ARIC Manuscript Proposal Form

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1.a. Full Title: Identifying populations with rapid cognitive decline using plasma biomarkers of neurodegeneration

b. Abbreviated Title (Length 26 characters): Identifying cognitive decline

2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. X **[please confirm with your initials electronically or in writing]**

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ARIC sponsor to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located. The ARIC sponsor is responsible for **carefully reviewing the proposal and ensuring its soundness prior to submission to the ARIC Publications Committee.** (The ARIC sponsor should be involved enough in ARIC to be able to point the lead author to appropriate ancillary study PIs and to be able to search ARIC manuscript proposals if the lead author doesn't have the access needed to do such a search).

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3. Timeline: The proposed manuscript will be finalized and submitted for review by the ARIC Publications committee within one month of approval.

4. Rationale:

Over the last three decades, the number of older adults aged ≥65 years with Alzheimer's Disease and Alzheimer's Disease Related Dementias (AD/ADRD) increased from 18.7 million to 49 million.[1] Addressing this escalating public health challenge requires the implementation of randomized controlled trials that test the efficacy of pharmacological[2,3] and non-pharmacological[4-6] interventions designed to reduce late-life cognitive decline. A critical factor that often complicates such trials is the heterogeneity of cognitive decline in older adults.[7] If healthy volunteers show little or no cognitive decline, then the overall progression rate is closer to the null and the effect of a treatment designed to reduce cognitive decline becomes too small to detect.

Enrichment strategies that identify individuals likely to undergo rapid cognitive decline constitute one solution that may improve randomized trials.[8] Prior trials have used cognitive tests[2-6] and positron emission tomography (PET) scans[2,3] to enrich trial populations. However, cognitive tests alone often fail to produce control groups with cognitive decline[4-6] and PET scans are costly and burdensome. A viable alternative is blood-based biomarkers. Obtaining blood samples from potential trial participants is safe, inexpensive, and minimally burdensome. Moreover, faster cognitive decline has been observed in older adults with abnormal levels of glial fibrillary acid protein (GFAP),[9-14] neurofilament light (NfL),[10,13-15] phosphorylated tau at threonine (pTau) 181,[11,13,14] pTau217,[11,13] and amyloid-β 42 to amyloid-β 40 (Aβ42:Aβ40).[9,11] Trials of pharmacological interventions[2,3] often focus on biomarkers of tau tangles and amyloid plaque, such as pTau181, pTau217, and Aβ42:Aβ40. However, general lifestyle interventions[4-6] may benefit from nonspecific biomarkers of neurodegeneration, such as GFAP and NfL.

To inform future randomized trials, the proposed investigation will examine whether distribution-based thresholds of plasma biomarkers defined in the Atherosclerosis Risk in Communities (ARIC) cohort[16] can be used to identify older adults who undergo rapid cognitive decline as validated in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort.[17] The utility of distribution-based thresholds will also be examined in participants enrolled in the Aging and Cognitive Health Evaluation in Elders (ACHIEVE) trial.[5] Collectively, these two examinations will assess whether plasma biomarkers can be used as a screening tool in AD/ADRD trials..

5. Main Hypothesis/Study Aims:

Study Question: Can plasma biomarkers of neurodegeneration as well as amyloid and tau enrich randomized controlled trial populations by identifying older adults who undergo rapid cognitive decline.

Hypothesis 1: Distribution-based thresholds of plasma biomarkers of neurodegeneration defined in the ARIC cohort will identify older adults with rapid cognitive decline in the MESA cohort and ACHIEVE trial.

Hypothesis 2: The addition of biomarkers of AD pathology will not increase the progression much more than selection based on NfL and GFAP, supporting a strategy that focuses on reversible neurodegeneration biomarkers as a target for selection.

Hypothesis 3: Using plasma biomarkers as a screening tool will decrease the sample size required for future randomized controlled trials that evaluate interventions designed to reduce cognitive decline.

