U.S. Study to Protect Brain Health through Lifestyle Intervention to Reduce Risk

Study Acronym:

U.S. POINTER

Short Study Name:

POINTER

Protocol Version 5.0
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Confidentiality

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ABBREVIATIONS

AB	**BETA-AMYLOID**
ACSM	**AMERICAN ACADEMY OF SPORTS MEDICINE**
ACTIVE	**ADVANCED COGNITIVE TRAINING FOR INDEPENDENT AND VITAL ELDERLY (TRIAL)**
AD	**ALZHEIMER'S DISEASE**
ADA	**AMERICAN DIABETES ASSOCIATION**
AE	**ADVERSE EVENT**
AGEWISE	**AGING WELL THROUGH INTERACTION AND SCIENTIFIC EDUCATION PROGRAM**
AHA	**AMERICAN HEART ASSOCIATION**
APOE/APOE4	**APOLIPOPROTEIN E/APOLIPOPROTEIN E EPSILON 4**
ATRI	**ALZHEIMER'S THERAPEUTIC RESEARCH INSTITUTE**
BMI	**BODY MASS INDEX**
BP	**BLOOD PRESSURE**
BPM	**BEATS PER MINUTE**
BPSO	**BEHAVIORAL PATTERN SEPARATION OF OBJECTS**
CC	**COORDINATING CENTER**
CCT	**COMPUTER-BASED COGNITIVE TRAINING**
CDR	**CLINICAL DEMENTIA RATING**
CDR-SB	**CLINICAL DEMENTIA RATING – SUM OF BOXES**
CFI	**COGNITIVE FUNCTION INSTRUMENT**
CFR	**CODE OF FEDERAL REGULATIONS**
CRF	**CASE REPORT FORM**
CSF	**CEREBROSPINAL FLUID**
CVD	**CARDIOVASCULAR DISEASE**

DCTCLOCK	**DIGITAL COGNITION TECHNOLOGIES CLOCK DRAWING TEST**
DET	**DETECTION TASK (COGSTATE)**
DHA	**DOCOSAHEXAENOIC ACID**
DNA	**DEOXYRIBONUCLEIC ACID**
DSM	**DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS**
DSMB	**DATA AND SAFETY MONITORING BOARD**
DSST	**DIGIT SYMBOL SUBSTITUTION TEST**
ECG	**ELECTROCARDIOGRAM**
ECOG	**EVERYDAY COGNITION**
ECRF	**ELECTRONIC CASE REPORT FORM**
EQ5D	**EUROQOL 5-ITEM HEALTH QUESTIONNAIRE**
EMR	**ELECTRONIC MEDICAL RECORD**
FCSRT	**FREE AND CUED SELECTIVE REMINDING TEST**
FDA	**FOOD AND DRUG ADMINISTRATION**
FINGER	**FINNISH GERIATRIC INTERVENTION STUDY TO PREVENT COGNITIVE IMPAIRMENT AND DISABILITY**
FNAME	**FACE-NAME ASSOCIATIVE MEMORY EXAM**
GCP	**GOOD CLINICAL PRACTICE**
GDS	**GERIATRIC DEPRESSION SCALE**
HBA1C	**HEMOGLOBIN A1C**
HIPAA	**HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT**
HR	**HEART RATE**
HRR	**HEART RATE RESERVE**
IADL	**INSTRUMENTAL ACTIVITIES OF DAILY LIVING**
ICF	**INFORMED CONSENT FORM**
ICH	**INTERNATIONAL CONFERENCE ON HARMONISATION**

IDN	**IDENTIFICATION TASK (COGSTATE)**
IRB	**INSTITUTIONAL REVIEW BOARD**
ITT	**INTENT-TO-TREAT**
LDL	**LOW-DENSITY LIPOPROTEIN**
MCI	**MILD COGNITIVE IMPAIRMENT**
MEDDRA	**MEDICAL DICTIONARY FOR REGULATORY ACTIVITIES**
MIND	**MEDITERRANEAN-DASH INTERVENTION FOR NEURODEGENERATIVE DELAY**
MMRM	**MIXED EFFECTS MODEL FOR REPEATED MEASURES**
NTB	**NEUROPSYCHOLOGICAL TEST BATTERY**
OBK	**ONE BACK TASK (COGSTATE)**
OCL	**ONE CARD LEARNING (COGSTATE)**
OHRP	**OFFICE FOR HUMAN RESEARCH PROTECTIONS**
PAL	**PERSONAL ACTIVITY LOG**
PCP	**PRIMARY CARE PROVIDER**
PHI	**PROTECTED HEALTH INFORMATION**
PI	**PRINCIPAL INVESTIGATOR**
PID	**PARTICIPANT IDENTIFICATION NUMBER**
PMNTB	**POINTER MODIFIED NEUROPSYCHOLOGICAL TEST BATTERY**
QC	**QUALITY CONTROL**
RCT	**RANDOMIZED CONTROLLED TRIAL**
RE-AIM	**THE REACH, EFFECTIVENESS, ADOPTION, IMPLEMENTATION, AND MAINTENANCE**
RPE	**RATING OF PERCEIVED EXERTION**
SAE	**SERIOUS ADVERSE EVENT**
SD	**STANDARD DEVIATION**

SF-36	**36-ITEM SHORT FORM HEALTH SURVEY**
SG	**SELF-GUIDED LIFESTYLE INTERVENTION**
SPPB	**SHORT PHYSICAL PERFORMANCE BATTERY**
SPRINT	**SYSTOLIC BLOOD PRESSURE INTERVENTION TRIAL**
SR	**STORY RECALL**
STR	**STRUCTURED LIFESTYLE INTERVENTION**
TEAE	**TREATMENT-EMERGENT ADVERSE EVENT**
TIA	**TRANSIENT ISCHEMIC ATTACK**
TICSM	**TELEPHONE INTERVIEW OF COGNITIVE STATUS - MODIFIED**
TMT	**TRAIL-MAKING TEST**
VPA	**VISUAL PAIRED ASSOCIATES**
WAIS-R	**WECHSLER ADULT INTELLIGENCE SCALE – REVISED**
WHISCA	**WOMEN'S HEALTH INITIATIVE STUDY OF COGNITIVE AGING**
WMS-R	**WECHSLER MEMORY SCALE – REVISED**

