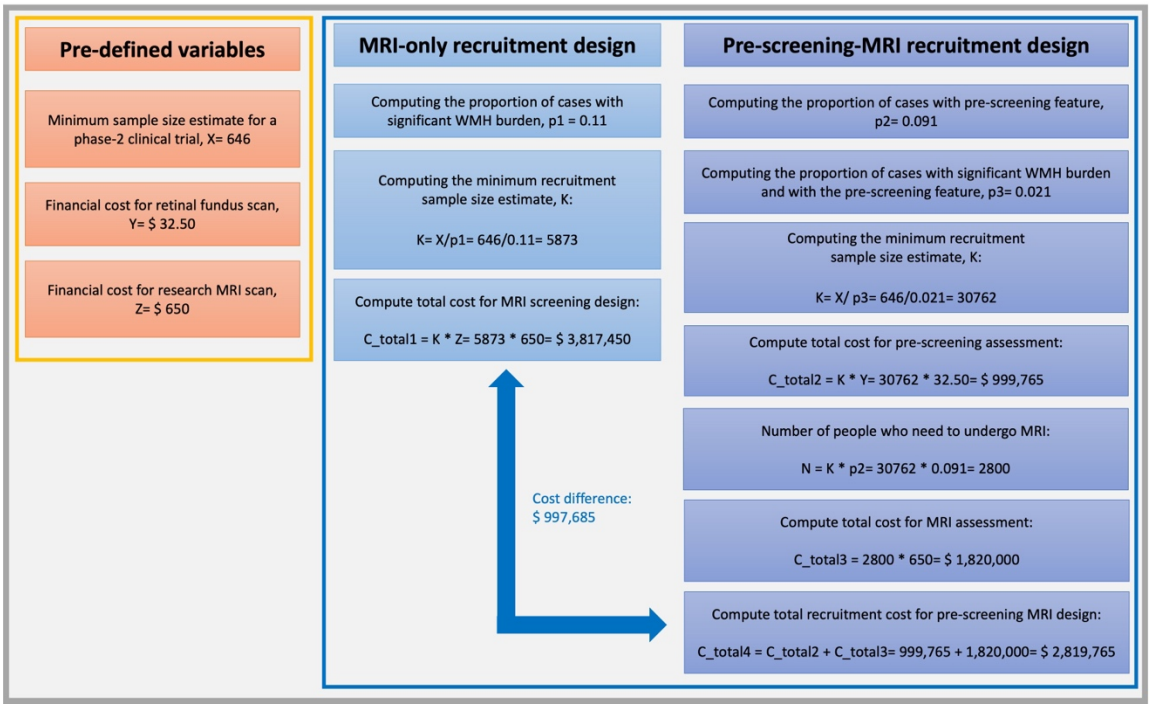
Figure 2. A flow chart showing the computation of the MRI-only and the pre-screening MRI recruitment design.



Data analysis in action using retinopathy as the only pre-screening measure- an illustration

Using the results from a previously published study (Wong et al., 2002), the total recruitment sample size and the financial costs of the MRI-only vs. pre-screening MRI recruitment designs were computed. The minimum sample size estimate for a phase-2 clinical trial in cSVD were derived from previous work by Egle and colleagues (2022) [18]. For a treatment effect size of 20%, a minimum sample size of 646 participants with mild-moderate SVD would need to be enrolled at baseline.The computation shown below is for illustration purposes only (**Figure 3**). Only one pre-screening measure was included in this example. In the proposed study multiple pre-screening measures will be included. The results of this theoretical recruitment design demonstrated that adding retinopathy as the only pre-screening feature makes the recruitment significantly less expensive by $985,393.

Figure 3. A flow chart showing the computation of the MRI-only and the pre-screening MRI recruitment design using retinopathy as a pre-screening feature



7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes _x__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ___ Yes _x__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ___ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.
ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/aricproposals/dtSearch.html

___x___ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

MP # 753 Retinal microvascular abnormalities and its relation to cerebral white matter lesions and atrophy: the Atherosclerosis Risk in Communities Study

MP # 1432 Retinal Signs and Risk of Incident MRI Brain Abnormalities.

MP # 1894 Retinal Microvascular Abnormalities predict Progression of White Matter Disease and Incident Lacunar Infarcts: The ARIC MRI study

MP # 2565 Retinal Microvascular Abnormalities and Subsequent MRI Cerebrovascular and Neurodegenerative Signs: the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC NCS)

MP # 841 Prevalence And Risk Factors Of Retinal Vein Occlusion And Retinal Arteriolar Emboli: Combined ARIC and CHS Study

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _x__ Yes ___ No

11.b. If yes, is the proposal

__x_ A. primarily the result of an ancillary study (list number* __ARIC Brain MRI: _1999.01_____)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number https://sites.cscc.unc.edu/aric/approved-ancillary-studies

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

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