6. Design and analysis - please address the following aspects:

a) **Inclusion/exclusion**

See next section.

b) **Study design**

Discovery Sample: ARIC

Thresholds for plasma biomarkers will be defined using the ARIC cohort.[16] ARIC recruited 15,792 predominantly Black and White participants from 4 US communities (Washington County, Maryland; Forsyth County, North Carolina; selected suburbs of Minneapolis, Minnesota; and Jackson, Mississippi) between 1987 and 1989. The baseline assessment was followed by Visit 2 (1990–1992, N = 14,348), Visit 3 (1993–1995, N = 12,887), and Visit 4 (1996–1998, N = 11,656). The ARIC Neurocognitive Study (ARIC-NCS) was initiated 15 years later at Visit 5 (2011–2013, N = 6,538) and succeeded by Visit 6 (2016–2017, N = 4,214), Visit 7 (2018–2019, N = 3,589), Visit 8 (2020, N = 3,226), and Visit 9 (2021–2022, N = 2,105). The ARIC and ARIC-NCS protocols were approved by the institutional review boards (IRBs) at each participating institution. Written informed consent was obtained from each participant or their legal representative.

During Visit 5, participants were screened for eligibility for a neuroimaging substudy (**see Figure 1 below**).[18] Participants were eligible if they had no contraindications and previously participated in a brain magnetic resonance imaging (MRI) study,[19] had evidence of cognitive impairment, or were part of a random sample of participants without cognitive impairment. Among 1,977 participants who completed a

valid MRI scan at Visit 5, a subset of 1,829 participants had stored plasma samples that were analyzed using Quanterix assays.[20] Three of the samples produced invalid results, resulting in an analytic sample of 1,826 participants with plasma samples obtained from 2011 to 2013 and cognitive assessments conducted between 2011 and 2022.

Validation Sample: MESA

Thresholds identified in ARIC will be validated in the MESA cohort.[17] From 2000 to 2002, MESA enrolled 6,814 White, Black, Hispanic/Latino, and Chinese adults from 6 US communities (Baltimore, Maryland; Chicago, Illinois, Forsyth County, North Carolina; Los Angeles County, California; Northern Manhattan and Southern Bronx, New York; and St Paul, Minnesota). Follow-up assessments included Exam 2 (2002–2004, N = 6,239), Exam 3 (2004–2005, N = 5,946), Exam 4 (2005–2008, N = 5,818), Exam 5 (2010–2012, N = 4,655), Exam 6 (2016–2018, N = 3,303), and Exam 7 (2022–2024, N = 2,276). The MESA protocol was approved by the IRBs at each institution and written informed consent was obtained for each participant.

At Exam 6, 743 White, Black, and Hispanic/Latino participants had stored plasma samples that were analyzed using Quanterix assays (**see Figure 1 below**). Within this subsample, 360 participants did not complete a follow-up cognitive assessment. The validation sample will comprise 343 participants with plasma samples obtained from 2016 to 2018 and cognitive assessments conducted between 2016 and 2024.