PROTOCOL SYNOPSIS

STUDY TITLE	U.S. Study to Protect Brain Health through Lifestyle Intervention to Reduce Risk
STUDY NAME	U.S. POINTER
ABBREVIATED STUDY NAME	POINTER
PRINCIPAL INVESTIGATORS	Laura Baker, PhD, Mark Espeland, PhD, Miia Kivipelto, MD PhD, Rachel Whitmer, PhD
STUDY SPONSOR	Alzheimer's Association
STUDY DESIGN	Phase 3, multicenter, randomized 2-year clinical trial of two lifestyle interventions varying in intensity and format, in approximately 2000 older adults who are at increased risk of cognitive decline and dementia in the United States
DURATION OF STUDY PARTICIPATION	• Screening period of up to 8 months • Intervention duration of at least 24 months
INVESTIGATIONAL INTERVENTION	The trial will include two multidomain lifestyle interventions that differ in intensity and format: 1. **Self-Guided Lifestyle Intervention** that involves group meetings 2-3 times per year to provide education and support to encourage healthy lifestyle practices, and annual guideline-based health monitoring that includes blood laboratory testing, measurement of weight, blood pressure and lipid levels. 2. **Structured Lifestyle Intervention** that includes: • **Physical exercise** involving aerobic activities at 70-80% heart rate reserve (moderate-to-intense level of exertion) carried out primarily at a participating exercise facility such as the YMCA. • **Dietary counseling** to support adherence to the MIND diet (Mediterranean-DASH Intervention for Neurodegenerative Delay) to encourage increased consumption of berries, green leafy and other vegetables, whole grains, nuts, fish, poultry, beans and olive oil, and to reduce consumption of fried/fast foods, red meat, whole fat cheese, sweets, butter and trans-fat margarines. • **Cognitive exercise** involving computer-based cognitive training and facilitated group meetings to support increased cognitive and social engagement. • **Guideline-based health coaching to promote improved self-management of cardiometabolic risk factors** through frequent review of blood laboratory results, weight measurements, blood pressure and lipid levels, and goal-setting.

SUMMARY OF KEY ELIGIBILITY CRITERIA	• Age 60 to 79 years • Sedentary (not a regular exerciser, determined using the POINTER Physical Activity Questionnaire) • Low MIND Diet score (determined using the MIND Diet Screener) • Absence of significant cognitive impairment assessed using a validated telephone-administered cognitive battery (TICSm score ≥32: includes adjustments for demographics such as age, education, and race) and the Clinical Dementia Rating Scale (CDR ≤0.5, CDR-Sum of Boxes ≤1) • Risk Score for cognitive decline ≥2, using the following scoring algorithm: 1 pt: Suboptimum cardiovascular health (treated or untreated): systolic BP ≥125 mmHg ~OR~ LDL cholesterol ≥115 mg/dL~OR~ glycated hemoglobin (HbA1c) ≥6.0% 1 pt: First degree family history (mother, father, sister, brother) of memory impairment 1 pt: Race/ethnicity: African American/Black, Native American, or Hispanic/Latinx 1 pt: Older age: 70-79 years 1 pt: Sex: male
PRIMARY OUTCOME MEASURE	Global cognitive composite score derived from subtest scores on the POINTER modified Neuropsychological Test Battery that includes: Free and Cued Selective Reminding Test, Story Recall, Visual Paired Associates, Number Span, Word Fluency, Trail-Making Test, and Digit Symbol Substitution Test.
SECONDARY OUTCOME MEASURES	Episodic Memory Composite, Executive Function Composite, Processing Speed Composite, Clinical Dementia Rating–Sum of Boxes, Instrumental Activities of Daily Living, Everyday Cognition, Digital Clock Drawing Test, Lifestyle Composite Score.

1 INTRODUCTION

An urgent need exists to find effective treatments for Alzheimer's disease (AD) that can arrest or reverse the disease at its earliest stages. The emotional and financial burden on individuals living with AD, their family members, and the society is enormous, and is predicted to grow exponentially as the median population age increases. However, prior studies testing interventions to prevent or arrest cognitive decline in older adults using a variety of different pharmaceutical approaches have been largely negative. Contemporary approaches in modern health care are beginning to acknowledge lifestyle modification as a potential effective health-promoting and disease-modifying strategy to preserve or improve cognitive function and quality of life for older adults.

Lifestyle interventions focused on combining healthy diet, physical activity, and social and intellectual challenges may represent a promising therapeutic strategy to protect brain health. The recent results of the population-based 2-year clinical trial, Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), indicated that a multidomain intervention of physical activity, nutritional guidance, cognitive training, social activities, and management of heart health risk factors protected cognitive function in healthy older adults at increased risk of cognitive decline.[1] As yet, there are no pharmacological treatment options that can rival this effect. Thus, there is an urgent need to expand this work to test the generalizability, adaptability and sustainability of its findings in diverse and global populations. This pivotal U.S. Study to Protect Brain Health through Lifestyle Intervention to Reduce Risk (U.S. POINTER) will test whether a similar 2-year intensive lifestyle intervention, adapted to American culture and delivered within the community, can protect cognitive function in older adults in the U.S. who are at increased risk for cognitive decline and dementia. If successful, the results of this study will have large-scale implications for public policy regarding standard of clinical care and prescriptive practices for a fast-growing and vulnerable population of older adults.

1.1 Primary Aim

Aim 1: In approximately 2000 cognitively asymptomatic older adults (60-79 years) who are at increased risk for cognitive decline due to factors such as sedentary lifestyle, an unhealthy diet, suboptimum cardiovascular and metabolic health status, first degree family history of memory impairment, race/ethnicity or older age, we will test whether random assignment to a Self-Guided versus Structured Lifestyle Intervention focused on increasing aerobic exercise, adherence to the MIND diet (Mediterranean-DASH Intervention for Neurodegenerative Delay), cognitive and social stimulation, and guideline-based health coaching to manage cardiometabolic risk factors alters performance on a global cognitive composite score derived from the Neuropsychological Test Battery modified for POINTER, or PmNTB (includes Free and Cued Selective Reminding Test, Story Recall, Visual Paired Associates, Number Span, Word Fluency, Trail-Making, Digit Symbol Substitution Test), assessed at baseline and at 6 month intervals for a minimum of 2 years.

