

Aging and Cognitive Health Evaluation in Elders (ACHIEVE) Randomized Trial

Protocol

Co-Principal Investigators:

Frank R. Lin, MD PhD
Josef Coresh, MD PhD
Johns Hopkins University

Supported by:

The National Institute on Aging

Grant # R01AG055426



ACHIEVE
HEALTHY AGING

V.1.7 July 28, 2017

Changes from protocol version 1.6 to 1.7

Minor changes to page numbering were made throughout the document.

Substantive modifications were made to the following sections:

3. Overview of the ACHIEVE trial design

- Removal of reference to group booster sessions.

4.1 Inclusion criteria

- Word recognition score >60% bilaterally changed to word recognition score \geq 60% in better ear (to parallel PTA requirements)

7.2.2. Ensuring speech understanding test

- Removed sentence about presentation of instructions (to be consistent with what is stated in the CRF).

7.5.2. CHAMPS questionnaire

- Replaced with Baecke questionnaire

7.5.12. Removed Physical Activity Questionnaire

7.5.12 Added Intervention feedback form description.

7.6 Communication partners assessments

- Added clarification on the process for replacement of communication partners.

7.7. Schedule of evaluations

- CHAMPS questionnaire replaced with Baecke.
- Added Intervention feedback form at 6 months and 3 years
- Combined International Outcome Inventory-Hearing aids and International Outcome Inventory-Alternate Interventions to one measure (International Outcome Inventory for comprehensive intervention)
- Hospitalizations: Added assessment at 6 months, 18 months, and 30 months.
- Physical Ability Questionnaire removed.
- Collapsed Successful aging visit and successful aging booster session into one row. Added 'X' at 12 and 24 months to match with the text description in section 9.2.
- Removed Prevention in Practice report as this is captured by the successful aging intervention visit.

8 Randomization

- Changes spouse-pair to spouse/partner pair

9.2. Successful Aging intervention

- Overview: Removal of reference to participants selecting keys of their choice. Replaced with specific keys being presented.
- Module options: Addition of key currently under development at the University of Pittsburgh
- Contact mode and frequency: Removal of session content following the Life study model from Booster sessions. Replaced with keys 5-9 (or 6-10 for non-smokers). Removal of reference to group booster sessions.
- Audiometric baseline: Case history row removed.

12 Statistics

- Removed adjustment for other baseline variables found imbalanced from the primary analysis
- Edited terminology so “global cognitive function factor score” is referred to consistently

19. References

- Reference 14 (CHAMPS questionnaire) replaced with reference for Baecke questionnaire

CONTENTS

Study Summary	8
1 Study objectives	10
2 Background and rationale.....	11
2.1 Hearing loss and cognition	11
2.2 Pilot research.....	11
3 Overview of the ACHIEVE trial design	12
4 Study population and eligibility	13
4.1 Inclusion criteria.....	14
4.2 Exclusion Criteria.....	14
5 Recruitment and retention	15
5.1 Integration within ARIC-NCS	15
5.2 Field centers	16
5.3 Recruitment strategies.....	18
5.4 Retention strategies.....	18
6 Participant rights and confidentiality	19
6.1 Informed consent.....	19
6.2 Participant confidentiality	20
7 Data collection and measurements	20
7.1 Audiometric assessment	20
7.1.1 Case history	21
7.1.2 Air conduction audiometry.....	21
7.1.3 Tympanometry	21
7.1.4 Bone conduction audiometry.....	21
7.1.5 Word Recognition in Quiet.	21
7.1.6 Quick Speech in Noise (unaided).....	21
7.2 Cognitive battery.....	22
7.2.1 Administration	22
7.2.2 Ensuring speech understanding test.....	22
7.2.3 Cognitive domains.....	22
7.2.4 Delayed word recall test (DWRT).....	23
7.2.5 Digit Symbol Substitution test (DSST).....	23

7.2.6	Incidental learning	23
7.2.7	Trail Making Test Part A (TMT A).....	23
7.2.8	Trail Making Test Part B (TMT B).....	24
7.2.9	Logical Memory I and II	24
7.2.10	Digit Span Backwards	24
7.2.11	Boston Naming test (BNT)	24
7.2.12	Word Fluency	25
7.2.13	Animal Naming.....	25
7.3	Dementia and MCI Assessments	25
7.3.1	Neurological interviews	26
7.3.2	Clinical Dementia Rating Scale (CDR).....	26
7.3.3	Functional Assessment Questionnaire (FAQ).....	27
7.3.4	Neuropsychiatric Inventory (NPI)	27
7.3.5	Characterization of participants who leave the study early	27
7.4	Inclusion/exclusion/covariates	28
7.4.1	Demographics questionnaire	28
7.4.2	Health history questionnaire.....	28
7.4.3	Neurologic History	28
7.4.4	Anthropometry.....	28
7.4.5	Seated blood pressure	28
7.4.6	Blood draw	28
7.4.7	Wide Range Achievement Test (WRAT).....	29
7.4.8	Pure-tone audiometry (screening).....	29
7.4.9	Vision screening.....	29
7.4.10	Mini-Mental State Exam (MMSE)	29
7.4.11	Activities of Daily Living (ADL)	29
7.5	Secondary Outcomes	29
7.5.1	Center for Epidemiological Studies Depression and Hopelessness Scale (CES-D)	29
7.5.2	Baecke Physical Activity Questionnaire (BAQ)	30
7.5.3	Hearing Handicap Inventory for the Elderly – Screening Version	30
7.5.4	SF-12v2 Health Survey	31
7.5.5	Social Network Index	31

7.5.6	UCLA Loneliness Scale	31
7.5.7	Accelerometry	31
7.5.8	Falls and mobility	32
7.5.9	Hospitalizations	32
7.5.10	Grip strength	32
7.5.11	Short Physical Performance Battery (SPPB)	32
7.5.12	Intervention Feedback Form	32
7.6	Communication Partners Assessments.....	33
7.7	Schedule of evaluations	33
8	Randomization.....	38
9	Interventions	38
9.1	Hearing intervention	38
9.2	Successful Aging intervention	40
10	Strategies to Promote Intervention Adherence/Compliance & Minimize Bias from Unblinded Study Participants and Staff	42
11	Safety monitoring.....	45
11.1	Data safety monitoring board	45
11.2	Adverse events.....	45
12	Statistical considerations	47
12.1	Sample size	47
12.2	Analytic approach	49
12.3	Global cognitive function factor score.....	53
12.4	Interim Analysis for futility and sample size re-estimation	54
13	Data management.....	55
14	Data Handling and Record Keeping	56
15	Quality assurance and quality control.....	57
15.1	Fidelity of hearing intervention.....	57
15.2	Fidelity of successful aging intervention	58
15.3	Quality assurance of data entry	58
16	Study Monitoring, Auditing, and Inspecting	58
17	Timeline	59
18	Organization of the Study	61
18.1	Key roles of committees	61

19 References62

Study Summary

Title	Aging and Cognitive Health Evaluation in Elders (ACHIEVE) Randomized Trial
Short Title	ACHIEVE
Study Site(s)	<ul style="list-style-type: none"> • George Comstock Field Center, Johns Hopkins Bloomberg School of Public Health, Washington County, MD • University of Mississippi Medical Center, Jackson, MS • University of Minnesota, Minneapolis, MN • Wake Forest University, Forsyth County, NC
Data Coordinating Center	University of North Carolina, Chapel Hill, NC
Design	Randomized, open-label trial comparing hearing rehabilitative intervention versus successful aging control intervention for rate of cognitive decline.
Sample Size and Population	850 participants, approximately 50% from the ongoing Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS) and 50% non-ARIC participants.
Objectives	<p>Primary: To determine the effect of hearing rehabilitative intervention versus a successful aging control intervention on rates of global cognitive decline (primary outcome measure), decline in cognitive domains, adjudicated incident dementia and mild cognitive impairment, physical and social functioning, HRQL, and physical activity in 70-84 year-old well-functioning and cognitively-normal adults with hearing loss.</p> <p>Secondary: To investigate whether hearing rehabilitative intervention alters established trajectories of cognitive decline in participants recruited from ARIC-NCS, and to investigate the effect of hearing rehabilitative intervention on rates of cognitive decline in persons with Alzheimer's disease risk factors and biomarkers.</p>
Main Inclusion/Exclusion Criteria	Community-dwelling adults aged 70-84 years with mild to moderate audiometric hearing impairment, and free from substantial cognitive impairment at baseline.
Randomization and stratification	1:1 permuted block randomization, stratified by severity of hearing loss (mild, moderate), ARIC status (ARIC or non-ARIC participant), and field center. Qualifying spouse/partner pairs are randomized as a unit, stratified by ARIC status and field center.

Study Interventions	<p>Participants in the hearing intervention group are fitted with a hearing aid, instructed to be worn on a daily basis for study duration, and attend four 1-hour intervention sessions spaced over the 2-3 months post-randomization. Re-instruction in use of devices and hearing rehabilitative strategies will be provided every 6 months.</p> <p>The Successful Aging intervention consists of four 1-hour intervention sessions spaced over the 2-3 months post-randomization focusing on participant-selected topics from the 10 Keys™ to Healthy Aging program and upper body stretching. Additional sessions will be provided every 6 months.</p>
Study Duration	<p>Three years. Four intervention visits in the 2-3 months following baseline, with follow-up visits every 6 months until Month 36.</p>
Outcomes	<p>Primary: 3-year cognitive decline, as measured by the change from baseline in the global cognitive function domain factor score.</p> <p>Key secondary: change from baseline to year 3 in the memory, executive function, and language domain factor scores, and time until composite outcome of adjudicated diagnosis of dementia, mild cognitive impairment (MCI), or 3 point decline in MMSE.</p> <p>Additional: measures of social and physical function, physical activity, and Health Related Quality of Life (HRQL).</p>

<p>Statistical Methodology</p>	<p>Primary: Groups will be compared for the primary outcome using a multiple imputation ANCOVA model of change from baseline to year 3 with adjustment for baseline cognitive factor score, baseline hearing loss stratum, race*center, ARIC vs de Novo status, age, and education (\leq high school, $>$ high school). Missing cognitive scores due to adjudicated dementia diagnosis will be imputed based on data from other ACHIEVE dementia cases plus non-ACHIEVE ARIC participants diagnosed with dementia at either ARIC visit 6 or ARIC visit 7. Missing scores for all other reasons including death without dementia will be imputed using ACHIEVE data under the missing at random assumption.</p> <p>An independent DSMB will review safety outcomes on a regular basis. A formal interim analysis to evaluate for sample-size re-estimation will be performed after 66% of subjects have completed the study. In the unexpected event of low study enrollment, an assessment for futility may also be performed at this interim.</p>
--------------------------------	---

1 Study objectives

The aims of the Aging and Cognition Health Evaluation in Elders Randomized Trial (ACHIEVE) are:

Primary aims

Aim 1 To determine the effect of hearing rehabilitative intervention versus a successful aging control intervention on rates of decline in global cognitive function (primary outcome measure) in 70-84 year-old well-functioning and cognitively-normal older adults with hearing loss.

Aim 2 To determine the effects of hearing rehabilitative intervention versus a successful aging control intervention on secondary outcome measures of decline in cognitive domains (memory, executive function, and language); composite outcome consisting of adjudicated incident dementia, MCI or a 3 point decline in the MMSE; physical and social functioning; HRQL; and physical activity.

Secondary Aims

1. To investigate whether hearing rehabilitative intervention alters established trajectories of cognitive decline in participants recruited from ARIC-NCS. We will leverage cognitive data gathered over the previous 30 years in ARIC to model prior cognitive change as well as prospective change after enrollment in ACHIEVE.

2. To investigate the effect of hearing rehabilitative intervention on rates of cognitive decline in persons with Alzheimer's disease risk factors (ApoE4 allele) and biomarkers (neurodegeneration based on structural brain MRI; brain amyloid based on PET). Hearing loss may act as an additional "hit" on the brain in addition to AD and vascular processes. However, unlike these other processes, the effects of hearing loss may still be modifiable with hearing interventions in late life

2 Background and rationale

2.1 Hearing loss and cognition

Novel approaches for reducing cognitive decline in older adults are needed given the aging of the population and the personal, socioeconomic, and public health implications of cognitive impairment and dementia in older adults. Epidemiologic data now strongly suggest that age-related peripheral hearing loss in older adults is independently associated with accelerated cognitive decline and incident dementia. Mechanistic pathways that could underlie this observed association include the effects of poor audition and distorted peripheral encoding of sound on cognitive load, brain structure, and/or reduced social engagement. These pathways may be amenable to comprehensive hearing rehabilitative treatment consisting of the use of hearing assistive technologies (hearing aids, other integrated hearing assistive devices) and rehabilitative training. To date, however, there has never been a randomized trial that has investigated whether hearing loss treatment could reduce cognitive and other functional declines in older adults. The ACHIEVE study will be a randomized controlled trial nested within the Atherosclerosis Risk in Communities (ARIC) study. 850 70-84 year-old cognitively normal older adults with hearing loss will be randomized 1:1 to the hearing intervention (hearing needs assessment, fitting of hearing devices, education/counseling) or successful aging intervention (individual sessions with a health educator covering healthy aging topics)

2.2 Pilot research

We conducted a pilot study (ACHIEVE-P) from 2015-16 at the Washington County, MD ARIC field site. The objectives of ACHIEVE-P were to determine feasibility of study recruitment, randomization, and retention, assess compliance with study interventions, refine study protocols, and observe for an efficacy signal of the hearing intervention on early 6-month outcomes that may mediate downstream effects of hearing intervention on cognitive functioning. 40 participants were randomized to either the hearing intervention or successful aging intervention in a 1:1 allocation ratio. Among the 40 randomized participants, 27 were from ARIC and 13 were recruited de novo from the community. Participants were followed until study completion (6 months), excluding one participant who died during follow-up for reasons unrelated to the study intervention.

The hearing intervention demonstrated a clear efficacy signal for early proximal outcomes of communication and social functioning. Estimated changes in standardized (z-score) outcomes were qualitatively different by intervention assignment for all measures, including perceived

handicap due to hearing loss (as measured by the Hearing Handicap Inventory for the Elderly, $p < 0.0001$), loneliness (as measured by the UCLA Loneliness Scale), number of contacts ($p = 0.007$), and diversity of social network (as measured by the Cohen Social Network Index) and social, mental, and physical function (as measured by the Short Form (SF)-12). For all measures, estimates of change since baseline are suggestive of improvement or no change for the hearing intervention group, as compared to poorer function in the successful aging group (Table 1).

Table 1. 6-month change in standardized proximal outcomes.

Outcome	Hearing Intervention	Successful Aging
	Mean (SD)	Mean (SD)
Perceived handicap due to HI*	-1.40 (0.96)	0.02 (0.68)
Loneliness*	-0.19 (0.87)	0.22 (0.94)
Social Network [†]		
Number of people	0.17 (0.65)	-0.42 (0.66)
Diversity	0.15 (1.25)	-0.12 (0.70)
Social Function [†]	0.00 (0.65)	-0.26 (0.91)
Mental Function [†]	0.26 (0.80)	-0.14 (0.60)
Physical Function [†]	0.11 (0.76)	-0.07 (0.40)

* Lower scores are better; † Higher scores are better.

Cognitive performance by intervention assignment

Estimated changes in standardized (z-score) cognitive domain scores over 6 months of follow-up were suggestive of improvement or no change for *all* participants (Table 2). The greatest estimated improvement in cognition was for participants who received the hearing intervention in the domain of memory. The mean change in memory for participants randomized to the hearing intervention was 0.48 ± 0.69 SD, as compared to 0.19 ± 0.66 SD for participants randomized to the successful aging intervention.