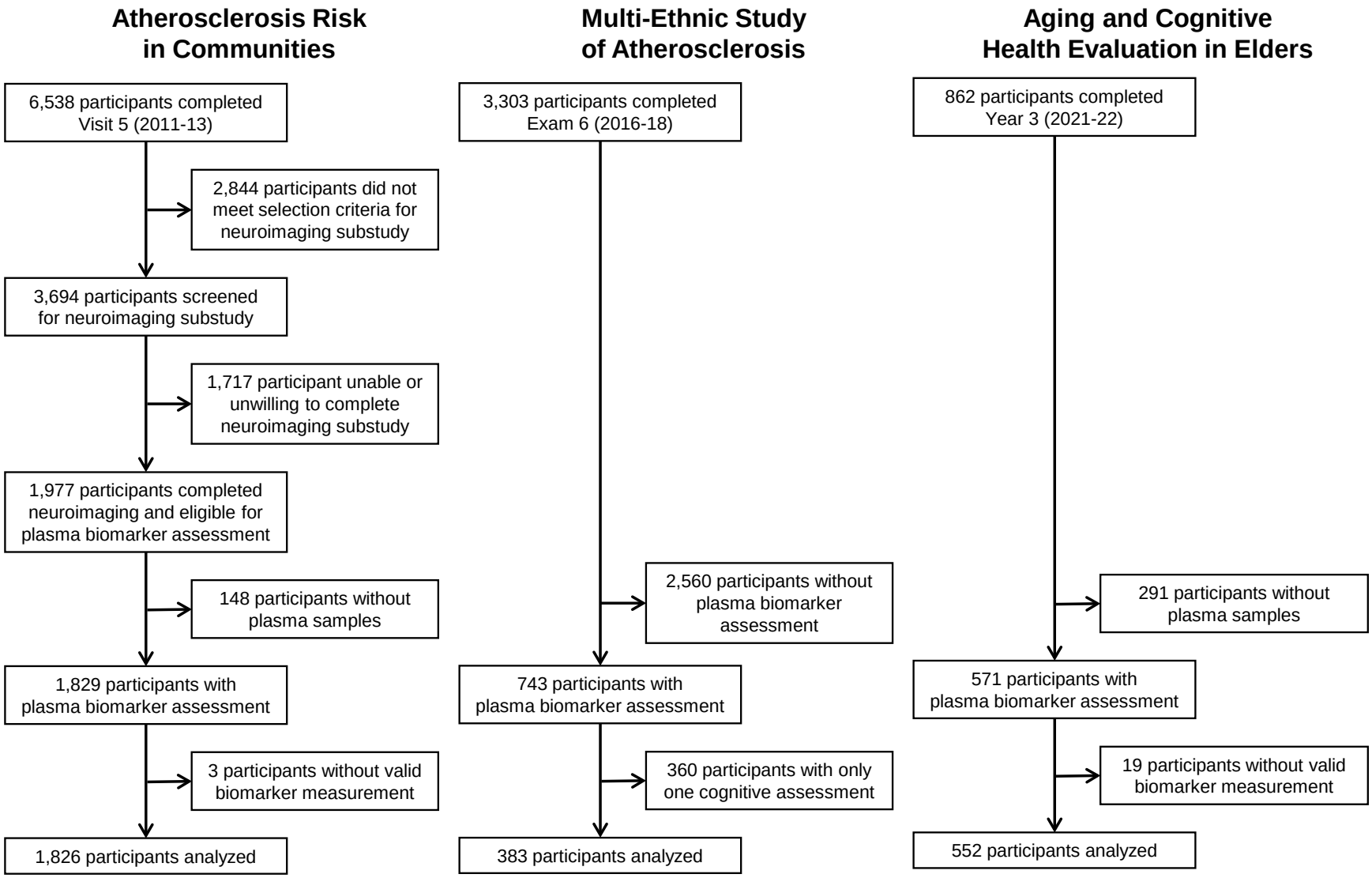
Exploratory Sample: ACHIEVE

Data from the ACHIEVE trial[5] will be used to evaluate whether distribution-based thresholds of an Alamar assay can be used to identify older adults who undergo rapid cognitive decline. The ACHIEVE trial is a multicenter, parallel-group, unblinded randomized controlled trial[5,21] that investigated the effects of a best-practice hearing intervention versus a health education control on 3-year change in cognition among community-dwelling older adults (ClinicalTrials.gov identifier: NCT03243422). The trial was partially embedded within the ARIC cohort and conducted at the same 4 US communities (Washington County, Maryland; Forsyth County, North Carolina; Minneapolis, Minnesota; and Jackson, Mississippi). Recruitment methodologies[22] and screening procedures[21,22] have been reported. The eligibility criteria were age (70-84 years), living situation (community-dwelling, not planning to move from the area), English language fluency, adult-onset bilateral hearing loss as defined by better-ear 4-frequency pure-tone average (PTA) at 0.5, 1, 2, and 4 kHz between 30-70 decibel (dB), free from substantial cognitive impairment (mini-mental state examination [MMSE][23] score of ≥23 for participants with a high school degree or less and ≥25 for those with some college education or more), no difficulty with ≥2 or more activities of daily living (getting in/out of bed or chairs, bathing, dressing, eating, and toileting), visual acuity better than 20/63 on the MNREAD (University of Minnesota) acuity chart, no hearing aid use within the prior year, no concurrent enrollment in trials focused on auditory or cognitive exposures or outcomes, and a willingness to be randomized and participate in study interventions. A total of 3004 participants were screened for eligibility and 977 participants underwent 1:1 permuted block randomization stratified by severity of