1.2 Secondary Aims

Aim 2: To examine intervention effects on specific cognitive domains including Episodic Memory (composite score from PmNTB subtests Free and Cued Selective Reminding Test, Story Recall, Visual Paired Associates; and experimental measures: Cogstate One-Card Learning, Face Name Associative Memory Exam, Behavioral Pattern Separation of Objects), Executive Function (composite score from PmNTB subtests Number Span, Word Fluency, Trail-Making Test Part B, Digit Symbol Substitution Test; and experimental measures: Cogstate One Back, Digital Clock Drawing Test), and Processing Speed (composite score from PmNTB subtests Trail-Making Test Part A and Digit Symbol Substitution Test; and experimental

measures: Cogstate Detection and Identification, Digital Clock Drawing Test).

Aim 3: To test whether random assignment to the Self-Guided or the Structured Lifestyle Intervention alters Clinical Dementia Rating–Sum of Boxes, a deficit accumulation frailty index, and functional abilities as measured on the Instrumental Activities of Daily Living and Everyday Cognition scales.

Aim 4: To test whether random assignment to the Self-Guided or Structured Lifestyle Intervention alters lifestyle (composite score based on self-reported physical activity, diet, and cognitive activity, and separately by domain).

Aim 5: To examine whether differences between intervention groups with respect to the primary and secondary composite cognitive outcomes vary among subgroups defined by baseline cognitive status and genetic risk (APOE).

1.3 Exploratory Aims

Aim 6: To assess separately within the two intervention groups the degree to which participants adopt and sustain behaviors related to brain health, including increased physical activity, improved diet, improved risk factor management, and engagement in cognitively and socially stimulating behaviors.

Aim 7: To assess whether the magnitude of behavioral changes in the two intervention groups varies among subgroups defined by baseline demographics (e.g., sex, age), and baseline cardiovascular and metabolic health status (using Framingham Risk Scores based on age, BP and BP treatment, total and HDL cholesterol, triglycerides, fasting glucose, hemoglobin A1c, body mass, and diabetes and smoking history).

Aim 8: To examine the degree to which any differences between intervention groups with respect to the primary and secondary outcome measures may be attributed to relative differences in adherence to the intervention (e.g., based on a composite score across all domains, and by individual domain).

Aim 9: To examine differences between intervention groups in cardiometabolic disease risk, as measured by changes in blood pressure, lipid profile and glucose regulation, and incident events using serious adverse event reports.

Aim 10: To assess differences between intervention groups in physical function, mood, sleep quality, subjective memory concerns, overall quality of life, cost of delivery, and measures of health care utilization.

Aim 11: To identify and develop an integrated community partnership network for intervention delivery and assess its effectiveness and success in engaging and retaining partners and participants in the program.

Aim 12: To collaborate with other international investigators conducting similar lifestyle intervention trials to promote harmonization of intervention protocols, outcomes, data management and data analytics to facilitate data sharing and inter-study comparisons.

2 BACKGROUND AND SIGNIFICANCE

2.1 Rationale for Multimodal Lifestyle Modification as an Intervention to Protect Cognitive Function in Older Adults at Increased Risk for Cognitive Decline

About one-third of AD dementia cases worldwide are estimated to be attributable to several modifiable lifestyle and vascular/metabolic risk factors.[2] Reducing the prevalence of each of these risk factors by 10% or 20% per decade may reduce AD prevalence worldwide by 8 to 15%, that is, between 8.8 million and 16.2 million cases in 2050. Thus, even smaller-magnitude reductions in these risk factors over a longer period of time would have a major public health impact.

The 2017 Consensus Study Report of the National Academies of Sciences, Engineering, and Medicine has recently concluded that previous randomized controlled trials of single-domain preventive interventions (single drug or lifestyle domain, e.g., only nutrition, or exercise, or cognitive training) have been at best inconclusive.[3] This Consensus Report also stated, “Although most available research on preventing cognitive decline and dementia reflects the quest for a single strong solution, multimodal approaches may be more effective than single-component interventions.”

Given the multifactorial etiology of late-onset dementia and AD, the main POINTER hypothesis is that simultaneous changes in several risk factors (even of smaller magnitude) over a longer period of time will have a protective effect on cognition. This approach is particularly important given that different individuals have different risk factor constellations, and individuals with similar overall dementia risk may have very different contributions from various risk factors.[4,5] In addition, risk factors for dementia, cardiovascular disease (CVD), and diabetes have complex interrelations. A ‘one size fits all’, single-component intervention attempting radical short-term changes in a single risk factor is thus less likely to be effective long-term in a public health context. Moreover, the rationale for combining multiple intervention components is supported by evidence suggesting synergistic effects.[6] Importantly, POINTER interventions are based on standard health care recommendations, which may facilitate adoption into clinical care for all individuals if the study’s results are positive.

POINTER will test the relative effectiveness of two approaches to multidomain lifestyle modification. One approach involves delivery of evidence-based health education and support through standardized curricula in group-based settings. For participants assigned to this intervention, referred to as the Self-Guided Lifestyle (SG), group meetings provide education about the importance of a healthy lifestyle as a preventive strategy and support to encourage change. Providing participants with this information permits them to choose approaches and goals that work best for them. To help participants “self-guide” their own program of behavior change, they will be given access to online resources (e.g., Alzheimer’s Association, NIH) and a variety of print education materials covering topics related to brain health that include healthy recipes and exercise strategies. These educational tools for initiating and sustaining behavioral change are similar to those that were provided to the Health Education group in the FINGER trial. The second intervention approach in POINTER, referred to as the Structured Lifestyle Intervention (STR), involves providing participants with intensive structure and support by a team of professionals to increase physical exercise, adhere to a healthy diet, increase intellectual/social stimulation, and better manage cardiovascular risks.