Table 2. 6-month change in standardized cognitive domain score, $n = 40$

Cognitive Domain	Hearing Intervention	Successful Aging
	Mean (SD)	Mean (SD)
Memory	0.48 (0.69)	0.19 (0.66)
Language	0.05 (0.38)	0.00 (0.42)
Executive Function	0.03 (0.42)	0.17 (0.47)
Global Function	0.16 (0.42)	0.14 (0.39)

3 Overview of the ACHIEVE trial design

The study is a randomized controlled trial. Approximately 850 participants will be randomly assigned to one of two groups and followed for three years: hearing intervention with hearing aids or successful aging intervention. Participants will be community-dwelling adults aged 70-84 years with audiometric hearing impairment defined as a four-frequency (0.5, 1, 2, 4 kHz) pure-tone average threshold in the better-hearing ear of ≥ 30 decibels (dB) and < 70 dB.

The ACHIEVE clinical trial will be nested within the ongoing Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS) which provides an existing, well-characterized cohort of African American and white participants who have been followed for nearly 30 years.

Recruitment will be based at the four established ARIC field sites (Washington County, MD; Jackson, MS; Forsyth County, NC; Minneapolis Suburbs, MN). To fulfill the ACHIEVE sample size, non-ARIC “de Novo” participants recruited from the community within the ARIC fields centers will also be concurrently enrolled. The recruitment ratio goal is 50% ARIC participants within each field center.

The hearing intervention consists of fitting with hearing aids and other hearing assistive technologies supplied by a single hearing technology manufacturer (Phonak) plus four 1-hour comprehensive, individualized hearing rehabilitation sessions spaced over the 2-3 months post-randomization designed to provide all of the active components of the intervention. Hearing aids are instructed to be worn on a daily basis for study duration. Audiologic outcomes (e.g., hearing aid data logging, real ear measures, speech in noise, etc.) to verify the best-practices hearing intervention are gathered during study intervention visits and semi-annually beginning at 6 months post-randomization. Participants are encouraged to specify an optional Communication Partner (CP) who is encouraged to attend the hearing intervention sessions.

The Successful Aging intervention will follow the protocol and materials developed for the 10 Keys™ to Healthy Aging program by the Center for Aging and Population Health Prevention Research Center at the University of Pittsburgh¹. This interactive, dynamic program informs older adults about risk factors for diseases. Participants will meet individually with a health educator certified to administer the program every 2-3 weeks for a total of 4 visits over 8-10 weeks, and the session content will focus on a “Key”. Each session will also include a 5-10 minute active upper body extremity stretching program as used in the Lifestyle Interventions and Independence for Elders (LIFE) study². Participants are encouraged to bring a friend or family member with them to intervention visits (analogous to the communication partner for participants randomized to the hearing intervention). Participants will return for booster sessions semi-annually.

Participants will be followed for at least 3 years after randomization with annual assessments, and this study is designed to detect a 0.26 S.D. difference in rate of decline on domain-specific composite scores between the hearing intervention and control groups over 3 years of post-randomization follow-up with 90% power.

At the completion of the study, participants in the successful aging intervention may also choose to be fitted for a study-supplied hearing aid and provided hearing rehabilitation resource materials over 2-3 intervention sessions if they are interested. Participants in the hearing rehabilitative may also choose to meet with a health educator to cover topics in the 10 Keys™ to Healthy Aging program over 2-3 intervention sessions.

4 Study population and eligibility

The study population will consist of approximately 850 adults aged 70-84 years free from substantial cognitive impairment at baseline. All eligible participants must have an adult-onset audiometric hearing loss as measured by a pure tone average across 4 frequencies (0.5, 1, 2, 4 kHz) ≥ 30 dB HL in the better-hearing ear. Participants with hearing loss that is unlikely to

benefit from amplification (e.g., poor word recognition in quiet) will be excluded from the study. Eligibility will be determined over a telephone screening and an in-person screening visit or based on audiometric and other data collected during ARIC-NCS study visits for existing ARIC-NCS participants. Confirmatory audiometric testing will be conducted at the baseline visit (performed on the same day or a separate day from the screening visit) by the study audiologist. Participants who initially qualify for the study based on screening (telephone screening, in-person screening, or screening based on ARIC-NCS data) but who do not meet study eligibility criteria based on data gathered at the baseline visit will be excluded from the study. Eligibility criteria are as follows:

4.1 Inclusion criteria

To be eligible for the study, participants must meet all of the following criteria:

- **Age 70-84 years.** Individuals aged 70-84 at the time of randomization are eligible for participation. This age range will allow recruitment of participants who are at risk for cognitive decline but who may also be expected to survive for the duration of the trial. This age range is estimated to allow for potential participation of 61% of participants currently enrolled in the ARIC study.
- **Community-dwelling.**
- **Fluent English-speaker.**
- **Residency.** Participants must plan to reside in the local area for the study duration.
- **Audiometric hearing impairment.** Participants must have adult-onset hearing impairment with a four-frequency pure tone average (0.5, 1, 2, 4 kHz) in the better-hearing ear of ≥ 30 decibels and <70 dB. This level of hearing impairment is the level at which individuals would be most likely to benefit from the use of conventional amplification devices such as hearing aids.
- **Word Recognition in Quiet score $\geq 60\%$ in better ear.** A word recognition in quiet score $<60\%$ suggests hearing impairment that is too severe to benefit from conventional amplification devices such as hearing aids.
- **Mini-Mental State Exam (MMSE) score ≥ 23 for individuals with high-school degree or less; Mini-Mental State Exam (MMSE) score ≥ 25 for individuals with some college or more;** Participants must be at risk for cognitive decline in the range quantified well by neurocognitive testing, and so must be free from more substantial cognitive impairment at baseline.
- **Willingness to participate be randomized and adhere to the protocol.** Participants must be willing and able to consent to participate in the study, be willing to be randomized to either the Hearing intervention or to the Successful Aging intervention, and be willing to commit to adhere to the study protocol for the duration of the trial (3 years of a randomly assigned intervention).

4.2 Exclusion Criteria

Potential candidates for enrollment who meet one or more of the following criteria are excluded from participation in the study:

- **Self-reported disability in ≥ 2 or more Activities of Daily Living (ADL)**
- **Any self-reported hearing aid use in the past year.** Trial participants will be randomized to hearing intervention or successful aging intervention and, therefore, participants cannot be currently already receiving treatment for their hearing loss.
- **ARIC participants only: Diagnosis of adjudicated dementia based on a previous ARIC visit or participant required a proxy to assist with completing informed consent and responding to questions at ARIC Visit 6 or 7.**
- **Vision impairment** (worse than 20/40 on MN Near Vision Card). Participants who cannot see (with correction) well enough to complete the neurocognitive assessment are excluded.
- **Medical contraindication to use of hearing aids** (e.g., draining ear). Because hearing aids will be the primary device used in the hearing intervention, participants with medical contraindications to hearing aid use are excluded.
- **Conductive hearing impairment** as determined by a difference in air audiometry and bone audiometry (“air-bone gap”) greater than 15 dB in 2 or more contiguous frequencies in both ears. Because the impact of a conductive (versus a sensorineural) hearing loss on cognitive functioning may potentially differ and programming for hearing aids differs for conductive hearing loss, participants with permanent conductive hearing loss are excluded from the trial. Participants with an air-bone gap due to fluid in the ears or other resolvable medical issue may be enrolled in the trial following successful medical resolution of the cause of the air-bone gap.
- **Unwilling to wear hearing aids on a regular (i.e., daily or near daily) basis**
- No participants are excluded based on race or sex.

Temporary Exclusion Criteria

Participants determined to have a conductive hearing impairment as measured by a difference in air audiometry and bone audiometry (“air-bone gap”) greater than 15 dB in 2 or more contiguous frequencies in both ears are excluded from the trial and referred for medical follow-up. Should the cause of the air-bone gap be determined to be due to a temporary or treatable medical issue (e.g., fluid or wax in the ears), participants may be enrolled following resolution of the issue (i.e., air-bone gap). Participants with asymmetrical sensorineural hearing (≥ 20 dB at 2 adjacent frequencies or ≥ 10 dB at 3 adjacent frequencies) or with other symptoms/signs concerning for a retrocochlear etiology based on the assessment of the audiologist will also not be eligible to participate until a medical clearance/evaluation is obtained.

5 Recruitment and retention

The Operations committee (see section 18.1) monitors recruitment and retention of participants.

5.1 Integration within ARIC-NCS

The ARIC study is a large, biracial prospective cohort study that enrolled 15,792 participants aged 45-64 years from four US communities in 1987-1989: Jackson, MS, Forsyth County, NC,

Washington County, MD, and Minneapolis suburbs, MN. The Jackson cohort was entirely African-American, and the Forsyth County site was about 15% African-American, with all other participants being primarily white. ARIC participants have received multiple assessments of cardiovascular risk factors, measurement of microvascular and macrovascular markers, cognitive testing, PET amyloid, and brain MRI over the last 30 years. The ARIC study is well described with over 1700 papers published in peer-reviewed journals. Details of the overall ARIC study design have been published³ and can also be found at www2.csc.unc.edu/aric/. From 2011 to 2014, ARIC participants returned for Visit 5 (V5) as part of the ARIC Neurocognitive Study (ARIC-NCS) to evaluate midlife vascular risk factors as predictors of late-life cognitive impairment. Beginning in 2015, ARIC-NCS was jointly funded by NHLBI, NIA, NIDCD, and NINDS (Co-PI: Coresh/Mosley) to conduct an additional ARIC-NCS Visit 6 (V6, 2016-17) and Visit 7 (V7, 2018-19) that will consist of a neurocognitive battery, audiometric testing, and physical functional assessments. The ACHIEVE trial will be nested within ARIC-NCS, and recruitment will occur directly during V7. As such, V6 and V7 data will be used to directly screen and recruit ARIC participants for ACHIEVE in parallel with participants also recruited de novo from the community.

To maximize efficiency and minimize participant burden, overlapping assessments between the ACHIEVE baseline visit and ARIC-NCS Visit 7 will generally be collected only once and shared across studies. If ACHIEVE baseline is completed first, the remaining ARIC Visit 7 assessments will be completed at a later visit, but shared elements will be omitted from NCS since ACHIEVE baseline data without randomized treatment group will be shared with ARIC NCS for approved uses. If ARIC Visit 7 is completed first, the ACHIEVE baseline visit must be completed within 2 months to share overlapping data; otherwise a full ACHIEVE baseline must be completed at least 6 months after ARIC Visit 7. Overlapping items are identified in the schedule of assessments and further described in the MOP.

5.2 Field centers

Recruitment will be based at the four established ARIC field sites (Washington County, MD; Jackson, MS; Forsyth County, NC; Minneapolis Suburbs, MN). Participants will be preferentially recruited from ARIC-NCS to increase efficiency through targeted recruitment and use of existing ARIC resources (previously collected data, etc.). Highly trained ARIC staff at the four field centers will be responsible for the recruitment of ACHIEVE participants. Conservative estimates based on recruitment rates during the ACHIEVE-P pilot study project that ~425 of the 850 ACHIEVE participants will be from the ARIC-NCS study.

George Comstock Field Center in Washington County, MD

The George Comstock Field Center is a dedicated research facility where County residents were recruited and followed for ARIC. The ARIC study as well as a number of other NIH-funded studies are conducted in the Comstock research facility which houses 30 employees in approximately 10,000 square feet of space dedicated to community-based research with multiple examination rooms, conference rooms, and research space. Dr. Coresh is the director of this Center. The Comstock Center is located in Hagerstown, Washington County, Maryland, 75 miles from the Johns Hopkins University campus. The research center has handicap

accessible entrances from the street, waiting rooms, examination rooms, interview rooms, phlebotomy and blood processing rooms with space for refrigerators and a freezer, lounge, conference rooms, file rooms, storage space, kitchens for preparation of snacks, and handicap accessible restrooms. The center has adjacent free parking. The Department of Epidemiology faculty and administrative staff oversee and advise on clinical and study conduct issues. The current project coordinator at the Center oversees space and staff sharing issues.

The University of Mississippi Medical Center in Jackson, MS

The University of Mississippi Medical Center (UMMC) has a long history of excellence in cardiovascular and neuro-epidemiologic research including recruitment and retention of African American participants for several large NIH-funded population-based studies (such as ARIC). The site has recruited and followed City residents for ARIC. The Memory Impairment and Neurodegenerative Dementia (MIND) Center was launched in 2010 at UMMC as a new initiative to elucidate the mechanisms and risk factors for brain aging and age-related diseases such as Alzheimer's. To enhance synergy across projects, cohort and clinical studies focused on aging and neurologic endpoints were brought together under the MIND Center umbrella. Dr. Tom Mosley is the principal investigator for the ARIC Jackson Field Center at UMMC and the director of the MIND Center. Housed in the MIND Center, the ARIC Field Center is conveniently located on UMMC's main campus. The ARIC Field Center includes 18,000 square feet of space including office, interview, and examination rooms. Facilities consist of a reception area and waiting room, multiple interview/procedure rooms, nurses' work station and office space, kitchen, storage areas with locking file cabinets, and phlebotomy and sample processing area with multiple -70°C freezers. Parking is conveniently located immediately behind the building. A dedicated van is available to shuttle study participants to diagnostic facilities on campus (e.g., MR imaging) or to conduct assessments in the participant's home, if needed. In 2017, the MIND Center (and the ARIC Field Center) will move to a new state-of-the-art research building located on UMMC's main campus (also, with convenient parking). The ARIC clinic space will be outfitted with new state-of-the-art equipment and has been ergonomically designed specifically to enhance research with older participants (e.g., equipped with high/low powered exam tables to facilitate transfer on/off the table, etc.). The ACHIEVE trial at UMMC will be conducted in this new space.

University of Minnesota, Minneapolis, MN

The ARIC Field Site in Minneapolis, located at the Epidemiology Clinical Research Center at the University of Minnesota has recruited and followed residents of selected Minneapolis suburbs for ARIC. The Epidemiology Clinical Research Center (ECRC) is located one block away from the offices of the Division of Epidemiology and Community Health, about 0.5 miles from the University of Minnesota Hospital on the Minneapolis campus, and is readily accessible from all parts of the Twin Cities metropolitan area (within three blocks from two major interstate highways). The ECRC occupies one floor (17,758 square feet) of a two-story building and includes reception area, offices for staff, examination rooms, interview rooms, ultrasound, phlebotomy and blood processing rooms, freezer room, lounge, conference rooms, and storage space. The building meets current regulations for handicapped accessibility and has 100 free

adjacent parking spaces. The site was established in February 2000 and is currently providing space and infrastructure for 25 research projects including multi-center epidemiologic studies and clinical trials.

Wake Forest University, Forsyth County, NC.

The Forsyth County ARIC Field Site is located at Wake Forest University. The Public Health Research Center (PHRC) is the site for clinic examinations for County residents for ARIC and is located in the Piedmont Plaza I building on the Wake Forest University Baptist Medical Center campus. The PHRC provides investigators within the Division of Public Health Sciences with facilities and staff to perform multi-center clinical trials and observational research. The PHRC is easily accessible to all study participants as it is located on the ground floor of the Piedmont Plaza I Building, within a half mile of the main hospital, and is handicap accessible. With over 5,600 square feet of space, the PHRC has 18 rooms, a laboratory, a large waiting area, adequate parking that is free of charge, and many additional amenities to enhance the research experience of our participants. This clinic is equipped to handle all examinations and tests associated with the ACHIEVE clinical trial.