hearing loss (PTA <40 or ≥40 dB), recruitment source (ARIC or de novo), and field site.[5] Eligible spousal pairs or partners were randomly assigned as a unit and stratified by recruitment source and field site. The ACHIEVE protocol was approved by the IRBs at each institution and each participant provided written informed consent. An independent data and safety monitoring board met every six months to review study progress.

Randomization occurred between 2018 and 2019 (N = 977). At the three-year follow-up assessment (2021–2022, N = 862), each participant randomized to the health education control was allowed to participate in the hearing intervention. All participants were also invited to complete additional annual follow-up assessments. Among participants that completed the three-year follow-up (**see Figure 1 below**), 571 had plasma samples that were analyzed using an Alamar assay. Nineteen samples generated invalid results, resulting in an analytic sample of 552 participants with plasma samples obtained from 2021 to 2022 and cognitive assessments conducted between 2021 and 2025.

Figure 1. Flowchart of participants analyzed in each sample



c) **Outcome and other variables of interest with specific reference to the time of their collection**

Exposure: Plasma Biomarkers

In each cohort, ethylenediaminetetraacetic acid plasma samples[17,24] were collected and placed in an ice bath until plasma was separated by centrifugation. Plasma was divided into aliquots in cryovial tubes, frozen, and stored in -80°C freezers. Plasma was thawed immediately before being aliquoted, plated, and analyzed.

Plasma samples from the ARIC and MESA cohorts were analyzed by the Advanced Research and Diagnostic Laboratory (ARDL) at the University of Minnesota using single molecule array technology (Simoa) Neurology 4-Plex E (N4PE) from Quanterix. ARIC used the original N4PE while MESA used the N4PE Advantage. Simoa is an ultrasensitive, digital immunoassay platform that can detect proteins in plasma at sub-femtomolar concentrations.[25,26] The N4PE assay included measures of GFAP which quantified inflammation and astrocytic activation, NfL which quantified axonal injury, and amyloid β isoforms that were 40 (Aβ40) or 42 (Aβ42) residues long and measured the accumulation of extracellular amyloid plaques. A singleplex assay (version 1.0) for pTau181 measured intracellular neurofibrillary tangles.

Plasma samples from the ACHIEVE trial were analyzed by the ARDL using the Alamar Biosciences NUcleic acid Linked Immuno-Sandwich Assay (NULISA™) central nervous system (CNS) kit (Alamar Part# 800104, Lot# 2407305). Utilizing the automated Alamar Argo HT workflow, target analytes within each sample were bound through multiple capture, wash, and release steps, resulting in immunocomplexes with both sample-specific and target-specific DNA tags that were pooled into a single library for next generation sequencing. The library was sequenced using a P2 100 cycle flow cell (Illumina Part# 20046811, Reagent Lot# 20841078, Flow cell Lot# 20846922) on a NexSeq1000. After sequencing, the FASTQ file was uploaded to Argo Command Center for automatic normalization using internal and inter-plate controls and then log2-transformed for conversion to NULISA protein quantification (NPQ) units for each biomarker.[27] Aβ42:Aβ40 was calculated as the difference between Aβ42 and Aβ40 since the units were log2-transformed before the ratio was generated.