2.2 Rationale for Including Physical Exercise as a Component of the POINTER Lifestyle Intervention

The rationale for including physical exercise as a key component of the lifestyle intervention is based on growing evidence that aerobic exercise has numerous health-restoring effects in the brain, and that a sedentary lifestyle may contribute to AD pathogenesis.[7,8] Increased physical activity improves cardiovascular health, glucose regulation, and lipid metabolism, and has positive effects on mood and stress in older adults.[9] In clinical studies, aerobic exercise in particular is associated with improved

cognitive function,[10,11] increased brain volume,[12,13] increased brain perfusion,[11] and reduced levels of AD biomarkers in cerebrospinal fluid (CSF).[8,11]

Although not without controversy,[14] the majority of cross-sectional and longitudinal epidemiologic studies to date,[15] including the Canadian Study on Health and Aging,[16] the Hisayama Study,[17] the Cardiovascular Health Cognitive Study,[18] the MacArthur Study,[19] and the Mayo Clinic Study,[20] indicate reduced risk of cognitive decline with increased physical activity, even among the oldest old.[21] The results of a meta-analysis support an overall benefit of aerobic exercise on episodic memory, attention, processing speed, and executive function in non-demented older adults.[22] Short-term aerobic training (e.g., 4-12 months) increases whole brain and hippocampal volume, and regional gray and white matter volumes in prefrontal cortex.[12,13] Short-term aerobic exercise also augments hippocampal perfusion,[23] consistent with findings from longitudinal observational studies of lifelong fitness training.[24] Other exercise effects on brain function include favorable changes in neuronal network activity, notably in brain regions supporting higher cognitive functions.[23]

While studies of exercise in healthy older adults support benefits for cognitive health, the impact of aerobic exercise on brain structure and function in adults who are at increased risk of dementia has only recently been examined. In adults with mild cognitive impairment (MCI), increasing fitness is associated with less regional brain atrophy in medial temporal cortex,[25] and although only a few controlled exercise trials have been completed to date, the results thus far provide encouraging support for cognition-enhancing effects in these individuals as well. For example, in Baker et al.'s pilot 6-month study of supervised aerobic exercise versus a stretching/balance control in adults with MCI, they reported positive effects of exercise on cognition, particularly on tasks of executive function.[10] They also observed positive intervention effects on glucoregulation and AD biomarkers in plasma. In a larger 6-month trial of home-based aerobic exercise (walking) versus usual care in adults with MCI, Lautenschlager et al.[26] reported exercise benefits on a global test of cognitive function (ADAS-Cog), on delayed word list recall, and on a clinician-based assessment – with evidence for persisting benefits at the 18-month follow-up. More recently, Baker et al. completed a larger randomized controlled trial of aerobic exercise in adults with MCI and showed positive intervention effects not only on cognition, but also on other markers of brain health (e.g., increased blood flow in brain regions that typically show reduced flow with aging or with progression of AD; and reduced CSF levels of phosphorylated tau protein – a hallmark biomarker of disease progression).[11] Together, the results of these studies provide a strong rationale for including moderate-high intensity aerobic exercise as one component of the Structured Lifestyle Intervention in POINTER.

The largest physical activity trial to include cognitive outcomes, the Lifestyle Interventions and Independence for Elders (LIFE) study, featured a physical activity intervention to preserve mobility in sedentary adults 70-89 years old with functional impairments that included walking, resistance training, and flexibility exercises.[27] Cognitive function, which was a preplanned secondary outcome for the trial, was not improved overall across two years,[28] although exploratory analyses provided some evidence for cognitive benefit among individuals who were older, who had greater physical limitations, or who had diabetes.[28,29] Overall, the LIFE findings suggest that physical activity interventions delivered later in life among individuals with physical limitations may only be effective in preserving cognitive function for some individuals. In contrast to LIFE, POINTER includes a multi-domain rather than a single-domain lifestyle intervention, a physical activity component that is designed to be much more intensive (i.e., higher aerobic intensity, greater frequency of exercise bouts, more supervision, increased accountability) to produce greater cardiorespiratory responses,[30] and importantly, a younger cohort selected for cognitive vulnerability but not physical vulnerability, which may allow health corrections before it's too late.

2.3 Rationale for Supporting the MIND Diet as a Component of the POINTER Lifestyle

Intervention

A large and growing body of scientific evidence from animal and human studies has linked diet to risk of developing dementia and cognitive decline. There is good evidence that consumption of saturated and trans fats increase brain neurodegeneration and dementia risk.[31-34] Western diets that include regular intake of these fats have been linked to increased risk for cognitive decline and dementia.[35,36] Alternatively, strong to moderate evidence exists to support the neuroprotection roles of a number of nutrients, including vitamin E,[37-41] docosahexaenoic acid (DHA),[42-46] folate,[47-51] lutein,[52-54] and beta-carotene,[55-57] and foods, including fish,[32,42,43,58,59] vegetables (in particular leafy greens),[54,60-64] berries,[65-67] nuts[68-70] and oils (especially extra virgin olive oil).[71] For example, plant-based diets (DASH, Mediterranean, and MIND: Mediterranean-DASH Intervention for Neurodegenerative Delay – a hybrid of these diets) have been associated with decreased risk of Alzheimer's disease and slower cognitive decline with age.[68,72-75] The MIND diet was developed to incorporate the specific foods and nutrients that have been demonstrated to protect the aging brain. The basic components of the Mediterranean and DASH diets, demonstrated in randomized trials to effectively reduce cardiovascular conditions, are used as the basis of the MIND diet. Modifications to these basic components were made to reflect the best scientific evidence to date regarding nutrition as it relates to cognitive decline and dementia.