5.3 Recruitment strategies

Each field site will implement a variety of strategies to achieve their recruitment targets with ACHIEVE participants being recruited both from ARIC-NCS and de novo from the surrounding communities. Recruitment of ARIC participants will occur concurrently with ARIC-NCS Visit 7 (V7) in close collaboration with the ARIC-NCS steering committee and as described in 5.1. Recruitment of de novo participants will be from the surrounding ARIC communities. ACHIEVE field site PIs and field site staff have overseen recruitment of older adults for other epidemiologic clinical studies and will employ site-specific strategies that have demonstrated prior success with recruitment of older adults. Such strategies include: utilizing established research registries, targeted advertisements in aging-related publications/radio, established field site relationships with local churches/retirement centers, mass mailings, etc.

5.4 Retention strategies

In order to maximize adherence, at the time of screening, only those participants who are determined by study personnel to fully understand the commitments of the study and are likely to follow the study protocol including regular use or not (as randomized) of a hearing aid are enrolled. Enrolling dedicated participants from those still attending ARIC examinations after nearly 30 years is likely to maximize study retention.

The following procedures are implemented in order to enhance retention:

- When scheduling the clinic visit, participants will be asked about:
 - Preferred time and date of examination
 - How participants prefer to get to the clinic visit
 - Need for assistance getting to or moving around the clinic
 - Existence of any medical conditions (e.g., diabetes, dietary restrictions) which might affect the examination and/or type of snack provided.

- To enhance response following the scheduling telephone call by ACHIEVE staff, a packet will be mailed to the participant prior to the scheduled appointment. This pre-appointment packet confirms the examination date and time and reviews the preparation procedures. Prior to the examination a reminder call will also be made to the participant.
- Free parking is provided to all participants. Participants will be reimbursed for travel costs, or transportation will be covered for a participant if he/she is not able to drive and/or obtain a ride to attend a study visit.
- Participant study incentives will include study-related items (pens, bags, mailed holiday cards) and/or modest payments (~\$20) for participating in each study visit. Individual field sites will determine the participant incentives to provide based on their previous experience and knowledge of their participants and community.
- Participants will be contacted by telephone to reschedule the appointment if eligible participants fail to arrive for a scheduled appointment or cancel their appointments.
- Home visits by study staff will be conducted as necessary when participants may be physically unable to come to the field site (e.g., from illness or injury). These visits will be informed by the experiences of study staff in performing such visits in ARIC-NCS Visits 5 and 6.
- Participants randomized to the hearing intervention and successful aging intervention group will also be informed that they will have the option of receiving the other intervention when the comparison of the two randomized interventions is completed.
- Each no-show case will be individually reviewed by the interviewer and when necessary by the supervisor. Conversion efforts include a combination of telephone contacts, conversion letters, and the possibility of offering an abbreviated exam. A participant is considered to have refused following three conversion contacts or three broken appointments, or if they otherwise firmly refuse. Participants are free to refuse or re-enter the study protocol after refusal at any time.

6 Participant rights and confidentiality

6.1 Informed consent

A signed consent form is obtained from each participant. The consent form describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation. The purpose of the informed consent form is:

- To inform the prospective participant as much and as accurately as possible about:
 - The procedures involved in the study
 - What is expected of participants who consent to enroll
 - What the study can and cannot provide to the participant
 - What are the reasonable risks and benefits
 - What are the alternatives to participation
- To document the participant's consent to participate in screening, and all of the respective procedures involved.

- To provide a prospective participant with a legal document summarizing the study and his or her rights as a study participant.
- To provide the participant with ongoing explanations and continuing information that help the participant decide whether to begin or continue in the research study.

6.2 Participant confidentiality

Data from the ACHIEVE study are used only in aggregate, and no identifying characteristics of individuals will be published or presented. Per existing ARIC-NCS protocols used at Visits 6 and 7, results of testing (body mass index, blood pressure, audiometry, evidence of substantive cognitive impairment based on 3 domain cognitive failure) are sent to participants' private physicians if participants agree. Information, including results of testing to be shared with a participant's primary care physician, is not released without written permission of the participant, except as necessary for monitoring by IRB.

Confidentiality of data is maintained by using research identification numbers that uniquely identify each individual. This study utilizes safeguards established as part of the parent study (ARIC) to ensure the security and privacy of participants' study records. Research records are kept in locked file cabinets within locked rooms at the study site. Only selected study personnel will have access to participants' study records on a need to know basis. Data are stored on password-protected computers with regularly updated virus software. Identifying information is only kept in the files where it is necessary for the conduct of the study and linkage to other files. In analysis files, study ID's only are used to identify participants.

In compliance with the Health Insurance Portability and Accountability Act (HIPAA) and the Standards for Privacy of Individually Identifiable Health Information of the Department of Health and Human Services, ACHIEVE accesses personal health information and medical records only after receiving signed informed consent. Participants' medical records that are obtained for review and abstraction are kept in a locked cabinet that is separate from other file cabinets. Only selected study personnel have access to these files.

7 Data collection and measurements

7.1 Audiometric assessment

The audiometric diagnostic battery will be conducted by a trained audiologist for all participants, regardless of treatment assignment. The diagnostic battery is based on current American Academy of Audiology guidelines⁴. Cerumen management by the study audiologist will be performed as needed. Participants with more severe cerumen impactions that cannot be easily cleared by the study audiologist will be provided with over-the-counter cerumenolytic ear drops (e.g., Debrox, Murine) and advised to follow-up with their primary care provider or an otolaryngologist.

All audiometric testing will occur in a sound-attenuated booth. The WhisperRoom (www.whisperroom.com/) was chosen due to its small footprint and lower weight compared to traditional metal sound booths.

7.1.1 Case history

Audiological history including history of noise exposure, prior hearing aid use, etc.

7.1.2 Air conduction audiometry.

Behavioral measurement of minimally perceptible tones tested across the frequencies most important for speech communication delivered through headphones.

7.1.3 Tympanometry

Objective measurement that determines integrity of the tympanic membrane/ossicles and assists in determination of a sensorineural hearing loss free of middle ear problems.

7.1.4 Bone conduction audiometry.

Behavioral measurement of minimally perceptible tones tested across the frequencies most important for speech communication delivered through a bone oscillator, which allows determination of a sensorineural hearing loss free of middle ear problems.

7.1.5 Word Recognition in Quiet.

Confirms that the speech perception abilities are consistent with a hearing loss that can be helped through traditional hearing aid intervention⁵.

7.1.6 Quick Speech in Noise (unaided).

The QuickSIN is a speech-in-noise test that measures the signal-to-noise (SNR) necessary for a listener to correctly identify 50% of key words on sentences presented in a babble background noise. A listener's abilities to understand speech in noisy backgrounds cannot be predicted by the audiogram, and this measure provides a tool to counsel the patient on realistic expectations for success with hearing aids and guides intervention decisions regarding hearing assistive technology (e.g., remote FM microphone). [Development of the test article⁶; Validation article⁷]

7.2 Cognitive battery

7.2.1 Administration

To assess cognitive decline and characterize dementia and Mild Cognitive Impairment (MCI), an efficient but comprehensive neuropsychological assessment will be administered by trained and certified examiners. The battery of cognitive measures (described below) are well-validated, standardized instruments that are widely used in clinical and epidemiologic studies of cognitive function and dementia, including ARIC NCS, and include most of the measures recommended in the Uniform Data Set (UDS) implemented in 2005 across all National Institute on Aging-sponsored Alzheimer's Disease Centers.

A trained examiner administers the cognitive function tests in a fixed order, one right after the other, during a single session in a quiet room. To ensure that the participant understands each task, test instructions are presented verbally and visually (e.g., with a practice template or written instructions). The measures in the cognitive battery are briefly described below. Note that the MMSE (screening and secondary outcome) and WRAT (covariate) are also administered during the cognitive assessment and are described in sections 7.4.9 and 7.4.6.

7.2.2 Ensuring speech understanding test

Prior to performing the neurocognitive assessment, a brief test will be conducted to determine whether or not the participant can adequately hear the examiner. In this test, five sentences are read aloud to the participant by the psychometrist, and the participant is asked to repeat back the sentence. Participants are scored on the number of target words repeated back correctly (3 target words/sentence). Steps on how to proceed with neurocognitive testing if audibility is not established are outlined in the MOP..

The ACHIEVE Steering Committee developed this protocol to guard against poor speech understanding from hearing loss directly confounding administration of neurocognitive tests with auditory stimuli. This protocol was developed in collaboration with ACHIEVE Co-I's with expertise in neuropsychology (Albert, Mosley, Knopman, Rebok) and audiology (Chisolm, Eddins) and was successfully pilot tested in the ACHIEVE pilot study.

7.2.3 Cognitive domains

The ACHIEVE study will utilize the neurocognitive battery that was previously administered in ARIC-NCS⁸ (sections 7.2.3 – 7.2.11). Four cognitive domains are derived from factor scores⁹ (see Section 12.3). These domains include:

- Global function
- Memory
- Executive function
- Language

7.2.4 Delayed word recall test (DWRT)

The DWRT is a measure of verbal memory that requires the participant to recall a list of 10 common nouns following a short delay. The participant is presented with a stimulus card for each of 10 words. The examiner reads each word aloud, and asks the participant to repeat the word and use it in a sentence. This procedure is repeated, providing two exposures to the words. Following an approximate 5-minute delay, during which the (non-verbal) digit symbol substitution test (DSST) is given, the participant is asked to recall as many words as possible. Scores range from 0 to 10 words recalled.

7.2.5 Digit Symbol Substitution test (DSST)

The DSST is a measure of psychomotor speed and sustained attention. Besides its own value, the DSST also serves as a nonverbal distracter task, interposed between learning and recall for the DWRT above. The participant is asked to translate numbers (1-9) to symbols using a key provided at the top of the test form. The participant is provided with a pencil (without an eraser). Instructions are provided in a deliberate and slow pace. One point is given for each correctly drawn symbol completed within the 90-second time limit. Scores range from 0 - 93.

7.2.6 Incidental learning

The Incidental Learning Test was adapted from the WAIS-R NI and provides a non-verbal measure of recent memory. Following the DSST, the participant is presented with the Incidental Learning Template. The participant is asked to write down as many of the DSST symbols as he/she can remember, in any order. Next, the participant is asked to write down the number that was paired with each of the symbols from the DSST. Two scores are yielded: 1) Free Recall: total number of symbols recalled, regardless of pairing and 2) Pairing: number of correct symbols correctly paired with corresponding numbers. Scores for each range from 0-9.

7.2.7 Trail Making Test Part A (TMT A)

The TMT A is a timed task in which participants connect numbers in sequence as quickly as possible. TMT measures attention, sequencing, mental flexibility, and visual search and motor function. In TMT A, the participant is asked to draw a line and connect a series of numbers (from 1-25) as quickly as possible. Prior to the test part, the participant is given a sample test to demonstrate the task. The score for TMT A is the number of seconds required to complete the task. A maximum of 240 seconds (4 minutes) and 5 errors is allowed.

7.2.8 Trail Making Test Part B (TMT B)

The TMT Part B is a timed task in which participants connect letters and numbers in sequence as quickly as possible. TMT measures attention, sequencing, mental flexibility, and visual search and motor function. In TMT B, the participant is asked to draw a line and connect a series of numbers and letters, alternating between a given number and letter (e.g., 1 to A, A to 2, 2 to B, B to 3, etc.) as quickly as possible. Prior to the test part, the participant is given a sample test to demonstrate the task. The score for TMT B is the number of seconds required to complete the task. A maximum of 240 seconds (4 minutes) and 5 errors is allowed.

7.2.9 Logical Memory I and II

This test, part of the Wechsler Memory Scale-Revised version, provides a measure of immediate and delayed verbal recall for the number of ideas presented in two stories which are read to the participant. Two stories are read to the participant, each at a slow and deliberate pace. After each story is presented, the participant is asked to recall as much of the story as possible. The Logical Memory I score provides a measure of immediate recall and is calculated as the average number of ideas recalled from Story A and B. Each story contains 25 scoring units, the maximum score is 25 ($25+25/2$).

An approximate 20 minute delay follows, during which the remaining (non-memory) tests are administered. Following the delay period, the participant is again asked to recall the stories. The Logical Memory II score provides a measure of delayed recall and is calculated as the average number of story elements recalled from Story A and B. As each story contains 25 scoring units, the maximum score is 25 ($25+25/2$).

7.2.10 Digit Span Backwards

Digit Span Backwards is part of the Wechsler Memory Scale-Revised and provides a measure of attention and working memory. The participant is read a series of numbers progressively increasing in length from two to eight digits. After the numbers are read, the participant is asked to repeat the numbers in the reverse order. Two trials at each digit length are performed (i.e., 2 trials with 2 digits, 2 trials with 3 digits, etc.). The test is discontinued after two consecutive errors of the same length item. Scores range from 0 – 12.

7.2.11 Boston Naming test (BNT)

The BNT assess visual naming ability using black-and-white drawings of common objects. For this study, the 30-item version used by the National Alzheimer's Coordinating Centers Uniform Data Set will be used. The participant is presented with a series of line drawings of objects and asked to name each object. The items become progressive more difficult based on their

frequency of occurrence in the English language. A total score is calculated as the number of spontaneously produced correct responses. Scores may range from 0 – 30.

7.2.12 Word Fluency

The Word Fluency Test is a measure of verbal functioning. In this task, the participant is asked to produce as many words as possible that begin with the letters F, A, and S within a time limit of 60 seconds for each letter, avoiding proper nouns, variations, plurals, and repetitions. The score is the total number of admissible words produced across letters.

7.2.13 Animal Naming

Animal Naming is a measure of category fluency (semantic association). Category fluency, and specifically animal naming, is part of the Boston Diagnostic Aphasia Examination, the Stanford-Binet test, and the CERAD. The participant is asked to name as many different animals as possible within a 60 second time limit. The score is given as the sum of all admissible names.

7.3 Dementia and MCI Assessments

A syndromic diagnosis of MCI and dementia will be determined and used as secondary outcomes. Current criteria for MCI¹⁰ and dementia¹¹, which prominently included investigators for this project, are now well-established and have been employed successfully in ARIC NCS. Details of the diagnostic procedures and normative data have been published and are enumerated in the MOP. Briefly, MCI and dementia syndromic diagnoses are determined by a panel of clinicians taking into account performance on the neuropsychological battery (test scores are compared to age, education, and race-specific norms), cognitive decline across study visits, and subject and informant interviews regarding cognitive functional status. Based on these elements, all examined participants have a computer-algorithmic classification followed by expert-adjudicated review. The computer algorithm, also developed by the expert panel for ARIC NCS, has been used successfully to enhance uniformity in applying the diagnostic criteria. In ARIC NCS, the computer algorithm-reviewer agreement was high: 99% for normal, 94% for MCI, and 95% for dementia, suggesting that the algorithm accords well with clinical judgment.

An MCI diagnosis is assigned in persons without dementia who meet the 3 criteria below:

1. FAQ < 5 or CDR Sum of Boxes < 3 (these measures are described below),
2. At least one neuropsychological cognitive domain Z score < -1.5 Z, and
3. Cognitive decline in general cognitive performance

A dementia diagnosis is assigned by either:

A) By a low MMSE score (<21 for Caucasians or <19 for African Americans), even in the absence of more complete cognitive testing or

B) By meeting all three of the following criteria:

1. FAQ > 5 or CDR Sum of Boxes > 3, and
2. At least two neuropsychological cognitive domain scores < -1.5 Z, and
3. Cognitive decline in general cognitive performance.