To evaluate test-retest reliability of the Quanterix assays in the ARIC cohort,[20] two plasma aliquots were obtained from the same participant (N=90). The plasma samples were blindly analyzed using the same reagent batch. Repeatability was quantified by calculating the coefficient of variation as the average of each within-participant ratio of the standard deviation to the mean. The coefficient of variation was good (CV: 2.3-11.3). The same process was used to assess reliability in the MESA cohort using two plasma aliquots from the same participant (N=38). The coefficient of variation of the Quanterix assays remained good (9.0-10.0). In the ACHIEVE cohort, two plasma aliquots from the same participant (N=16) were analyzed to assess the repeatability of the Alamar assay. The coefficient of variation was excellent (0.6-1.9).

The 50th and 75th percentiles of each plasma biomarker will be defined in the ARIC cohort for GFAP, NfL, pTau181, and Aβ42:Aβ40. A rank-based inverse normal transformation[28] will be applied to each biomarker and composite scores will be

calculated as the mean of z-scores. Composite scores will be generated for (1) GFAP and NfL, (2) GFAP and pTau-181, (3) NfL and pTau-181, (4) GFAP, NfL, and pTau-181, and (5) GFAP, NfL, pTau-181, and an inverted Aβ42:Aβ40 ratio. The 50th and 75th percentiles will be determined for each composite score. Thresholds identified for each biomarker and composite score in the ARIC cohort will be applied to the MESA cohort.

In the ACHIEVE trial, NPQ units generated by the Alamar NULISA™ CNS kit are on a sample relative scale rather than an absolute scale. Consequently, it is not possible to translate Quanterix thresholds defined in ARIC to Alamar NPQ units. Instead, the process of defining sample-specific thresholds and composite scores conducted in ARIC will be performed in ACHIEVE.

The composite score of GFAP and NfL will be the primary measure of interest. Although prior evidence suggests that each plasma biomarker is associated with cognitive decline in older adults,[9-15] choice of a specific biomarker or composite score for trial enrichment depends on the target of the intervention. Individuals with low levels of Aβ42:Aβ40 are likely to have amyloid plaque and may benefit from pharmacological anti-amyloid therapies.[2,3] Similarly, individuals with high levels of pTau181 or pTau217 are likely to have tau tangles for which pharmacological treatments are currently being developed.[29] High levels of GFAP may be an indicator of dense amyloid plaques,[30,31] tau accumulation,[30,31] or neuroinflammation,[32] making it a reasonable option for pharmacological interventions that target amyloid,[2,3] tau,[29] or astrocytes[33] as well as non-pharmacological interventions that reduce neuroinflammation.[34] High levels of NfL are indicative of general neurodegeneration[35] making it an ideal choice for non-specific lifestyle interventions.[4-6] For this investigation, the composite score of GFAP and NfL was chosen as the primary measure because its use as a tool for trial enrichment may be relevant to a wide range of interventions.

Outcome: Cognition

In ARIC and ACHIEVE, cognition was assessed by the MMSE[23] and a 10-test cognitive battery administered in-person. The in-person battery included the Digit Span Backwards,[36] Boston Naming Test,[37] Word Fluency Test,[38] Animal Naming Score,[38] Digit Symbol Substitution,[36] Trail Making Tests A and B,[39] Incidental Learning,[40] Logical Memory Test,[36] and the Delayed Word Recall.[41] In-person assessments were stopped in March 2020 due to the coronavirus pandemic. A modified 6-test cognitive battery was implemented by phone between July and December 2020. The phone-based battery included the Digit Span Backwards,[36] Word Fluency Test,[38] Animal Naming Score,[38] Oral Trail Making Tests A and B, [42] and Consortium to Establish a Registry for Alzheimer's Disease Word List.[43] Scores from the in-person battery were used to compute a factor score of cognitio.[5,44] A co-calibrated factor score model[45,46] that treated the Digit Span Backwards, Word Fluency Test, and Animal Naming Score as linking items[47,48] was used to harmonize the phone battery to the in-person battery. The resulting factors scores in ARIC will be standardized to Visit 5 and the factor scores in ACHIEVE will be standardized to the three-year follow-up.