2.4 Rationale for Including Cognitive Exercise as a Component of the POINTER Lifestyle Intervention

Aging leads to gradual and numerous losses that affect brain function, but the nervous system retains the ability to adjust structural organization in response to stimulation, even in advanced age.[76] Several recent studies indicate that cognitive stimulation for older adults can alter brain function at the molecular and synaptic level, as well as at the neural network level,[77-79] and that a cognitively stimulating lifestyle may be associated with reduced beta-amyloid burden.[80] Computer-based cognitive training (CCT) involves structured practice on standardized and cognitively challenging tasks, includes visually appealing interfaces and varied content, and delivery is both efficient (e.g., requires a small amount of time and can be completed alone at home) and scalable (e.g., accommodates any number of users, task difficulty is iteratively adapted to individual performance).[81,82] The rationale for including CCT and other forms of cognitive exercise as a component of the Structured Lifestyle Intervention is based on the results of a few large-scale RCTs,[83,84] which include the FINGER trial,[1] and the results of systematic reviews and meta-analyses.[81,85] The results of one meta-analysis of 52 randomized controlled trials revealed that CCT significantly improved verbal memory (g =0.16), non-verbal memory (g =0.24), working memory (g =0.22), processing speed (g =0.31), and visuospatial skills (g =0.22).[81] According to this report, larger effect sizes were associated with group-based versus home-based training, and training that included only 2-3 sessions per week. Interventions that combine cognitive training and physical exercise also show cognitive benefits across several cognitive domains.[1,86] Of note, there remains much heterogeneity in the field with regard to consistency of effects across studies, and evidence to indicate transfer of cognitive benefit to an untrained task.[1,81,82,87-90]

2.5 Rationale for Including Intensive Guideline-Based Medical Monitoring as a Component of the POINTER Lifestyle Intervention

Interventions that include modification of cardiovascular and metabolic risks may stall or correct conditions that have been linked to cognitive compromise when left untreated.[91] As summarized in the 2016 American Heart Association (AHA) Scientific Statement,[92] although there is convincing evidence linking midlife hypertension to increased risk of cognitive decline in later life, the association between later life hypertension and cognitive function is not as clear. Also, in underrepresented populations in clinical research (e.g., race minorities), the link between blood pressure and cognition has not been adequately characterized. Nonetheless, without regard to age or other demographics, hypertension

unequivocally increases risk of stroke, which, in turn, increases risk for dementia.[93] The results of the SPRINT trial that included older adults indicate that reducing systolic blood pressure (pharmacologically) successfully reduced stroke risk, and thus may also protect cognition.[94] Again, as per the AHA Scientific Statement, "despite numerous outstanding questions and caveats, personalized treatment of hypertension – taking into account age, sex, APOE genotype, metabolic traits and comorbidities, remains a most promising and eminently feasible approach to safeguard vascular health and, as a consequence, brain heath."[92] The recent AHA and American Stroke Association guideline supports lowering of blood pressure, total cholesterol, and fasting blood glucose to promote optimal brain health in adults.[95] Accordingly, the two lifestyle interventions will include guideline-based monitoring of cholesterol and blood glucose to encourage better management of these levels, which, when elevated, have been linked to increased risk for cognitive impairment and dementia.[96,97]

2.6 Rationale for the Overall Design of U.S. POINTER

The POINTER trial is designed primarily from a public health perspective, and uses a multimodal intervention approach that has previously been successful for cardiovascular disease and diabetes prevention.[98,99] From this public health perspective, the most relevant reference or comparator for the POINTER multimodal lifestyle intervention can only be represented by currently established healthy lifestyle recommendations for cardiovascular/diabetes prevention. This comparison will provide crucial information for successful future wider-scale implementation of dementia prevention strategies. Both interventions target behavioral changes to promote brain health, but differ in their intensity, format and resource requirements. While previous shorter-term single-domain lifestyle trials have typically used a 'sham intervention' control, this is less relevant for POINTER given the fundamental shift from an experimental to a public health perspective.

The 2017 Consensus Study Report of the National Academies of Sciences, Engineering, and Medicine has provided the following relevant set of methodological recommendations that will be followed in POINTER:

- *Identify individuals who are at higher risk of cognitive decline and dementia and tailor interventions accordingly.*
    - POINTER inclusion criteria are designed to identify at-risk individuals who may benefit most from a multimodal lifestyle intervention.
- *Increase participation of underrepresented populations to study intervention effectiveness in these populations.*
    - The POINTER recruitment process is designed to ensure that a diverse, multi-ethnic population is included.
- *Begin more interventions at younger ages and have longer follow-up periods.*
    - The lower age limit for inclusion in POINTER will be 60 years, and intervention duration will be two years.
- *Use consistent cognitive outcome measures across trials to enable pooling.*
    - POINTER is part of the World-Wide FINGERS initiative, a collaborative network of trial investigators working together to adapt and test the successful FINGER multimodal intervention model across various geographical, economic and cultural settings in several continents. The FINGER trial design is used as a starting point to ensure maximum harmonization of protocols and facilitate joint analyses.
- *Conduct large trials designed to test the effectiveness of an intervention in broad, routine clinical practices or community settings.*
    - POINTER will utilize an integrated community partnership network for intervention delivery.

2.7 Rationale for Population Selection

The primary aim in POINTER is to test the effects of two lifestyle interventions that differ in intensity and format on 2-year cognitive trajectory in older, cognitively normal adults. Sensitivity to detect differences in cognitive trajectory between intervention groups in this study hinges on inclusion of a cohort that is enriched for risk of cognitive decline. Enriched risk will be achieved in POINTER by enrolling older adults (60-79 years old) who are largely sedentary, consume an unhealthy diet, and meet other well-established and pre-specified criteria that have been linked to increased risk for cognitive decline. This risk enrichment strategy for U.S. POINTER was informed, in large part, by the results of the FINGER trial.

2.8 Rationale for Intervention Delivery within the Community

One aim of POINTER is to identify, develop, and support an integrated community partnership network for intervention delivery, and assess its success with regard to retention of both partners and participants in the program. As has been noted by others,[85] any hope of significantly impacting the public health burden of cognitive decline and dementia will likely depend on the sustainability of the lifestyle intervention. As such, POINTER provides the opportunity to establish multiple academic-community/health systems partnerships to facilitate systemic changes in intervention delivery models to include community-based infrastructure that can support portable and sustainable intervention programs for older adults, while minimizing costs. Meeting participants where they live, work and play is important for sustaining healthy lifestyle behaviors and ensuring the project can be translated and accessible to communities across the country.