Participants failing to meet criteria for MCI or dementia are classified “normal”.

The informant interviews noted above are conducted with a knowledgeable informant at every exam where the participants meet a priori criteria for poor cognitive performance and who have significant cognitive decline from prior exams. These measures are no longer collected once criteria for dementia are met. Participants who leave the study early will have procedures for ascertainment of dementia detailed in Section 7.3.5.

7.3.1 Neurological interviews

The neurologic interviews include the Clinical Dementia Rating Scale (CDR) and the Neuropsychiatric Inventory (NPI). In addition, the Functional Activities Questionnaire (FAQ) is used in determining a participant’s level of daily functioning, but does not have a dedicated interview or form; rather, all FAQ items are embedded within the CDR interview. Each of the measures are well-validated, standardized instruments that have been widely used in both clinical and epidemiologic studies of dementia.

7.3.2 Clinical Dementia Rating Scale (CDR)

The CDR gives important information about daily functioning, and is a required element in the determination as to whether an individual is demented or has MCI, or is normal. The CDR includes the CDR Participant (CDP), and the CDR Informant (CDI), and the CDR Summary (CDS).

The CDP (the portion of the CDR administered to the participant) is administered to all participants. The CDP form is administered by a certified staff member to the participant while the participant is seated, and requires no equipment for administration.

The CDI is administered by a certified staff member with a knowledgeable informant and can be administered in the clinic, if the informant is available, or may be collected by phone.

After completion of these two components (and not in the presence of the subject or informant) a trained staff member will score the CDR (on the CDS form) based on the responses to the questions on both the CDP and CDI. The CDR scores range from 0 (normal) to 3 (severe impairment) for each of the following 6 areas: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.

7.3.3 Functional Assessment Questionnaire (FAQ)

The FAQ score is embedded within the CDR. Scores range from a 0 (normal function), 1 (has difficulty, but does by self), 2 (requires assistance), to 3 (dependent). There are 9 items from the CDR which are also FAQ questions (there are 10 FAQ questions; one CDR question encompasses two FAQ questions).

7.3.4 Neuropsychiatric Inventory (NPI)

The NPI consists of questions relating to personality and behavioral changes commonly seen in dementia. This scale is completed with a knowledgeable informant after the CDI, either in clinic or by telephone.

7.3.5 Characterization of participants who leave the study early

A final interview will be attempted with all participants who are either unable (e.g., due to illness or death) or unwilling to complete the study. Trained interviewers will collect information by telephone regarding the reason for withdrawal and offer to schedule a home visit for an abbreviated final exam (comprised of only core primary outcomes). In the absence of a final home exam, because dropouts may be more likely to have dementia, we will attempt to ascertain dementia status using a telephone-based assessment with the participant or informant interview conducted with a knowledgeable informant.

In the case where the participant is alive and able to communicate by phone, we will administer the Six Item Screener (SIS). The SIS is a short instrument developed to identify cognitive impairment in older adults. In the case where the participant has died or is otherwise unable to communicate by phone, dementia status will be characterized by informant interview using the AD8--a brief instrument, derived from the Clinical Dementia Rating Scale, developed to discriminate between normal aging and dementia. Notably, these procedures parallel ARIC's ongoing dementia surveillance methods. For ARIC participants, additional sources of information may also be used to complete ascertainment of dementia cases (e.g., discharge codes from hospitalizations, CMS, and ICD codes on death certificates).

7.4 Inclusion/exclusion/covariates

7.4.1 Demographics questionnaire

This is an interviewer-administered questionnaire given to each participant to gather demographic data from participants. Data gathered includes age, sex, employment status, race, ethnicity, education, and marital status.

7.4.2 Health history questionnaire

This is an interviewer-administered questionnaire given to each participant. This documents a number of chronic diseases or conditions (e.g. hypertension, diabetes, stroke, Parkinson's disease, osteoporosis, among others). The collection of a medical history on each participant permits the assessment of overall health.

7.4.3 Neurologic History

This questionnaire includes items about past neurologic diagnoses and treatments. This information will be used as possible covariates and by MCI/dementia adjudicators.

7.4.4 Anthropometry

Participant height and weight will be measured using standardized study protocols from the parent study (ARIC). These are detailed in the MOP. Anthropometric measures include height, weight, waist and hip circumference and body fat. These measures are used to assess the relationship between overweight and risk of disease.

7.4.5 Seated blood pressure

Seated systolic and diastolic blood pressure will be measured using standardized study protocols from the parent study (ARIC). These are detailed in the MOP.

7.4.6 Blood draw

A blood draw for ApoE genotyping in non-ARIC participants in ACHIEVE will be conducted at baseline and done using standardized study protocols. ARIC participants have already previously had ApoE genotyping performed.

7.4.7 Wide Range Achievement Test (WRAT)

The WRAT is a widely used measure of academic achievement and commonly used to provide an estimate of premorbid functioning in adults with neurological conditions. In addition to education level, scores on the WRAT Reading subtest will be taken into account by Dementia/MCI reviewers when interpreting neuropsychological tests results. Following brief instructions, the participant is handed a test card and asked to read the words on the card aloud. Responses are recorded on the paper form. The test is discontinued following 5 consecutive errors. Scores range from 0 – 70.

7.4.8 Pure-tone audiometry (screening)

Air conduction audiometry is conducted to see if the participant meets the audiometric inclusion criteria. Confirmatory audiologic testing performed by an audiologist is conducted during the baseline assessment.

7.4.9 Vision screening

This test is to determine the smallest print the participant can read. The MNREAD Acuity Chart is used as the vision screener. Full details can be found in the MOP.

7.4.10 Mini-Mental State Exam (MMSE)

The MMSE was developed as a brief, standardized instrument for screening a limited number of cognitive functions¹². We will use the MMSE to exclude those with significant cognitive impairment at baseline, and as a secondary outcome for tracking cognitive decline, and dementia. The MMSE is administered by interview and should be attempted in all participants. A detailed script is provided for each item and task. Scores range from 0-30.

7.4.11 Activities of Daily Living (ADL)

ADLs assess a person's ability to perform basic activities of daily living (e.g., getting in/out of bed or chairs, bathing, dressing, eating, toileting)

7.5 Secondary Outcomes

7.5.1 Center for Epidemiological Studies Depression and Hopelessness Scale (CES-D)

Depressive symptoms have been linked to a number of important health outcomes including cardiovascular disease risk factors, CHD morbidity and mortality, cognitive functioning, and MCI/dementia. In ACHIEVE, depressive symptoms will be assessed using the Center for

Epidemiologic Studies Depression Scale (CES-D) Short Form. The CES-D Short Form is derived from the original 20-item CES-D¹³. In addition to a reduced administration time and clearer response options (relative to the 20-item version), the Short Form is highly correlated with the original ($r > .94$), has a high internal consistency, retains the same factor structure as the original, and has a similar positive predictive value as a screening tool for identifying clinical depression. It takes approximately 3 minutes to complete this questionnaire. The questionnaire is administered by interview. As a scale for depression, responses must be provided by the participant, not a proxy. Because of the sensitive nature of some of the questions, interviewers must take care to ask questions and record responses in a sensitive and non-judgmental manner. Most of the questions are self-explanatory; however, if the respondent is unclear, the interviewer will repeat the question and use general phrases, such as: "Answer as best you can, based on how you have felt over the past week." Interviewers should not lead participants to an answer but remaining neutral. Participants are asked to rate each item on a 3-point scale (scored 0 to 2) on the basis of "how often you have felt this way during the past week." Response categories are:

- Hardly ever or never (scored as 0)
- Some of the time (scored as 1)
- Much or most of the time of (scored as 3)

A total score is calculated as the sum of the responses to questions 1-11.

7.5.2 Baecke Physical Activity Questionnaire (BAQ)

This is an interviewer-administered questionnaire¹⁴ given to each participant that measures the frequency and duration of self-reported activities, which is currently used in ARIC. This questionnaire asks about habitual physical activities including sport-related activities during leisure time, non-sport related physical activity during leisure time, and television viewing.

7.5.3 Hearing Handicap Inventory for the Elderly – Screening Version

This is an interviewer-administered questionnaire given to each participant to gather data on the perception of the impact of hearing loss¹⁵. This questionnaire assesses the social and emotional components of perceived hearing impairment such as embarrassment, and limits on personal and social life.

7.5.4 SF-12v2 Health Survey

The 12-item Short-Form Health Survey, SF-12, is a shortened version of the SF-36 Health Survey which assesses health-related quality of life¹⁶. Like the SF-36, it is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. The SF-36 is the most widely-used health survey throughout the world because it is both brief and comprehensive, readily available, psychometrically-sound, and of proven usefulness in measuring health status and monitoring health outcomes. However, the SF-36 has been judged to be too long for the ARIC examination. The ACHIEVE study will be using a shortened version of the SF-36. The same eight domains of health that can be estimated from the SF-36 can be constructed using the SF-12v2, but estimation of the physical and mental health domains have the greatest accuracy. All of the questions and response categories on the SF-12 Version 2 are identical to those on the SF-36. The SF-12v2 was chosen because (1) it has been demonstrated to have reproducibility and validity compared with other health-related quality of life (HR-QOL) forms, and (2) U.S. population norms exist.

7.5.5 Social Network Index

The Cohen Social Network Index (SNI) is an interviewer-administered questionnaire given to each participant to gather social network data¹⁷. The Social Network Index evaluates two outcome variables: (1) Social Network Diversity – Number of social roles in which the participant had regular contact with for at least once every 2 weeks, and (2) People in Social Network – Total number of people with whom the participant had regular contact (at least once every 2 weeks). Examples of items include “How many other relatives (other than your spouse, parents & children) do you feel close to?”, “Do you attend any classes (school, university, technical training, or adult education) on a regular basis?”, “Are you currently involved in regular volunteer work?”, among others.

7.5.6 UCLA Loneliness Scale

This is an interviewer-administered questionnaire given to each participant to gather loneliness data¹⁸. This questionnaire measures subjective ratings of social isolation and loneliness (e.g. lacking companionship, feeling left out, and isolated from others, among others).

7.5.7 Accelerometry

Physical activity is objectively assessed using the Actigraph Link accelerometer, an FDA approved, triaxial, water-resistant, wrist-worn device that can be worn 24 hours a day, continuously measuring intensity, duration, and frequency of physical activity. Participants will be fitted with the device during their clinic visit and asked to continue wearing the device at all times for the subsequent 7 days¹⁹. Participants will be asked to wear the accelerometer at baseline and again at follow-up to detect differences in physical activity and sedentary behaviors.

7.5.8 Falls and mobility

This is an interviewer-administered questionnaire given to each participant to record living circumstances, self-reported physical ability, fatigue, and falls.

7.5.9 Hospitalizations

This is an interviewer-administered questionnaire given to each participant to record recent hospitalizations since the last time of study contact.

7.5.10 Grip strength

Grip strength will be measured using standardized study protocols from the parent study (ARIC). These are detailed in the MOP. Grip strength is objectively assessed with a hand held dynamometer. After one practice trial, participants are asked to complete two trials, squeezing as hard as possible, with a 15-20 second rest between trials. Grip strength exclusion is limited to those who have had surgery on both hands or on both wrists in the previous 3 months. If only one side is affected, the unaffected side is tested. The test can be performed if the participant has a current flare-up of pain in their wrist or hand, for example arthritis or tendonitis. This information is recorded on the data collection form.

7.5.11 Short Physical Performance Battery (SPPB)

The Short Physical Performance Battery²⁰ will be conducted using standardized study protocols from the parent study (ARIC). These are detailed in the MOP. The SPPB is a series of physical performance tests designed to assess lower extremity function in older adults. The SPPB ranges in score from 0-12; higher scores indicate better function. The total score is the sum of 3 component scores: chair stands, balance and 4-meter walk; each component score ranges from 0-4. Exclusion from any performance test is based on examiner assessment or participant concerns that the test would be unsafe. Walking aids are allowed during the 4-meter walk only, if participants feel they are necessary.

7.5.12 Intervention Feedback Form

This gathers feedback about the study intervention that participants are receiving. Participants rate how strongly they agree or disagree with a series of statements about the ACHIEVE study intervention they received.

7.6 Communication Partners Assessments

Communication partners (e.g., spouse) of participants randomized to the hearing intervention group are invited to join the study and contribute data related to their own quality of life and their observations of the effects of the hearing intervention on the participant. Communication partners are adults (18+ years) who communicate with the participant on a daily or near-daily basis. Informed consent is obtained during the 1-2 months after randomization when the hearing intervention participant is receiving the first 2 study intervention visits which the communication partner may also be attending in a supportive role. Demographic data will be gathered at enrollment, and health-related quality of life data (SF-12; 7.4.6) and data on the communication partner's observations of the effects of the hearing intervention on the participant (International Outcomes Inventory – Significant Other) will be gathered semi-annually to annually. Individuals who are also enrolled in the ACHIEVE study as a randomized participant are not eligible to also be enrolled/consented as a communication partner in the ACHIEVE study for another randomized participant (e.g., spousal pairs randomized as a dyad to the hearing intervention group). If the communication partner can no longer participate, data collection for the communication partner will end. Participants are welcome to invite a new communication partner to join them at the study visits but no data will be gathered from this communication partner.

7.7 Schedule of evaluations

Table 3 details when data will be gathered.