In MESA, cognition was assessed by the Cognitive Abilities Screening Instrument, [48] Digit Span Forwards and Backwards,[36] and Digit Symbol Substitution.[36] The in-person battery was stopped in March 2020 and a modified phone-based battery

was implemented between June 2020 and February 2022. The phone-based battery included the Cognitive Abilities Screening Instrument and the Digit Span Forwards and Backwards. Each test will be standardized to Exam 6. A mean of z-scores will be computed to generate a composite measure of cognition.

Baseline Measures

Multiple measures will be used to characterize each sample. Date of birth, sex, race/ethnicity, and education were self-reported. Date of birth was used to calculate age. Education was discretized into a three-level variable (less than high school education, high school education or equivalent, greater than high school). The location of the field site each participant was recruited by was documented.

Body weight was measured to the nearest 0.1 kilograms. Height was measured to the nearest centimeter. Body mass index was calculated as weight in kilograms divided by height in meters squared. Diabetes was defined as fasting glucose ≥126 mg/dL, non-fasting glucose ≥200 mg/dL, use of glucose-lowering medication, or self-reported physician diagnosis. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using an automated sphygmomanometer. Hypertension was defined as SBP ≥140 mmHg, DBP ≥90 mmHg, use of anti-hypertensive medication, or self-reported physician diagnosis. Current use of cigarettes or alcohol were self-reported. The presence of Apolipoprotein E (APOE) ε4 alleles was ascertained by the TaqMan assay.[49-51]

d) **Summary of data analysis**

Analyses will be conducted in SAS version 9.4 (SAS Institute Inc) and Stata version 18.5 (StataCorp). Descriptive statistics will be generated to compare the analytic samples for ARIC (N = 1,826), MESA (N = 383), and ACHIEVE (N = 552). Annualized change in cognition will be calculated in each sample using a linear mixed effects model that specifies time from baseline as the timescale, includes a random intercept and time slope, and employs an unstructured variance-covariance matrix. The resulting best linear unbiased estimates of the fixed effects and best linear unbiased predictions of the random effects will be combined to create subject-specific estimates of cognitive change.

In the ARIC cohort, the 50th and 75th percentiles of age and an inverted MMSE score will be identified. The point estimate and 95% confidence intervals (CIs) of annualized cognitive change at specific thresholds of age, the inverted MMSE score, plasma biomarkers, and composite scores of plasma biomarkers will be estimated by fitting separate linear mixed effects models for each discretized predictor. Each model will specify time from Visit 5 as the timescale, include a random intercept and time slope, employ an unstructured variance-covariance matrix, and use the interaction between time and the discretized predictor to estimate the rate of change. The rate of change associated with the bottom half and top half of the discretized predictor will be estimated from a model that includes a 2-level variable (1=bottom half, 2=top half). The rate of change associated with the top quartile of the discretized predictor will be estimated from a model that includes a 3-level predictor (1=bottom two quartiles, 2=third

quartile, 3=top quartile). To mitigate bias caused by informative attrition,[52] multiple imputation by chained equations (MICE)[53] with auxiliary variables[54] will be used to impute measures of cognition among participants who were alive during each visit but did not complete an assessment. To reduce selection bias,[20] sampling weights will be included in each model.

Linear mixed effects models with the same specifications will estimate the association between thresholds of the composite score of GFAP and NfL and annualized cognitive change in MESA and ACHIEVE. To mitigate attrition bias, MICE will be used in ACHIEVE and inverse probability of attrition weighting will be used in MESA. The resulting best linear unbiased estimates of the fixed effects and best linear unbiased predictions of the random effects will be combined to create subject-specific estimates of annualized cognitive change. Heterogeneity in each sample will be visualized by generating histograms of annualized cognitive change for (1) all participants, (2) participants in the bottom half of the composite score, (3) participants in the top half, and (4) participants in the top quartile.