2.9 Rationale for Selection of Primary Cognitive Outcome

The primary outcome in the FINGER trial, on which POINTER is modelled, included a composite outcome that was based on test scores from the Neuropsychological Test Battery (NTB) and supplemental measures. The NTB was originally designed to yield a single efficacy measure of cognitive change using a composite score of performance on multiple well-validated neuropsychological measures.[100] Contemporary versions of the NTB have begun to include more computerized measures resulting in hybrid systems of computer and 'paper and pencil' assessments.[101] In the FINGER trial, separation between control and intervention groups was most strongly observed on a subset of NTB measures targeting executive function (e.g., Category Fluency, Digit Span, Trail-Making Test Part B), processing speed (e.g., Digit Symbol Substitution Test, Stroop Read Word condition), and delayed memory.[1] The goal of the NTB modified for POINTER (PmNTB) is to optimize a composite to detect improvement in cognition, using the latest findings from the FINGER study to facilitate cross-study comparisons. In addition, the POINTER composite was selected to also include other contemporary yet well-validated tests allowing for harmonization of outcomes with other large prevention trials (e.g., A4, EARLY, EXERT).

2.10 Rationale for Phase 3 Trial

POINTER is designed as a Phase 3 randomized controlled clinical trial to provide the highest level of evidence to address whether a lifestyle intervention may benefit cognitive function. As noted in **Section 2.1**, the current consensus is that evidence is inconclusive as to whether any of the individual lifestyle intervention components in POINTER benefits cognitive function, as summarized in the 2017 report from the National Academies of Sciences, Engineering, and Medicine.[3] The report notes the importance of designing clinical trials to assess multidomain interventions.

POINTER investigators considered but did not adopt the design of a demonstration project, i.e., an uncontrolled study to assess whether its intervention is effective in changing behaviors. As noted above, while each of the components of the intervention might be expected to provide potential health benefits, there is insufficient evidence at this time to conclude that adherence to the intervention produces meaningful cognitive benefits. Investigators also considered whether POINTER should be designed as a Phase 4 trial to assess the long-term benefits of intervention, but rejected this approach for similar reasons, in that it is unproven whether the intervention conveys any cognitive benefits.

2.11 Rationale for Collection of Blood for Banking

Blood specimens will be collected for APOE genotyping, and for banking of plasma for future analysis of existing and evolving biomarkers associated with cognitive health and decline, and AD pathology. Analyses of banked specimens will be funded by other mechanisms.

3 POTENTIAL RISKS AND BENEFITS ASSOCIATED WITH THE LIFESTYLE INTERVENTIONS

3.1 Potential Benefits

There is an urgent need to identify promising interventions to protect cognitive health in older adults who are at increased risk for cognitive decline and dementia. There are significant potential scientific and clinical benefits for POINTER's selected at-risk population. Although regular exercise, a healthy diet, cognitive and social stimulation, and intensive monitoring and self-management of medical comorbidities represent standard recommendations to maintain optimum health, the *compilation* of these recommendations has not been tested as a single intervention strategy in a rigorous controlled clinical trial. Although the proposed Structured Lifestyle Intervention resulted in a cognitive benefit in the FINGER trial, it has not been tested in the U.S. where culture, health status and health practices are notably different. Cultural differences could be instrumental to the success or failure of the FINGER interventions in preventing cognitive decline for Americans. POINTER provides a unique opportunity to learn from the experiences of FINGER and adapt FINGER interventions to best fit American life. If successful, POINTER will help to identify and develop an adaptable and sustainable prevention program that is accessible and readily implemented in the community, by community partners.

Participants randomized to the Structured Lifestyle Intervention will receive access to an exercise facility such as the YMCA for exercise, one-on-one and group counseling to encourage adherence to the exercise program and the MIND diet, computer-based cognitive training, multiple opportunities for socialization and cognitive stimulation, regular access to experts in exercise, nutrition, and lifestyle health education for support and guidance, tools to encourage adherence, and quarterly health coaching and goal-setting to work toward improved health. Participants randomized to the Self-Guided Lifestyle group will receive health education, support and care that exceeds current healthcare standards in the U.S., including group meetings to discuss general practices of healthy living, guideline-based health monitoring, tools to support self-guided plans, blood laboratory testing every 6 months, and annual physical exams. Upon study exit, all SG and STR participants will meet with study personnel to review all health metrics collected during the study. The results of cognitive testing will be provided to the participant in a letter.

3.2 Potential Risks

3.2.1 Interventions

Although regular physical exercise, healthy diet, social and cognitive engagement, and guideline-based medical monitoring have numerous health benefits, there are also risks – primarily associated with

engagement in moderate-high intensity exercise. Although this level of physical activity is the standard recommendation provided by the American Heart Association (AHA) for older adults,[102] in some adults, moderate-high intensity aerobic exercise can be associated with greater risk of hypoglycemia,[103] adverse cardiovascular events,[104] as well as orthopedic[105] and soft tissue (muscle, tendon, cartilage) injury. Higher intensity exercise is also associated with lower adherence to a training regimen than lower-intensity exercise.[106] Evidence favoring moderate-high intensity over moderate intensity exercise, however, is provided by a joint report by the American Academy of Sports Medicine (ACSM) and the AHA[102] showing greater risk reduction for cardiovascular disease and all-cause mortality. The exercise prescription of the Structured Lifestyle Intervention is consistent with ACSM exercise recommendations for older adults.[107] Risk of injury is strongest for overweight and unfit older adults.[108] When sedentary adults begin to walk or jog, they may develop foot, leg, and knee injuries when training is performed more than 3 days per week and for more than 30 minutes per session,[109] while prolonged exercise may result in overuse-related orthopedic injuries.[108] In the LIFE study, the physical activity intervention was non-significantly associated with more frequent serious adverse events (these events did not diminish intervention effects on mobility).[110] However, in an ongoing multisite study of high intensity aerobic exercise in older adults (65-89 years) with mild cognitive impairment but without functional impairments (the EXERT study), 90 participants have completed over 3000 aerobic training sessions as of July 2018 with only one serious adverse event reported. This record in the EXERT trial attests to the safety of the POINTER physical activity intervention component in adults who are free of physical limitations and therefore not as vulnerable to mobility- and other health-related adverse events.