Table 3. Schedule of Evaluations

Assessment	Screening	Baseline	Intervention and Follow-Up Visits									
	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
	(Day -31 to Day 0)	Day 0	(W1-3)	(W3-5)	(W6-8)	(W8-10)	(6mo)	(12mo)	(18mo)	Visit 9	(30mo)	(36mo)
			A	B	C	D		Yr1		Yr2		Yr3
Inclusion Criteria and Covariates												
Informed Consent	X†	X										
Demographics	X†											
Health History	X†							X		X		X
Vision Screening	X											
Activities of daily living	X											
Anthropometry		X*						X		X		X
Seated blood pressure		X*						X		X		X
Blood draw for ApoE		X										
WRAT		X										
Neurologic history		X						X		X		X
Audiometric Baseline												
Air conduction audiometry	X	X						X		X		X
Bone conduction audiometry		X						(X)		(X)		(X)
Tympanometry		X						X		X		X

Word Recognition in Quiet		X						X		X		X
Quick Speech in Noise (unaided)		X						X		X		X
Primary Outcomes (Neurocognitive Battery)												
Ensuring speech understanding test		X*						X		X		X
MMSE	X*	X*					X	X	X	X	X	X
Delayed Word Recall Test		X*						X		X		X
Digit Symbol Substitution Test		X*						X		X		X
Incidental Learning		X*						X		X		X
Trail Making Test Part A		X*						X		X		X
Trail Making Test Part B		X*						X		X		X
Logical Memory 1		X*						X		X		X
Logical Memory 2		X*						X		X		X
Digit Span Backward		X*						X		X		X
Boston Naming Test		X*						X		X		X
Word Fluency (FAS)		X*						X		X		X
Animal Naming		X*						X		X		X
Secondary Outcomes												
Clinical Dementia Rating Scale - Participant (CDP)		X					(X) ^a	X	(X) ^a	X	(X) ^a	X
Dementia/MCI evaluation if applicable (CDI, CDS, NPI)		(X)					(X) ^{ab}	(X)	(X) ^{ab}	(X)	(X) ^{ab}	(X)

Qualifying S(AE) assessment		X	X	X	X	X	X	X	X	X	X	X
CES-D Scale		X*					X	X		X		X
Baecke activity questionnaire		X						X		X		X
Hearing Handicap Inventory for the Elderly - Screening Version		X*					X	X		X		X
SF-12 Health Survey		X					X	X		X		X
Cohen Social Network Index (SNI)		X					X	X		X		X
UCLA Loneliness Scale		X					X	X		X		X
Accelerometry		X						X		X		X
Falls and mobility questionnaire		X						X		X		X
Hospitalizations		X					X	X	X	X	X	X
Grip Strength		X*						X		X		X
Short Physical Performance Battery		X*						X		X		X
Intervention feedback form							X					X
SUCCESSFUL AGING INTERVENTION PARTICIPANTS ONLY												
Successful aging intervention visit/booster session			X	X	X	X	X	X	X	X	X	X
HEARING INTERVENTION PARTICIPANTS ONLY												
Hearing Intervention Assessment Outcomes												
Real-ear aided response				X	(X)	(X)	(X)			(X)		(X)
Speech Intelligibility Index (SII) (aided)				X	(X)	(X)	(X)			(X)		(X)

Quick Speech in Noise (aided)						X		X		X		X
Hearing Aid Data Log				X	X	X	X	X	X	X	X	X
International Outcome Inventory for comprehensive intervention						X	X	X	X	X	X	X
Client-Oriented Scale of Improvement			X	X	X	X	X	X	X	X	X	X
COMMUNICATION PARTNERS FOR PARTICIPANTS RANDOMIZED TO HEARING INTERVENTION												
Informed Consent Form			(X)	(X)								
Demographics			(X)	(X)								
Short Form 12			(X)	(X)			(X)	(X)		(X)		(X)
International Outcome Inventory – Significant Other						(X)		(X)		(X)		(X)

() Parentheticals denote procedures that are optional based on protocol; * denotes those measures shared across ACHIEVE and ARIC-NCS V7; † denotes procedures only needed for participants not in ARIC-NCS. ^a Administered if there is a drop of 3 points or more since baseline in the MMSE. ^b Excluding NPI.

8 Randomization

Randomization, stratified by ARIC study status, field center, and hearing impairment level is completed within the CDART web-based data management system. Although ACHIEVE hearing aid intervention is by nature un-masked, in order to minimize bias based on review of accumulating data by the project team, the ACHIEVE PI, co-investigators, and key project staff except Data Coordinating Center staff and one unblinded statistician will remain blinded to accumulating data by treatment group.

- The intervention group to which a participant is assigned is determined by an allocation schedule developed by the Data Coordinating Center.
- After final determination of eligibility and confirmation of informed consent, each participant will be randomized in a 1:1 ratio to either the hearing intervention or to the successful aging intervention. To ensure balance between the treatment groups, participants will be randomized in permuted order blocks of varying sizes within strata defined by severity of hearing loss, defined as mild ($PTA \geq 30dB$ and $< 40dB$) or moderate ($PTA \geq 40 dB$ and $< 70db$), participant status (ARIC or non-ARIC participant), and by field site. Block size will not be revealed to field center staff as this would allow them to determine the final treatment assignment of a block before ascertaining eligibility and obtaining consent.
- Randomization will be performed at the end of the baseline visit.
- When spouses or cohabitating partners are both eligible and randomized together, they will be randomized as a unit with, arbitrarily, the first spouse/partner of the pair to be selected according to the random assignment procedure and the second spouse/partner of the pair receiving the same assignment. Spouse/partner pairs will be randomized in spouse/partner-pair specific permuted order blocks of varying sizes within strata defined by participant status (at least one spouse/partner pair in ARIC or both non-ARIC participants) and by field site.

9 Interventions

9.1 Hearing intervention

The conceptual framework for the development of the manualized patient-centered, best-practices hearing intervention was the World Health Organization's International Classification of Functioning, Disability and Health (ICF, <http://www.who.int/classifications/icf/en/>). The ICF focuses on a person's ability to engage in activities and participate in life situations, as impacted by changes in body structures and/or functions, and influenced by environmental and personal contextual factors. The main objective of intervention is improving a person's quality of life by eliminating or minimizing activity limitations and participation restrictions. To reach this objective the hearing intervention includes the identification of individual needs, the setting of specific goals, engagement in shared-informed decision-making, and the development of self-management abilities.

The hearing intervention (HI) steps were developed from review of the most current and comprehensive evidence-based practice guideline for the rehabilitative treatment of hearing loss in adults published by the American Academy of Audiology (AAA) in 2006, along with consideration of subsequent research. An outline of the ACHIEVE-HI components was reviewed by an expert panel of audiologists (including M. Valente, L. Humes, H. Solodar, and R. McArdle among others) during a meeting in Tampa, FL in December 2014. Recommended modifications were incorporated into the hearing intervention, which was utilized in a feasibility study conducted at the University of South Florida with 20 older adult participants and initiated in May 2015. The results of implementation in the feasibility study guided the use of the hearing intervention in the subsequent ACHIEVE-P randomized pilot study which was initiated at the Washington County, MD ARIC field site in August 2015. Recently, experiences of study participants and site staff from both the feasibility and pilot studies were used to revise the hearing intervention, and this revised protocol was then reviewed in a face-to-face meeting of ACHIEVE investigators and an external expert audiology consultant, Catherine Palmer in April 2016. Recommendations for clarification were incorporated into the final hearing intervention protocol which is included in the MOP.

The hearing intervention consists of 4 sessions (Sessions A-D, each session ~1 hr) spaced over the 2-3 months post-randomization and are designed to provide all of the active components of the intervention. Audiologic outcomes (e.g., hearing aid data logging, real ear measures, speech in noise, etc.) to verify the best-practices hearing intervention are gathered semi-annually beginning at 6 months post-randomization. Communication partners (CP) are often a key to success to intervention for older adults with hearing loss and are encouraged to attend the hearing intervention sessions.

Session A is focused on the identification of individualized goals utilizing the Client Oriented Scale of Improvement (COSI) and the fitting of hearing aids (Session A). In addition to standard audiometric testing conducted in all ACHIEVE participants at baseline, an auditory needs assessment, involving specialized behavioral and self-report assessments, is completed in order to determine patient-specific recommendations for hearing aid intervention, including determination of signal processing and features (e.g., directional microphones, direct auditory inputs, noise management programs, frequency modulation [FM] devices, Bluetooth streaming, etc.). Participants will be fit binaurally with substantively equivalent technology that is currently found in Phonak Audeo V90-312T receiver-in-the-canal (RIC) hearing aids. Specification for hearing aid fitting and verification can be found in the MOP. Participants will be provided with materials to support self-management of hearing loss and communication in real-world settings, via the hearing intervention Toolkit (full details in MOP). The toolkit materials were developed based on previous research by Hickson and colleagues and with consideration of variations in health literacy, and cover the following topics: understanding hearing loss, realistic expectations, communicating in quiet, listening at a distance, communicating in background noise, using communication strategies and tactics, and resources for adults with hearing loss and their communication partners. The written materials are supplemented with a series of reusable learning objects (e.g., video clips) entitled C₂HEAR which are designed to support first-time hearing aid users while they adapt to using hearing aids.

Session B occurs approximately 1-3 weeks after hearing aid fitting in order to allow for acclimatization to occur. If modifications are needed to the hearing aid fitting, they can occur and be documented in this or any subsequent sessions. During Session B, informal assessment of progress to goals will be determined and needs for various hearing assistive technologies (HATs) will be assessed. HATs provide a more direct coupling of the sound source to the hearing aid, minimizing the negative effects of distance and background noise. Additional materials to support self-management are provided.

Session C occurs approximately 1-3 weeks after Session B. Short-term hearing aid outcomes are assessed and individually selected HATs are dispensed. Each participant will receive at least one HAT, depending on his or her specific goals, and outcomes of hearing aid use. These HATs may include the following or generally equivalent devices: Phonak ComPilot II (streaming device); Phonak ComPilot Air II (streaming device); Phonak TVLink II; Phonak clip-on mic; and/or the Phonak Roger System. Systematic orientation to HAT use is provided and additional self-management tools are dispensed.

Session D occurs ~1-3 weeks after Session C. Short-term outcomes of the comprehensive intervention approach, including use of hearing aids, HATs, and development of self-management skills, are assessed. Additional materials as needed to support self-management are provided as well as a supply of batteries.

Booster Intervention/Interim Visits: Scheduled semi-annual visits will capture audiologic outcomes and verify that hearing aids and HATs are functioning properly. Re-instruction in use of devices and hearing rehabilitative strategies will be provided during these visits. Booster sessions may be offered in a group format to allow for group rehabilitation for participants who are interested. We anticipate that unscheduled interim visits may also be required periodically (e.g., hearing aid malfunction), and these visits to trouble-shoot and/or repair malfunctioning hearing aids and/or HATs will be scheduled as needed if the issue cannot be resolved through a telephone conversation.

Full details of the hearing intervention can be found in the MOP.

9.2 Successful Aging intervention

Overview

The Successful Aging intervention will follow the protocol and materials developed for the 10 Keys™ to Healthy Aging program by the Center for Aging and Population Health Prevention Research Center at the University of Pittsburgh¹. This interactive, dynamic program informs older adults about risk factors for diseases. This program was developed from evidence-based research and aims to target the causes of disease and disability that could be greatly reduced, postponed, or eliminated to promote successful and healthy aging in functional older adults. The Successful Aging intervention contains the most up-to-date prevention guidelines available based on the current recommendations from leading groups such as the United States Preventive Services Task Force, Centers for Disease Control, and Institute of Medicine. Many

adults age with more than one medical condition. A holistic approach to health provides a broad range of opportunities for individuals to become engaged and involved. This is important as the Successful Aging intervention focuses on the health and well-being of the whole person. Although the original “keys” had 10 domains, the “Social contact” key will not be used (to avoid crossover effects with the main hearing loss intervention being tested), and additional keys that are currently under development at the University of Pittsburgh (e.g., Nutrition and Reducing Stress) will be available.

Individual participants in the Successful Aging intervention group will receive educational information and materials on health-related topics relevant to older adults. As a participant in the Successful Aging intervention, each individual will have an opportunity to practice skills and learn about: the importance of preventing disease and disability, information on Keys or health topics of his/her choice, and personal risk factors. In general, participants will receive information on a variety of health topic areas of relevance to older adults and learn how to actively “take charge” of their health and well-being in seeking out appropriate medical information, services, and resources. The health educator will tailor the Successful Aging intervention to each participant; provide guidance through the educational materials and ongoing support and encouragement over the duration of the study.

At the first intervention visit, using a Prevention in Practice (PIP) report, the interventionist will present an introduction to all of the Keys and support the participant in identifying the specific topics of importance. At the first visit the interventionist will also go through the lowering systolic blood pressure key (this key was identified as the most popular key by Dr. Glynn and colleagues). Additionally, the interventionist will teach the participant proper technique for a series of upper body stretches. The second, third and fourth intervention sessions will contain a recap of the previous session and a new key. The participant will also do their body stretching routine. Each session will last approximately one hour, and each Key is designed to be presented during this time. Regardless of the specific Key being presented, each session will include a didactic education component as well as activities, goal-setting, and homework assignments to be completed by the following session.

Specific Successful Aging Module Options

Each participant randomized to the Successful Aging intervention will have the opportunity to cover the following Keys or health topics:

- Key #1: Lower Systolic Blood Pressure*
- Key #2: Stop Smoking (if the participant is a smoker; if the participant is not a smoker they will skip this key)*
- Key #3: Participate in Cancer Screening*
- Key #4: Get Immunized Regularly*
- Key #5: Regulate Blood Glucose*
- Key #6: Lower LDL Cholesterol*
- Key #7: Be Physically Active*
- Key #8: Maintain Healthy Bones, Joints, and Muscles*
- Key #9: Combat Depression*
- Key #10: Key currently under development at the University of Pittsburgh*

Contact Mode and Frequency

Participants randomized to this group will meet individually with a health educator certified to administer the program every 2-3 weeks for a total of 4 visits over 8-10 weeks. This program was effectively piloted in this cohort and previously implemented by Dr. Glynn in the Aging Successfully with Pain RCT ^{21,22}. To further enhance retention and perceived benefit, each session will also include a 5-10 minute active upper body extremity stretching program as used in the Lifestyle Interventions and Independence for Elders (LIFE) study². Participants will return for booster sessions semi-annually (+/- about one month). Session content for booster sessions will be keys 5-9 (or 6-10 for non-smokers). The upper body stretching program will also be implemented during the booster sessions.

Visit 1 (Session A): Weeks 1-3

Visit 2 (Session B): Weeks 3-5

Visit 3 (Session C): Weeks 6-8

Visit 4 (Session D): Weeks 8-10

Participants who miss a scheduled visit will be contacted by intervention staff to reschedule or to assist with overcoming barriers to attendance (e.g., transportation). Additional support will be provided by aging experts from the University of Pittsburgh who have years of experience overcoming barriers associated with adherence to the program.

Full details of the Successful aging intervention can be found in the MOP.

10 Strategies to Promote Intervention Adherence/Compliance & Minimize Bias from Unblinded Study Participants and Staff

Adherence to the study intervention will be assessed at each study visit using questions designed to capture adherence in both the hearing and successful aging intervention groups.

Strategies for Promoting Adherence in the Hearing Intervention

Strategies to promote adherence in the Hearing Intervention include:

- Expectations of potential benefits of the intervention are structured given the participant's level of hearing impairment in order to ensure that participants' expectations are reasonable and realistic.
- Individual assessment and instruction.
- Participants are asked to bring a communication partner with them to the intervention visits
- Repeated assessment of individualized hearing goals with the audiologist and development of strategies to meet those goals throughout the intervention period.

- Participants who miss a scheduled meeting are contacted by telephone by study staff to encourage continued participation and to evaluate and overcome barriers to participation.
- Home visits for intervention sessions will be considered on a case-by-case basis by the study staff and interventionist when needed because of participant inability to travel to clinic-based study visits.
- Participants are informed that they are allowed to keep the hearing aids and other hearing technologies for free if they complete all study visits.
- At the completion of the study, participants in the hearing intervention may also choose to receive the successful aging intervention

Strategies for Promoting Adherence in the Successful Aging Intervention

Strategies to promote adherence in the Successful Aging Intervention include:

- Expectations of potential benefits of the intervention are structured in order to ensure that participants' expectations are reasonable and realistic.
- Individual assessment and instruction.
- Participants are encouraged to bring a friend or family member with them to intervention visits (analogous to the communication partner for participants randomized to the hearing intervention).
- Establishes concrete and reasonable goals related to attending the Successful Aging sessions and participating in that intervention throughout the intervention period.
- Easy-to-read written materials are distributed at each visit to prompt regular and appropriate participation.
- Participants are encouraged to track behavior changes related to topics covered as part of the program.
- Participants who miss a scheduled meeting are contacted by telephone by study staff to encourage continued participation and to evaluate and overcome barriers to participation.
- Home visits for intervention sessions will be considered on a case-by-case basis by the study staff and interventionist when needed because of participant inability to travel to clinic-based study visits.
- At the completion of the study, participants in the successful aging intervention may also choose to be fitted for hearing aids and provided hearing rehabilitation resource materials if they are interested.