Power analyses will be conducted to quantify the effect of selecting participants for a trial based on specific thresholds of the composite score of GFAP and NfL. Power will be calculated under the assumptions that (1) there will be three repeated assessments of cognition over a period of three years, (2) the effect of the intervention will be determined from a linear mixed effects model, (3) the hypothetical intervention will reduce the rate of cognitive decline by 33%, (4) the variability of the rate of cognitive decline in the linear mixed effects model will be 0.2, and (5) the variability of measurement error in the linear mixed effects model will be 0.1. These assumptions were based on parameter estimates from the ACHIEVE trial.[5] The sample size required to reach 80% power with these assumptions will be calculated using Optimal Design.[55]

Two sensitivity analyses will be performed to evaluate the robustness of the results. The first sensitivity analysis will apply linear mixed effects to the ACHIEVE sample to generate point estimates and 95% CIs of annualized cognitive change at specific thresholds of age, the inverted MMSE score, plasma biomarkers, and composite scores of plasma biomarkers. This analysis will be performed for both pTau181 and pTau217. The second sensitivity analysis will determine the sample size required to reach 80% power if only NfL is used to select participants for a trial.

e) **Any anticipated methodologic limitations or challenges if present**

One key issue beyond the scope of this investigation is the role of comorbidities[56] such as kidney disease[57] that may bias plasma biomarkers. Such sources of bias would need to be accounted for if a trial protocol used plasma biomarkers to screen and select participants. Another limitation is that thresholds for this investigation will be defined using Quanterix assays, which prior research suggests have less classification accuracy than other assays.[58] Investigations that test different assays and facilitate crosswalks between assays are needed for trialists to determine which assay is ideal for enrichment. An aspect of the study design that should also be considered is that plasma samples were analyzed as a single batch (Alamar) or in the minimum number of batches possible (Quanterix). While beneficial for consistency in this investigation, a trial

that uses plasma biomarkers to screen trial participants over a period of months or years would likely need to develop a method to account for batch effects.[59]

f) **Will the author need Limited data to complete the proposed manuscript?**

☐ Yes, Limited data is needed. (Provide a brief (2-3 sentences) justification for requesting PHF data)
☒ No, De-identified data will be sufficient.

Please note, Limited dataset access is strict and rarely provided. Limited data includes identifiable information such as dates (birthdays, visit dates, etc.). CMS, Genomic, Geocoded, Proteomics/Somalogic, and other -omic data all fall under the limited data category. De-identified data does not include dates. All dates are date adjusted to "Days since Visit 1".

7. Will the data be used by a for-profit organization in this manuscript? ☐ Yes* ☒ No

8. Will the DNA data be used in this manuscript? ☒ Yes* ☐ No

The presence of Apolipoprotein E alleles will be included as a covariate.

* Please carefully review the instructions and documentation on the ARIC website at: https://aric.cscc.unc.edu/aric9/researchers/Obtain_Submit_Data [ARIC website > Researchers > Obtain/Submit Data] for instructions on proper data use.

9. The lead author or the ARIC sponsor 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 website at: https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC Website >Publications >Proposal Search]

☒ 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)?

4235 (Palta): Predictors of change in blood-based biomarkers of AD pathology and neurodegeneration measured from mid- to late-life and their associations with late-life measures of brain health in the ARIC Study

H4395 (Pike): Effect of a hearing intervention among older adults at high risk of cognitive decline: ACHIEVE randomized trial

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use current [or ongoing] ancillary study data (this includes ACHIEVE)?

☒ Yes ☐ No→ **Skip to question 12**

11.b. If yes to 11.a., is the proposal

☐ A. primarily the result of an ancillary study
☒ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables)

11.c. If yes to 11.a., list number* 2016.03 - ACHIEVE

*ancillary studies are listed by number
https://aric.cscc.unc.edu/aric9/researchers/ancillary_studies/approved_ancillary_studies [ARIC Website >Ancillary Studies >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. The NIH-NHLBI Public Access Brochure about the public access policy from http://publicaccess.nih.gov/ is posted in https://aric.cscc.unc.edu/aric9/publications/policies_forms_and_guidelines [ARIC Website > Publications >Publication Policies, Forms, and Guidelines]. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

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