To reduce risk of injury, POINTER participants will follow a program that involves gradual increase of exercise intensity and duration, under the guidance of an Interventionist who will be responsive to individual needs and limitations. This ramp-up process for sedentary older adults is in accordance with ACSM recommendations and has been safely deployed in other multisite high intensity aerobic exercise trials (e.g., EXERT; ClinicalTrials.gov: NCT02814526) and community-based exercise programs.[111-113] In previous pilot exercise studies in adults with MCI using similar exercise protocols and ramp-up procedures,[10,114,115] less than 3% discontinued due to cardiovascular adverse events, which were all incidentally attributed to pre-existing conditions.

There are no risks associated with participation in the Self-Guided Lifestyle Intervention.

3.2.2 Clinic Procedures

Blood collection may be associated with transient discomfort and bruising, and a small risk of infection. Cognitive testing may produce frustration in some participants. Questionnaires about mood and cognitive symptoms may uncover or potentiate feelings of dysthymia and helplessness. If needed, participants will have the opportunity to discuss such feelings and obtain appropriate support from the study team. Removal of adhesive pads following the baseline ECG could cause mild transient skin irritation.

4 SAMPLE SIZE AND STATISTICAL PLAN

POINTER is a multisite, single-blind, clinical trial that will test whether random assignment to the Self-Guided Lifestyle Intervention (SG) versus the Structured Lifestyle Intervention (STR) is associated with differences in global cognitive composite score (based on the PmNTB) across two years of planned biannual assessments. The general approach is described below. A detailed statistical plan will be completed and approved by the DSMB and Scientific Advisory Board prior to data analysis.

4.1 Randomization

In this single-blind study design, eligible participants will be randomized using a 1:1 schedule to either the SG or STR intervention arm. Randomization will be stratified by site and based on a variable-length blocking algorithm generated by the statistical team. The randomization scheme will be implemented using a centralized, secure, randomization algorithm that will be delivered to the sites within the password protected database management system.

4.2 Power and Sample Size Determination

The targeted sample size for POINTER is 2000 participants who will be followed for a planned 2.0 years. This target is chosen to provide a minimum of 85% power at the (two-sided) 0.05 significance level to detect a mean difference that is equivalent to what was observed in the FINGER trial.[1]

As described below, one interim analysis (in which intervention groups are masked and pooled) will be conducted to determine whether assumptions regarding variances and longitudinal correlations used in power projections are supported by the data and whether follow-up should be extended beyond 2 years.

To project statistical power, longitudinal sequences of cognitive test scores from the Women's Health Initiative Study of Cognitive Aging (WHISCA) trial[116] were used to estimate the longitudinal covariance of a standardized battery of test scores. While different from the test battery that POINTER will use, the WHISCA battery is expected to provide benchmark covariances that, as from potentially less precise measures, may lead to power estimates that are lower (i.e., conservative) than what will be achieved by POINTER. One hundred random sequences of N=2000 data points were simulated to project power under varying assumptions for the magnitude, pattern, and heterogeneity among participants of intervention effects, rates of lost follow-up, assessment schedules, and randomization allocation between intervention arms.

FINGER observed an intervention effect of 0.03 SD/year for its composite cognitive outcome. The recent Singapore Frailty Intervention Trial reported a larger effect from a multidomain intervention involving diet, physical activity, and cognitive stimulation of 0.19 SD/year on a composite measure of cognitive function.[117] Because the cognitive batteries in these studies were based on more recent advances in assessing cognitive function than the WHISCA battery, they are expected to be less affected by random error, and thus to have a smaller standard deviation than WHISCA when used in comparable cohorts. Thus, the approach we use to target effect sizes based on the WHISCA standard deviation is expected to underestimate the power to detect effect sizes based on standard deviations from more modern cognitive batteries.

POINTER is designed to provide a minimum of 85% power for its primary inference. This level of power is used in many trials. The goal of 85% power, rather than the more stringent goal of 90% power, was chosen because POINTER is being conducted in the context of several other similar trials in the Worldwide FINGER network, including FINGER. Thus, POINTER will not be viewed as a stand-alone assessment of a multidomain intervention for which a high independent degree of evidence is required, but as an important contributor to a broader assessment of efficacy. The choice to target 85%, rather than 90%, power also conserves resources and provides a more efficient trial.

The following projections of power are based on the analytical approach described for the primary outcome in **Section 4.4.1** and a lost follow-up rate accumulating at 2.5%/6 months (**Table 1**).
Note that 0.03 WHISCA standard deviations is expected to correspond to an effect that is larger when expressed in FINGER standard deviations. These projections support the plans for cognitive assessments to occur every 6 months, and for follow-up within the Vanguard sites to be extended until the end of the trial if such a change is warranted by the results of the interim analysis and approved by

Table 1. Power Projections for N=2000 Participants and 1:1 Random Allocation to Interventions

Planned Follow-up	Effect Sizes: Differences Between Intervention Group Slopes in Standard Deviation Units from the WHISCA Trial			
	0.0250 SD/yr	0.0275 SD/yr	0.0300 SD/yr	0.0325 SD/yr
2 years with 6-month assessments	0.761	0.837	0.897	0.939
2 years (2.5 years for Vanguard) with 6-month assessments	0.840	0.905	0.947	0.973

the Data Safety and Monitoring Board (DSMB).

Interim analyses to support power. The power for POINTER depends on how precisely slopes of cognitive change over time are estimated from the longitudinal sequences of cognitive test scores. This, in turn, depends on the covariance structure of the data and the relative contributions of underlying changes in cognition and random error to the observed covariance. An interim analysis of cognitive data (pooled across intervention groups to preserve masking) will be conducted to confirm assumptions used in designing the trial. The goals of this interim analysis, using mixed models for longitudinal data, will be to use estimates of the covariance structure of POINTER composite cognitive scores through 24 months and the rates of incomplete data to simulate data from which to estimate the distribution of results from the protocol-specified analysis of the primary outcome. The timing of this analysis will be set to facilitate, if warranted, extending follow-up by an additional 6 months at the Vanguard sites. Results from this analysis will be presented to the Data and Safety Monitoring Board and the Scientific Advisory Board for input to inform the course of action. Because the interim analysis is masked and does not reveal differences between the two intervention groups, no penalty with respect to type 1 error is required.

4.3 Selection of Participants to be Included in Analysis

The primary efficacy analysis will include all randomized participants (the intent-to-treat [ITT] data set).