Strategies to Minimize Bias from Unblinded Study Participants and Staff

Neither study participants nor study technicians collecting outcome data can feasibly be blinded to randomization status. We will minimize bias from unblinded study participants and staff through the following strategies based on recommendations from Boutron et al²⁴ for blinding in non-pharmacological trials:

- Use of an attention control intervention Participants are randomized to one of two interventions – hearing rehabilitative intervention vs. an established successful aging intervention that serves as an attention control. This successful aging intervention is based on the 10 Keys™ to Healthy Aging program developed by the Center for Aging

and Population Health Prevention Research Center at the University of Pittsburgh¹ and which was successfully implemented as the attention control intervention in the unblinded Lifestyle Interventions and Independence for Elders (LIFE) study². The use of an attention control intervention that is perceived as having value to study participants can minimize participant dissatisfaction with not obtaining the hearing loss intervention. In the ACHIEVE-Pilot study, study staff reported strong participant enthusiasm for the successful aging intervention. The study overall will communicate that it has two interventions aimed at successful aging. They are very different and expected to have different benefits which are unknown. The goal is to identify which intervention has which benefits including cognition and other measures of aging.

- Blinding of study participants to study hypothesis Informational material and the consent provided to study participants will emphasize that the ACHIEVE study is comparing two established interventions in which it is not known whether either intervention could affect cognitive decline. Blinding of study participants to the explicit hypothesis that the hearing intervention reduces cognitive decline can help promote acceptance and adherence to both study interventions.
- Standardized protocols for training of data collectors & assessment of study outcomes Strict and standardized protocols for assessment of neurocognitive functioning will be implemented to minimize bias during data collection. Protocols (see Manual of Procedures) for both training/certification of psychometrists and quality assurance/control have been well-established and tested in both ARIC-NCS and the ACHIEVE-Pilot study. These protocols incorporate regular recordings/observations of data collection sessions for feedback/quality control and centralized training of all psychometrists on a standardized protocol for neurocognitive test administration. Importantly, we will also utilize a supplementary standardized protocol incorporating an assessment of spoken language understanding to ensure that speech understanding is not confounding neurocognitive testing or other data assessments (section 7.2.1). Dementia adjudication procedures based on consensus conference review of study data will be blinded to randomization status. These procedures will help minimize potential bias from unblinded data collection staff.
- Data collectors & study coordinators will not have access to cognitive testing results from prior study visits Cognitive test data from prior study visits will not be available to data collectors and study coordinators in order to avoid unintentional and possibly unconscious bias by study staff during data collection. All data collection staff are distinct from staff who are involved with intervention administration. In addition, the primary and key secondary outcomes based on cognitive testing factor scores described in section 12.3 will not be made available to the site study staff.

Of note, the ACHIEVE Steering Committee did consider at length alternate study designs to allow for blinding of study technicians including having all participants use a body-worn sound amplifier at all visits, having all participants use no hearing devices at any visits (to mimic the state at baseline testing), having all participants wear “covers” over their ears, or having participants randomized to successful aging wear “sham” hearing aids during testing. The former two approaches would adversely affect neurocognitive testing (in which prevailing neuropsychometric standards stipulate that participants use whichever sensory aids they use on a regular daily basis). All four approaches were found to be pragmatically infeasible through discussion with field site staff and potential study participants.

11 Safety monitoring

11.1 Data safety monitoring board

An independent Data and Safety Monitoring Board (DSMB) has been constituted in collaboration with the NIA. The DSMB will provide oversight to ensure that the trial accrues at a sufficient rate and that the safety and privacy of all study participants are maintained. DSMB members are clinicians/investigators with expertise in clinical trials, neurology, dementia, biostatistics, audiology, and otolaryngology. A DSMB charter which was approved by the DSMB and the NIA specifies guidelines for DSMB conduct and early stopping rules for safety and futility. We anticipate meetings of the DSMB every 6 months after the first year, always focused on participant safety, but initially focusing on recruitment and follow-up.

There will be no interim analysis for efficacy. We do not expect to see an efficacy signal of sufficient magnitude to stop the trial with periods of follow-up shorter than 3 years. Combined with the comparatively shorter recruitment period, there is minimal expected benefit from an interim efficacy analysis. A formal interim analysis to evaluate for futility and sample-size re-estimation will be performed after 66% of subjects have completed the study, as described below in section 12.4.

11.2 Adverse events

Study participation and exposure to the hearing aid intervention is expected to have a low risk of adverse events for the participant. At the same time, the age of the participants may naturally lead to numerous deleterious health outcomes. In order to efficiently collect safety information that is relevant to study participation, interventions, and procedures, detailed information concerning a **pre-specified set** of adverse events and serious adverse events will be collected and evaluated throughout the conduct of the trial.

An **adverse event (AE)** is an untoward medical occurrence, whether or not considered study-related, which occurs during the conduct of a clinical trial

A **serious AE (SAE)** is any AE that results in any of the following outcomes:

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- A *major* congenital anomaly or birth defect
- Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed above.

For this study, ***only the following adverse events and serious adverse events will be recorded and reported:***

Adverse Events

Serious Adverse Events

Otitis externa

Death from any cause

Cerumen impaction or ear foreign body
requiring removal by a physician

An adverse event of otitis externa is defined as inflammation or infection of the ear canal resulting in pain, swelling, irritation, itching, or other related symptoms as diagnosed by the study audiologist or a physician. Adverse event severity is defined as:

- **Mild** if the symptoms are self-limited and resolve with interventions such as transiently limiting hearing aid use and/or the use of over-the-counter pharmacological therapies such as hydrocortisone cream or swimmer's ear drops.
- **Moderate** if the symptoms require evaluation and management by a physician *and* the use of topical prescription pharmacological therapies such as antibiotic ear drops.
- **Severe** if the symptoms require evaluation and management by a physician and the use of oral or parenteral antibiotics.

An adverse event of a cerumen impaction or ear foreign body requiring removal by a physician is defined as a cerumen impaction and/or ear foreign body that cannot be routinely managed by the study audiologist and requires evaluation and management by a physician (typically an otolaryngologist). Adverse event severity is defined as:

- **Mild** if the cerumen impaction or foreign body is resolved without further need for therapy besides over-the-counter pharmacological therapies such as cerumenolytic drops.
- **Moderate** if there is an associated otitis externa requiring the use of topical prescription pharmacological therapies such as antibiotic ear drops.
- **Severe** if the cerumen impaction or ear foreign body results in a perforation of the tympanic membrane or an associated otitis externa requiring the use of oral or parenteral antibiotics.

AEs or SAEs will be defined as **unexpected** or **expected** based on the judgement of the field site PI in consultation with the study audiologist and/or study PI Lin (who is a board-certified otolaryngologist) based on the following definitions:

- Unexpected – nature, severity, or frequency of the event is not consistent with information about the condition under study or intervention in the protocol and consent form
- Expected - event is known to be associated with the intervention or condition under study.

Study-relatedness of AEs or SAEs will be based on the judgement of the field site PI in consultation with the study audiologist and/or study PI Lin based on the following guidelines:

- **Definitely Related:** The adverse event is clearly related to the investigational intervention – i.e., an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject’s clinical state.
- **Possibly Related:** An adverse event that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.
- **Not Related:** The adverse event is clearly not related to the investigational agent/procedure - i.e., another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

The DSMB will review all recorded treatment-emergent adverse events and all serious adverse events (SAEs) from this pre-specified list and will provide a report to the Steering Committee and to the local IRBs. An SAE that is ***unexpected and possibly or definitely related to study participation or study intervention*** will be reported within 48 hours by the sites to the local IRB and the PI to the NIA and DSMB.

Adverse events and serious adverse events will be recorded on the electronic Adverse Events Form per study instructions. Additionally, for ***unexpected and possibly or definitely related serious adverse events only***, sites will record a narrative description of the serious adverse event, including any relevant lab test results and dates.

All completed AE forms will be forwarded promptly to the Coordinating Center where they will be reviewed for completeness by the Coordinating Center staff and the ACHIEVE Principal Investigator (Lin). In particular, the Principal Investigator will assure that documentation of each event is adequate to permit accurate inferences regarding causation (e.g., temporal associations, onset, course, response to patient or physician intervention, alternative etiologies) and severity.

Full details of procedures for reporting adverse events can be found in the MOP.

12 Statistical considerations

12.1 Sample size

Aim 1: Comparison of hearing rehabilitative intervention versus successful aging control intervention for 3-year rates of cognitive decline

Our sample size calculation is based on the primary outcome, the change in the Global Cognitive Function Factor Score from baseline to year 3. Estimates are based on the rate of

change in the global cognitive function factor score from the first third of participants in the ongoing ARIC Visit 6 study (2016 to 2017) in addition to data from other representative studies with similar cohort characteristics as ARIC/ACHIEVE (i.e., ACTIVE and HealthABC). We also take into account assumptions regarding the rate of loss to follow-up as well as the rate of cross-over, where participants in the successful aging control group begin to wear hearing aids and participants in the hearing intervention group stop wearing the devices.

We based these calculations on a t-test comparing groups on change from baseline at 3 years to align with the primary analysis (a mixed effects model treating time as categorical) and aimed to achieve 90% power using a 2-sided test with a $p=0.05$ significance level. We conservatively chose parameter estimates that fell within the mid-range of observed values from these studies.

Parameter assumptions include:

- Change in global cognitive function factor score in the control group per year:
Estimated at -0.08 standard deviations (SD)/year (corresponding to -0.24 SD in 3 years)
- Standard deviation of change in global cognitive function factor score per year:
Estimated at 0.09 (corresponding to 0.27 at 3 years)
- Drop-in/Drop-out: Estimated as a net total of 15% (drop-in + drop-out) for the 3-year study. This value is conservative. We assumed immediate drop-in/drop-out rather than later drop-in/drop-out (i.e., 1-2 years into the study) which would have less impact on reducing the observed effect size. We will continue to optimize the design to keep both drop-in and drop-out rates low (e.g. rigorous training for active group vs. energized successful aging group promised free hearing aids at trial completion). Among 13 participants in the ACHIEVE-Pilot study who were randomized to the hearing intervention and have since been followed to 1 year, we did not observe any drop-out (discontinuation of hearing aid use) at 1 year (12 participants reported > 8 hours of hearing aid use/day and 1 participant reported 4-8 hours use/day). Similarly, drop-in rates will likely be minimized because all participants in the successful aging group are informed that they will receive free hearing intervention after 3 years of follow-up (out-of-pocket costs for hearing aids are otherwise currently ~\$4700 and are rarely covered by insurance). Rates of uptake of hearing aid use remain low in the community. In the HealthABC study among individuals with hearing loss in the inclusion range for the ACHIEVE study, rates of hearing aid uptake were ~3-4% per year.
- Missing data/withdrawal from competing events (e.g., mortality not associated with dementia): Estimated at 10%/year (corresponding to 27% in 3 years)
- Hypothesized effect size: approximately 25%

Based on these parameters and with 850 total individuals randomized, we will have 90% power to detect a net effect size of 0.26 for the difference in cognitive change between the hearing intervention vs successful aging intervention at 3 years follow-up.

Under our assumptions, this corresponds to an annual cognitive decline of 0.052 SD/year in the hearing aid intervention group, which is a 35% slowing in the annual rate of cognitive decline compared to the control group deflated to 29% after drop-in and drop-out. We will correspondingly have 80% power for a net effect size of 0.225 (covering either a larger standard deviation or smaller decrease than predicted). These calculations are conservative since the primary mixed effects model gains power by adjusting for baseline values and including available data on participants who drop out before the end of the trial.

Aim 2: For the key secondary outcome of incidence of dementia, assuming a sample size of 850, we have 87% power to detect a difference in the incidence rate of 25 cases/1000 person-years in the control group versus 10 cases/1000 person-years in the intervention group.

12.2 Analytic approach

Analyses will follow the intention-to-treat (ITT) principle in which subjects will be analyzed in the group to which they were randomized, regardless of whether or not they received the assigned intervention. Primary analyses will be based on the intent-to-treat population, which includes all randomized subjects. In addition, a secondary analysis of the primary outcomes will be completed for the Per-protocol (PP) population, defined as a subset of the ITT population who completed the 8-10 week intervention period, had no hearing aid intervention drop-in for the control group, and had no major protocol deviations. Major protocol deviations include violations in inclusion and exclusion criteria at enrollment and poor compliance with hearing aids for the hearing aid intervention group, defined as subjects who discontinue hearing aid use. All major protocol deviations will be identified in a blinded fashion prior to database lock.

Consistent with best practices in clinical trials, we will assess the comparability of the randomized groups with respect to known confounders (e.g., age, education, race/ethnicity, smoking, hypertension, diabetes, etc.)²⁵. All analyses will adjust for baseline level of hearing (mild or moderate), baseline cognitive factor score, recruitment source (ARIC vs. *de novo*), 5-level race by field center (standard all ARIC analyses), age, and education (\leq High school, $>$ high school).

Primary Outcome

The primary outcome is 3-year cognitive decline, as measured by the change from baseline to year 3 of the global cognitive function factor score. Weights for the factor score calculation have been derived and validated using ARIC data (2011-13)^{9,26}. Factor scores for global cognitive function as well as the three domains (memory, executive function, and language) will be calculated for each visit as described in section 12.3. Factor scores are on the scale of standard deviation units relative to ARIC Visit 5 (mean 0, variance 1).

Primary Analysis

Groups will be compared for the primary outcome using a multiple imputation ANCOVA model of change from baseline to year 3 with adjustment for baseline cognitive factor score, baseline

hearing loss stratum, 5 level race*center, ARIC vs de Novo status, age, and education (\leq high school, $>$ high school).

Missing cognitive scores for reasons other than dementia diagnosis (including death without dementia) will be imputed using ACHIEVE data from participants not diagnosed with dementia. The imputation model for Year 3 cognitive score will include Year 2, Year 1, and baseline cognitive scores, MMSE and CDR scores, and other relevant covariates.

Missing cognitive scores due to adjudicated dementia diagnosis or dementia death will be imputed based on non-missing data from other adjudicated ACHIEVE dementia cases as well as non-ACHIEVE ARIC participants having an adjudicated dementia diagnosis within one year of either ARIC visit 6 or ARIC visit 7. The augmentation of ARIC data will provide a substantial increase in sample size to the imputation dataset, allowing for a more accurate imputation for these important cases that may have minimal data in the much smaller ACHIEVE sample. ARIC augmentation will include non-ACHIEVE participants meeting similar inclusion/exclusion criteria who attended both visits 5 and 6 with a diagnosis at visit 6 or within one year after visit 6, or correspondingly attended both visit 6 and visit 7 with a diagnosis at visit 7 or within one year after visit 7. Incident dementia cases adjudicated as occurring within a year of a visit will be included to increase the sample size for valid imputation of people who both attend a visit and have a dementia diagnosis. The imputation model will include baseline covariates similar to the non-dementia imputation, and will impute scores based on a model of annual cognitive decline in order to include ARIC visits that will range from 2 to over 5 years apart.

The imputation models including details for imputation of values after participant death will be fully specified in the Statistical Analysis Plan by fully blinded team members prior to the interim analysis. Properties of the imputation model will be assessed via simulation.

Sensitivity Analyses of the Primary Outcome

Additional analysis of the primary outcome may include, but are not limited to:

- (a) Control-based multiple imputation, in which missing values of the primary outcome for the hearing aid group without a dementia diagnosis are imputed based on the successful aging control intervention group. This analysis will investigate the strength of the primary analysis results to the missing at random assumption within these subjects.
- (b) Analysis of the per-protocol population. Drop-in/drop-out rates will be tracked at semiannual visits. Additionally, we will also estimate the complier average causal effect using the primary analysis model.
- (c) Using a repeated measures model, we will test for a linear slope within each group, and if confirmed we will fit a supportive random effects linear mixed model. An interaction term between treatment assignment and time will be used to test if rates of cognitive change differ by treatment assignment. Time on study will be the time scale. Model fit will be assessed with residual plots and other statistics (e.g., AIC, BIC). The impact of including dementia/MCI in a shared parameter model will also be considered.

- (d) Further sensitivity analyses of the primary model, particularly for participants confirmed as dementia cases, will be specified in the final Statistical Analysis Plan by fully blinded team members prior to the interim analysis.
- (e) We will repeat the primary and key secondary analyses stratified by subgroups of ARIC vs de novo participants. Interaction between intervention group and recruitment group will be tested in additional models relative to $p < 0.10$.
- (e) If more than 15% of the study sample is a spouse/partner pair, then a further sensitivity analysis of the primary model for the primary outcome will include adjustment for clustering of the spouse/partner pairs, to be specified further in the statistical analysis plan.
- (f) Exploration of the impact on the primary analysis by further adjustment for additional explanatory variables, as specified in the statistical analysis plan.

Exploratory Analyses of the Primary Outcome

- a) **Differential practice effects by recruitment source** To address this potential limitation, in a sensitivity analysis to Aim 1 we will use a structural equation modeling framework to model the practice effect using an indicator for the first visit in each group, allowing the practice effect parameter to vary by recruitment source and keeping the estimated intervention effect constant. We will test the fit of that model to one where the intervention effect differs by group to evaluate whether differential practice effects by recruitment source affects the intervention group difference. This is a test of effect modification.
- b) **Does intervention alter the trajectory of cognitive decline** In the subset of ARIC participants, we will model prior cognitive change (before the baseline ACHIEVE visit) as well as prospective change through study end (2021-22) using linear spline models, to determine if the rate of change of cognitive decline during ACHIEVE in each randomized group is different than the rate of change in the preceding years in ARIC visit 5 and 6. We will also test the interaction hypothesis that the hearing intervention deceleration in decline is larger than that in the successful aging intervention group.
- c) **Subgroup analyses by demographics** Given the higher prevalence of hearing loss in men compared to women and in whites compared to blacks, sensitivity analyses will be conducted stratifying by sex and race. We will also conduct sensitivity analyses stratifying by level of hearing loss and level of baseline global cognitive function factor score. Interaction between intervention group and subgroups will be tested in additional models relative to $p < 0.010$.
- d) **Subgroup analyses by AD risk factors** We will investigate a further refinement of the primary analysis with further adjustment for known AD risk factors, including but not limited to ≥ 1 APOE $\epsilon 4$ allele, and history of smoking, diabetes, or hypertension. The subset of ARIC participants will be defined as more likely to be at high risk of AD based on factors previously measured in ARIC: (i) ≥ 1 APOE $\epsilon 4$ allele, or (ii) reduced AD

signature region volume²⁷ by structural MRI and no small vessel disease (ARIC Visit 5, 2011-13), or (iii) high amyloid burden as measured by PET (ARIC Visit 6, 2016-18).

- e) **Exclusion of tests with only auditory stimuli** Among the full study cohort, we will derive a revised global cognitive function factor score excluding tests with only auditory stimuli (Logical Memory, Digits Backward). We will use model constraints in a latent variable modeling framework to scale these revised factor scores to be on the same metric as the factor scores in the primary analysis²⁶.
- f) **Mediation by social function** Investigate the extent to which the cognitive improvements are mediated by improvements *in social function*. Traditional mediation methods (e.g., Baron and Kenny²⁸) comparing intervention effects in models that do not include and include measures of social function as a covariate, as well as latent growth modeling, an extension of structural equation modeling for longitudinal data

Key Secondary Outcomes

There are **four key secondary outcomes**:

- Change from baseline to year 3 in the memory, executive function, and language factor scores⁹, and
- Time until composite outcome of adjudicated dementia or MCI diagnosis, or a 3-point decline in the MMSE.

Intervention groups will be compared for the factor scores using the same statistical methods as the primary analysis and supportive analysis of the primary outcome, described above.

Groups will be compared for the time until incident dementia, MCI, or a 3-point decline in the MMSE (composite outcome) by discrete-time time-to-event analysis (discrete time proportional hazard model with complementary log-log transformation to estimate the log hazard ratio of incident events by treatment assignment), adjusting for the same baseline covariates as specified for the primary outcome. Time scale = time on study. Because dementia adjudication procedures also utilize measures that report dementia diagnosis on a continuous time scale (e.g., diagnosis at hospitalization or death certificate), we will explore semi-parametric Cox proportional hazard models. In additional analyses, we will also analyze time until dementia, MCI, and 3 point decline as separate events.

Adjustment for Multiple Comparisons

If the primary analysis of the primary outcome is found statistically significant at $p < 0.05$, then the primary analysis of the key secondary outcomes will be evaluated for statistical significance with a Hochberg modification to the Bonferroni adjustment, in which the p-values of the 4 outcomes will be ordered. The largest p-value will be compared relative to $p < 0.05$, and if met, all parameters will be considered significant. If not, then the second largest p-value will be assessed relative to $p < 0.05/2 = 0.025$, and if met then it and all other parameters will be considered significant, and so on for the 3rd p-value compared at $0.05/3=0.017$ and the fourth compared to $0.05/4 = 0.012$.

Additional Outcomes

Additional measures include measures of social and physical function, physical activity, and HRQL. Analyses of all other outcomes are considered exploratory in nature and will not be viewed as providing confirmatory tests of hypotheses. There will be no adjustment for multiple comparisons of the exploratory secondary outcomes, and p-values will be provided for descriptive purposes only

Outcomes will be modeled continuously (outcomes transformed to account for non-normality if necessary) or categorized according to clinically-relevant cut-points. Intervention groups will be compared using the same multiple imputation ANCOVA methods as the primary analysis for the primary parameter for continuous parameters, or logistic regression for categorical outcomes²⁹.

12.3 Global cognitive function factor score

Properties and advantages

We developed an approach for harmonizing sufficiently unidimensional summary measures of global cognitive performance, memory, and executive functioning across ARIC study visits in which different cognitive test batteries were administered^{26,30,31}.

The global cognitive function factor score uses all available cognitive test data, has interval-level properties³², is internally consistent using ARIC NCS data (Cronbach's alpha=0.87), has minimal floor or ceiling effects⁹, and demonstrates reliable measurement precision over a broad range of cognitive ability. We have previously demonstrated criterion validity and established cut-points for clinically relevant impairment of the general cognitive performance factor score³⁰. We have since extended the harmonization to 26 studies with over 60,000 people, most of which have longitudinal data. Using simulation, we verified the cognitive metric is the same across dataset^{26,33}. We compared precision of our approach with other approaches to combining data using external data: underscoring enhanced precision in a sample of 10,875 persons in 9 datasets, our approach required the smallest sample size to detect cognitive decline with 80% power (N=232) compared to using only the Mini-Mental State Exam (MMSE) (N=277) or summarizing available tests into a z-score (N=291)^{26,33}. We further validated the approach against change in hippocampal volume and overall cortical thickness²⁶. The approach is consistent with other harmonization techniques including moderated non-linear factor model analysis³⁴ and IRT with differential item functioning, and has been used in several other published studies^{26,30,33-37}.

The approach has been described and used empirically, including demonstrations that the factors have the same meaning across dataset even with different cognitive tests^{9,26,30,31,33,35,36,38-40}

Methods

We estimated a confirmatory factor analysis, corresponding to a 2-parameter logistic item response theory model³⁹, of the ARIC cognitive test battery at ARIC Visit 5. The model estimates two sets of parameters for each test. Factor loadings, or weights, describe how well a

cognitive test separates persons of low and high ability on the latent trait, or equivalently, how strongly the cognitive test is correlated with other tests in the trait. These loadings give greater weight to tests more correlated with other tests than investigator-assigned weighting (e.g., equal weighting in z-scores). Thresholds, or boundaries, describe the location on the latent trait where the probability of responding in a given category or better of a test is 50%. This approach allows us to locate along the latent variable trait specific scores on individual tests where they are found to belong.

Factor scores are estimated from confirmatory factor analysis models that use a Bayesian estimator, in which the latent variables are on the scale of standard deviation units relative to ARIC Visit 5 (mean 0, variance 1). The factor scores themselves, being an average over 30 plausible values estimated from the posterior distribution of factor scores, may have a distribution with a standard deviation somewhat less than 1 due to the fact that they are estimated from a latent distribution.

Importantly, factor loadings and thresholds for the outcome are pre-determined based on ARIC Visit 5 data. To ensure cognitive performance is measured on the same metric for each study visit, loadings and thresholds for tests measured at multiple visits are fixed to be equal across ARIC visit. By constraining test thresholds to be the same across visit, change in cognitive performance over time is reflected in the levels of the latent variables at each study visit, which are then estimated as factor scores⁹.

Missingness in factor analysis models is handled using a maximum likelihood estimator with robust standard error estimation. This approach makes a less restrictive missing data assumption than the standardize and average approach by assuming missingness in specific cognitive tests are missing at random conditional on other cognitive tests in the model.

12.4 Interim Analysis for futility and sample size re-estimation

Sample size re-estimation will be assessed at one interim analysis at approximately 66% study completion/ early discontinuation based on conditional power. The DSMB may recommend to increase the sample size up to 100% (850 additional participants) in order to increase conditional power. The study will not be stopped for early efficacy, regardless of the interim results, in order to achieve maximum data collection for secondary parameters, including rates of incident MCI and dementia. The goal of increasing the sample size would be to increase the odds of a definitive result rather than an equivocal result in this unique study of an outcome of great societal importance. In the case of such a recommendation, the NIH and study investigators will need to determine the associated costs and feasibility. NIH and study investigators may also consider costs and feasibility of adding on additional years of participant follow-up after completion of the 3-year primary outcome.

The interim analysis will calculate the conditional power projected for the end of the study based on observed interim data for finding a treatment group difference at $p < 0.05$ for change in global cognitive function factor score from baseline to Year 3 using the primary multiple imputation

ANCOVA model as specified in section 12.2, assuming that the treatment effect for all future participants will be same as observed at the interim.

In the unlikely event of low enrollment, an assessment of futility may be conducted at the interim analysis, in which case the DSMB may recommend study stop due to futility based on conditional power

The conditional power will be categorized into one of 4 zones based on the below table: futile, unfavorable, promising, and favorable⁴¹. In the futile zone, the DSMB may recommend stopping the trial. If the futility analysis is not included in the interim, then the futile zone will be combined with the unfavorable zone. In the unfavorable and favorable zones, the DSMB may recommend that the trial continue at the original planned sample size (n=850), but would neither stop for futility nor increase the sample size. In the promising zone, the DSMB may recommend an increase in the sample size up to an additional 850 participants, in order to increase the conditional power up to 80%. For operational efficiency and to minimize the potential for back calculation, the sample size will be increased by one of the following increments: 200, 300, 425, 525, 625, 750, or 850.

Details and operational characteristics of the interim analysis methods will be documented in an Interim Analysis Plan approved by the DSMB prior to execution. Conditional power cut points defining the four zones in the below table may be adjusted based on the operational characteristics and/or exact timing of the interim analysis, although the cut points of the promising zone will remain within the range that requires no adjustment to the final analysis due to the interim look^{41,42}.

Zone	Conditional Power at Interim Analysis	Recommended Action	Final Sample Size
Futile	< 0.15	Stop Trial	<= 850 (depending on enrollment at time of interim)
Unfavorable	0.15 – < 0.35	Continue trial with no change	850
Promising	0.35 – < 0.80	Increase Sample size to increase conditional power to 0.80, or to a maximum of N=850	Up to 1700
Favorable	>= 0.80	Continue trial with no change	850

13 Data management

Trained data management and study management staff at the UNC CSCC will be responsible for coordinating data management. The Data Coordinating Center (DCC) will develop a

customized web-based data management system for the ACHIEVE trial, using the Carolina Data Acquisition and Reporting Tool (CDART), a state-of-the-art data management system that is currently used for ARIC-NCS. A complete description all data management procedures can be found in the MOP.

Data collection

The CSCC will lead the translation of the protocol data collection specifications into a consolidated set of clear, unambiguous data collection forms (electronic case report forms, eCRFs). Each eCRF will have a corresponding paper form to be used by sites in cases where data cannot be entered at the time of collection. Most of the CRFs have already been developed as part of ACHIEVE-P study and ARIC-NCS. Developing CRFs can uncover discrepancies within the protocol; thus forms, the protocol, and manual of procedures will be finalized in unison during study startup.

Randomization and Unblinding

Randomization, stratified by ARIC study status, center, and hearing impairment level is completed within CDART. Although ACHIEVE hearing aid intervention is by nature un-masked, in order to minimize bias based on review of accumulating data by the project team, the ACHIEVE PI, co-investigators and key project staff except data coordinating center staff and one unblinded statistician will remain blinded to accumulating data.

Data reporting & extraction

CDART reports are run from the database in real-time and can run across multiple research sites to provide participant feedback, assist in participant visit scheduling, monitoring data quality and protocol adherence, track study enrollment, and identify medical alert values (e.g., blood pressure, depression scores, etc.).

Data security and confidentiality

CDART uses a flexible, secure authentication system requiring a username and password. In accordance with HIPAA, all individually identifiable information is encrypted and decrypted for local on-screen display at clinical centers for their own participants.

14 Data Handling and Record Keeping

Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why

- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

In the event that a subject revokes authorization to collect or use PHI, the investigators, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Electronic Case Report Forms

The study electronic case report form (CRF) will be the primary data collection instrument for the study. All data requested on the CRF will be recorded and all missing data will be explained. For ease of data collection, paper forms can be used by the site, in which case the paper form becomes part of the source documents.

Records Retention

Co-PIs and field center PIs will retain study essential documents and specimens for up to 10 years following study completion.

15 Quality assurance and quality control

Established quality assurance procedures used in ARIC-NCS will be followed. Full details can be found in MOP.

15.1 Fidelity of hearing intervention

To ensure fidelity of the hearing intervention, field site training of study staff, including study audiologist and delegated hearing intervention study staff, as well as intervention delivery, receipt, and enactment will be monitored by the USF co-investigator team - Drs. Chisolm, Eddins, Sanchez, and Arnold. Fidelity assurance begins with centralized training conducted by the USF co-investigator team. Should there be personnel changes during the course of the

study, the new field site audiologist or study staff will be trained as-needed either during a site visit or remotely, depending on individual field site needs. Training will consist of informational and hands-on learning activities and will be assessed via skill observation with mock participants as well as a written examination. During the first quarter of participant testing, weekly phone calls will take place between each site and the USF team to address site-specific issues and monitor overall fidelity. During the second and third quarters, phone calls will take place biweekly, and during the fourth quarter and onward, phone calls will take place monthly. In addition, a random sample of paper data forms will be selected for chart review at regular intervals throughout the trial. Chart reviews will be conducted to verify accurate data entry from the paper source to CDART. Site visits and remote monitoring will also be conducted, determined based on sites' needs, for additional support or as supplemental training for new study audiologists. Study audiologists will be informed at centralized training that a sample of sessions will be video or audio recorded, and 10% will be chosen at random for remote review with feedback provided to the study audiologist by the USF team. Trackable documentation will be kept for accountability including certificates of study staff and study audiologist training and reports after site visits and phone calls.

15.2 Fidelity of successful aging intervention

To ensure fidelity of the Successful Aging intervention, observations of health educators will be conducted via a site visit conducted by Dr. Glynn. Health educators will be informed at centralized training that a sample of sessions will be also be audio taped; ten percent of the sessions will be chosen at random and feedback provided to the health educator by Dr. Glynn. Further, Dr. Glynn will lead monthly Successful Aging subcommittee calls to ensure the control program is being conducted in the manner outlined in the manual of procedures as well as to troubleshoot any participant-related issues.

15.3 Quality assurance of data entry

All staff involved with data collection will be required to have appropriate electronic data management system training. The training course includes a primer on using CDART for data collection and data reporting. In addition to training and providing reference documentation, the DCC may be contacted by telephone with questions about using CDART. CDART has embedded quality control measures in the application. These include reports on missing data fields and range-checks on each data field where applicable. Additional reports may be developed to check cross-form consistencies. These reports facilitate timely identification and resolution of problems in data collection and processing. The CDART User's Manual is found in MOP.

16 Study Monitoring, Auditing, and Inspecting

Study Monitoring Plan

The Co-PIs and field center PIs will monitor the study to ensure quality and integrity of data collected. They will review study files, regulatory documents, consent forms and allocate adequate time for other study monitoring activities. Field centers will be monitored periodically by representatives from the data coordinating center. The Co-PIs and field center PIs will also

ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities and has adequate space to conduct the monitoring visit.

Auditing and Inspecting

Co-PIs and field center PIs will permit study-related monitoring, audits, and inspections by the IRB, University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). PIs will ensure the capability for inspections of applicable study-related facilities.

Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, will be obtained before that subject undergoes any study procedure. The subject will sign the consent form, and the investigator-designated research professional obtaining the consents.

17 Timeline

Project YR	1				2				3				4				5			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Finalize Protocol	x																			
Finalize MOP/forms	x																			
Finalize Analytic Plan	x																			
Establish DSMB	x	x																		
Training		x				x				x				x				x		
Recruitment			x	x	x	x	x	x												
Intervention			x	x	x	x	x	x	x											

Follow-up				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Primary Analysis																					x	
Publication/Closeout																						x

*Interim analysis for sample size re-estimation will be done after 66% of study completion (expected during year 5).

18 Organization of the Study

Organizational structure for year one of the ACHIEVE study is shown in Figure 1. In brief, the Steering Committee will oversee all study activities and be chaired by the two Co-PI's (Lin, Coresh) and be comprised of all committee chairs and center leads. The ACHIEVE working group committees [Chairs] include Operations (Lin/Burgard), Design and Analysis (Davis/Coresh) Neurocognitive & Dementia Adjudication (Mosley/Albert), Secondary Outcomes/Ancillary Studies (Schrack/Coresh), Intervention Fidelity & Quality (Chisolm/Glynn), Publications (Deal/Coresh), DCC (Davis/Burgard). Any updates to the organizational structure will be noted in the MOP.

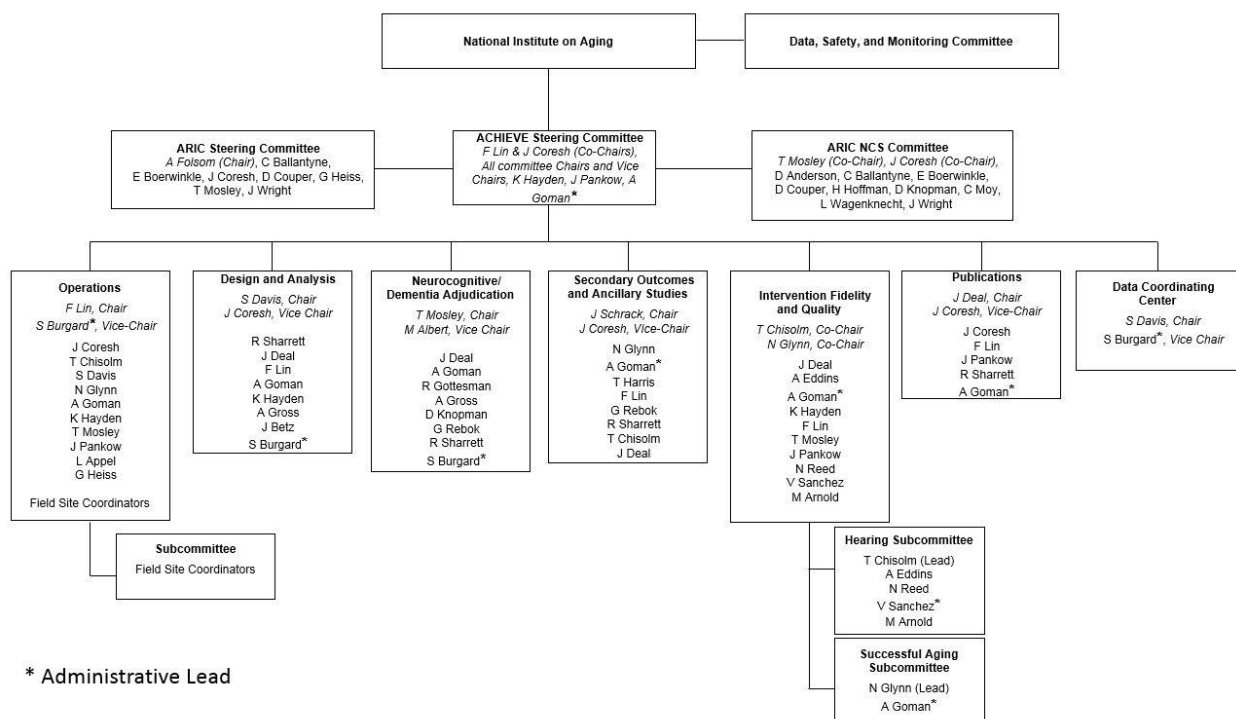


Figure 1. Organizational structure for year one of the ACHIEVE study

18.1 Key roles of committees

- **Steering Committee**
 - The steering committee will meet regularly to manage the study.
- **Operations Committee**
 - Monitoring recruitment/retention
 - Staff training
 - Development of MOP, CDART, data forms
 - Coordination with ARIC-NCS
 - Data management implementation
 - **Subcommittee:** Field Site Research Coordinators

- Design and Analysis Committee
 - Finalize analytic plan and protocol for ACHIEVE trial
 - Develop DSMB charter and DSMP for ACHIEVE in partnership with NIA
- Neurocognitive/ Dementia Adjudication Committee
 - Oversight of neurocognitive battery administration
 - MCI/dementia adjudication
 - QA/QI of neurocognitive battery administration and collected data
- Secondary Outcomes and Ancillary Studies Committee
 - Oversight of secondary outcome battery
 - Consideration of ancillary studies
 - QA/QI of secondary battery administration and collected data
- Intervention Fidelity and Quality Committee
 - Oversight of fidelity of study interventions
 - Subcommittee: Hearing intervention
 - Subcommittee: Successful aging intervention
- Publications Committee
 - Review of all planned conference abstracts and manuscripts
- Data coordinating center
 - Management of data.
 - Organization of centralized training.

19 References

1. Newman AB, Bayles CM, Milas CN, et al. The 10 Keys to Healthy Aging: Findings from an innovative prevention program in the community. *J Aging Health*. 2010;22(5):547-566.
2. Fielding RA, Rejeski WJ, Blair S, et al. The lifestyle interventions and independence for elders study: Design and methods. *J Gerontol - Ser Biol Sci Med Sci*. 2011;66 A(11):1226-1237. doi:10.1093/gerona/qlr123.
3. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. *Am J Epidemiol*. 1989;129(4):687-702.
4. American Academy of Audiology. American Academy of Audiology Task Force: Guidelines for the audiological management of adult hearing impairment. *Audio Today*. 2006;18:32-36.
5. Hornsby B, Mueller G. Monosyllabic word testing: Five simple steps to improve accuracy and efficiency. *AudiologyOnline*, Article #11978. <http://www.audiologyonline.com/>.
6. Killion MC, Niquette PA, Gudmundsen GI, Revit LJ, Banerjee S. Development of a quick speech-in-noise test for measuring signal-to-noise ratio loss in normal-hearing and hearing-impaired listeners. *J Acoust Soc Am*. 2004;116(4 Pt 1):2395-2405.

7. Wilson RH, Mcardle RA, Smith SL. An Evaluation of the BKB-SIN, HINT, QuickSIN, and WIN Materials on Listeners With Normal Hearing and Listeners With Hearing Loss. *J Speech Lang Hear Res.* 2007;50(August 2007):844-856.
8. ARIC Visit 5 and NCS Study protocol Manual of Operations 2 - Home and Field Center Procedures. <http://www.csc.unc.edu/aric/>. Accessed January 16, 2016.
9. Gross AL, Power MC, Albert MS, et al. Application of Latent Variable Methods to the Study of Cognitive Decline When Tests Change over Time. *Epidemiol Camb Mass.* 2015;26(6):878-887. doi:10.1097/EDE.0000000000000379.
10. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement J Alzheimers Assoc.* 2011;7(3):270-279. doi:10.1016/j.jalz.2011.03.008.
11. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement J Alzheimers Assoc.* 2011;7(3):263-269. doi:10.1016/j.jalz.2011.03.005.
12. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12(3):189-198.
13. Radloff LS. The CES-D Scale A Self-Report Depression Scale for Research in the General Population. *Appl Psychol Meas.* 1977;1(3):385-401. doi:10.1177/014662167700100306.
14. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *Am J Clin Nutr.* 1982;36(5):936-942.
15. Ventry IM, Weinstein BE. Identification of elderly people with hearing problems. *ASHA.* 1983;25(7):37-42.
16. Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care.* 1996;34(3):220-233.
17. Cohen S, J DW, Skoner DP, Rabin BS, Gwaltney JM. Social ties and susceptibility to the common cold. *JAMA.* 1997;277(24):1940-1944.
18. Russell D, Peplau L a, Cutrona CE. The revised UCLA Loneliness Scale: Concurrent and discriminant validity evidence. *J Pers Soc Psychol.* 1980;39(3):472-480. doi:10.1037/0022-3514.39.3.472.
19. Schrack JA, Zipunnikov V, Goldsmith J, et al. Assessing the "physical cliff": detailed quantification of age-related differences in daily patterns of physical activity. *J Gerontol A Biol Sci Med Sci.* 2014;69(8):973-979. doi:10.1093/gerona/glt199.
20. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol.* 1994;49(2):M85-M94.

21. Morone NE, Greco CM, Moore CG, et al. A Mind-Body Program for Older Adults With Chronic Low Back Pain. *JAMA Intern Med.* 2016;152(13):329-337. doi:10.1001/jamainternmed.2015.8033.
22. Morone NE, Greco CM, Rollman BL, et al. The design and methods of the aging successfully with pain study. *Contemp Clin Trials.* 2012;33(2):417-425. doi:10.1016/j.cct.2011.11.012.
23. Pahor M, Guralnik JM, Ambrosius WT, et al. Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE study randomized clinical trial. *JAMA J Am Med Assoc.* 2014;311(23):2387-2396. doi:10.1001/jama.2014.5616.
24. Boutron I, Guittet L, Estellat C, Moher D, Hróbjartsson A, Ravaud P. Reporting methods of blinding in randomized trials assessing nonpharmacological treatments. *PLoS Med.* 2007;4(2):e61. doi:10.1371/journal.pmed.0040061.
25. Senn S. Testing for baseline balance in clinical trials. *Stat Med.* 1994;13(17):1715-1726.
26. Gross AL, Sherva R, Mukherjee S, et al. Calibrating longitudinal cognition in Alzheimer's disease across diverse test batteries and datasets. *Neuroepidemiology.* 2014;43(3-4):194-205. doi:10.1159/000367970.
27. Knopman DS, Griswold ME, Lrette ST, et al. Vascular imaging abnormalities and cognition: mediation by cortical volume in nondemented individuals: atherosclerosis risk in communities-neurocognitive study. *Stroke J Cereb Circ.* 2015;46(2):433-440. doi:10.1161/STROKEAHA.114.007847.
28. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol.* 1986;51(6):1173-1182.
29. Davis SM. Mixed models for repeated measures with categorical time effects (MMRM). In: *Clinical Trials with Missing Data: A Guide for Practitioners.* John Wiley & Sons; 2014.
30. Gross AL, Jones RN, Fong TG, Tommet D, Inouye SK. Calibration and validation of an innovative approach for estimating general cognitive performance. *Neuroepidemiology.* 2014;42(3):144-153. doi:10.1159/000357647.
31. Gross AL, Jones RN, Inouye SK. Development of an Expanded Measure of Physical Functioning for Older Persons in Epidemiologic Research. *Res Aging.* 2015;37(7):671-694. doi:10.1177/0164027514550834.
32. Lord FM. The Relation of Test Score to the Trait Underlying the Test. *ETS Res Bull Ser.* 1952;1952(2):517-549. doi:10.1002/j.2333-8504.1952.tb00926.x.
33. Gross AL, Mungas DM, Crane PK, et al. Effects of education and race on cognitive decline: An integrative study of generalizability versus study-specific results. *Psychol Aging.* 2015;30(4):863-880. doi:10.1037/pag0000032.

34. Curran PJ, McGinley JS, Bauer DJ, et al. A Moderated Nonlinear Factor Model for the Development of Commensurate Measures in Integrative Data Analysis. *Multivar Behav Res.* 2014;49(3):214-231. doi:10.1080/00273171.2014.889594.
35. Schneider BC, Gross AL, Bangen KJ, et al. Association of vascular risk factors with cognition in a multiethnic sample. *J Gerontol B Psychol Sci Soc Sci.* 2015;70(4):532-544. doi:10.1093/geronb/gbu040.
36. Sisco S, Gross AL, Shih RA, et al. The role of early-life educational quality and literacy in explaining racial disparities in cognition in late life. *J Gerontol B Psychol Sci Soc Sci.* 2015;70(4):557-567. doi:10.1093/geronb/gbt133.
37. Fieo R, Mukherjee S, Dmitrieva NO, et al. Differential item functioning due to cognitive status does not impact depressive symptom measures in four heterogeneous samples of older adults. *Int J Geriatr Psychiatry.* 2015;30(9):911-918. doi:10.1002/gps.4234.
38. Purgato M, Gross AL, Jordans MJD, de Jong JTVM, Barbui C, Tol W. Psychosocial interventions for children exposed to traumatic events in low- and middle-income countries: study protocol of an individual patient data meta-analysis. *Syst Rev.* 2014;3:34. doi:10.1186/2046-4053-3-34.
39. Takane Y, Leeuw J de. On the relationship between item response theory and factor analysis of discretized variables. *Psychometrika.* 1987;52(3):393-408. doi:10.1007/BF02294363.
40. van der Leeuw G, Eggermont LHP, Shi L, et al. Pain and Cognitive Function Among Older Adults Living in the Community. *J Gerontol A Biol Sci Med Sci.* 2016;71(3):398-405. doi:10.1093/gerona/glv166.
41. Mehta CR, Pocock SJ. Adaptive increase in sample size when interim results are promising: A practical guide with examples. *Stat Med.* 2011;30(28):3267-3284. doi:10.1002/sim.4102.
42. Chen YHJ, DeMets DL, Gordon Lan KK. Increasing the sample size when the unblinded interim result is promising. *Stat Med.* 2004;23(7):1023-1038. doi:10.1002/sim.1688.