4.4 Efficacy Analysis

4.4.1 Analysis to Address Primary Aim

The primary outcome for POINTER is a composite measure of cognitive function that combines individual test scores from the PmNTB to create a global cognitive composite score. The composite provides a quantifiable measure of cognitive function across multiple domains and greater statistical power than individual measures, even if interventions effects vary moderately from one individual measure to another. It consolidates type 1 error into a single outcome. Secondary analyses, described in **Section 4.4.2**, will examine intervention effects on the constituent measures of the composite score.

The primary composite outcome for the POINTER trial will be calculated as follows:

- scores for each contributing test will be converted to z-scores by dividing the differences between individual scores from the cohort-wide mean at baseline by the cohort-wide standard deviation at baseline
- z-scores will be ordered so that positive scores reflect better performance and negative scores reflect worse performance
- an average of the contributing z-scores will be obtained by cognitive domain, provided that at least 50% are present (if not, the composite score will be considered missing)

- this average will be re-normalized by subtracting it from the cohort-wide mean at baseline and dividing this difference by the cohort-wide standard deviation at baseline
- the global cognitive composite score will be computed as long as the episodic memory and at least one other domain score (executive function, processing speed) is computable, and is the average of the contributing domain scores.

Cognitive assessments that are completed virtually are excluded from the primary analyses. Additional documentation appears in “Primary and Secondary Composite Outcomes Construction” and the Statistical Analysis Plan.

Inference will be based on a random effects linear model[118] with the dependent variable consisting of all composite outcomes measured from baseline through follow-up. Covariates will include site (stratification factor) and a clinic visit by age interaction to control for potentially non-linear factors (e.g., learning effects in participants; changes in outcomes assessors) that may systematically affect both intervention groups and vary by age. The fixed effects are intervention assignment and its interaction with follow-up time as a continuous variable. This interaction tests the primary hypothesis with one degree of freedom. Models will be fitted with restricted maximum likelihood to adjust for baseline differences among individual participants. Longitudinal correlations between measures collected over time within individual participants will be parameterized using an unstructured model. If this model for longitudinal covariance results in non-convergence, a first-order autocorrelation model will be used instead. The significance of the intervention will be determined based on a Wald test for the interaction between intervention assignment and time from randomization. Use of restricted maximum likelihood provides some robustness with respect to any missing data and weights individual’s contributions to inference according to the pattern and number of assessments that they provide. Limiting the number of covariates is recommended for clinical trials of POINTER’s size.[119] Addressing differences among individuals through restricted maximum likelihood rather than models for random effects does not require assumptions about their distribution and treats differences as nuisance parameters.[118,119]

The primary analysis will be based on the ITT approach, in which data from all participants will be analyzed according to their original intervention assignment and full follow-up will be attempted regardless of intervention adherence. The primary analysis will be two-tailed, i.e., will test simultaneously for relative differences in either direction between intervention groups.

The primary inference for comparing intervention groups will use the full span of cognitive data from each participant, including the baseline assessment. In this way, all participants will contribute to the analysis, including those with missing assessments. Focusing the primary inference on the rate that cognitive trajectories over time diverge between intervention groups (i) reflects the primary trajectories of change over time seen in the FINGER trial,[1] (ii) is expected to provide greater power than approaches that require more extensive parameterization (i.e., more degrees of freedom), and (iii) conveys a simple, straightforward message that can be communicated to the public. Other approaches, such as comparing the area between the trajectories of cognitive function data traced across time or comparing the differences between groups at pre-selected times, were thought to provide potentially less statistical power and a less clear public health message. All measures will be included in the primary inference, regardless of participant’s adherence (i.e., ITT). Additional details are included in the Statistical Analysis Plan.

It is possible that participants enrolled in the trial prior to the COVID19-related pause in outcomes assessments may experience intervention effects that differ from participants who enrolled later and had uninterrupted schedules. To examine this, supporting analyses will be conducted in which participants are stratified by when they were enrolled (before or after the study pause). The magnitude of any differences in relative intervention effects on outcomes between strata will be described,

however power will likely be too low to support inference comparing the magnitude of any differences.

4.4.2 Analyses to Address Secondary Aims

Secondary outcomes of composite cognitive functions (episodic memory, executive function, processing speed) will be analyzed in a manner paralleling the primary outcome. Because these are secondary to the primary outcome, we will report results using 95% confidence intervals.

Inference to test whether random assignment to the Self-Guided vs. the Structured Lifestyle Intervention alters Clinical Dementia Rating–Sum of Boxes scores, functional status (IADL, ECog), and a composite measure reflecting Lifestyle practices involving diet, physical and cognitive/social activity will be based on general linear models as for the cognitive measures.

The aim to examine whether differences between intervention groups with respect to the primary and secondary composite cognitive outcomes vary among subgroups defined by:

- baseline cognitive status (using the global cognitive composite score – above and below the cohort median at baseline), and
- genetic risk (APOE4 carrier status: no alleles versus 1 or 2 alleles),

will be based on formal tests of interaction terms added to the models described above. Each of these interactions will be tested at the 0.05 level, with the expressed caveat that omnibus type 1 error is not controlled in secondary outcome analyses. Results will be reported as estimates and 95% confidence intervals in each category using a forest plot, irrespective of whether the interaction term is significant or not.

4.5 Exploratory Aims

Additional subgroup analyses based on baseline demographics (e.g., sex, age) and baseline health status (e.g., systolic blood pressure, cholesterol level, % glycated hemoglobin) will be based on tests of interactions and portrayed with forest plots. Estimation of relative intervention effects on tertiary outcomes defined by cardiac, vascular, and metabolic disease risk factors and events will be based on general linear models and survival analyses. Similar approaches will be used for the tertiary outcomes of physical function (Short Physical Performance Battery, 400m Walk Test), mood (Geriatric Depression Scale), sleep (Sleep Questionnaire), health-related quality of life (composite score: 36-Item Short Form Health Survey, EuroQol 5-Item Health Questionnaire), subjective memory concerns (Cognitive Function Instrument), a deficit accumulation frailty index, and health care utilization.

Because both intervention conditions target behavioral change, POINTER will describe changes from baseline over time among participants assigned to each intervention arm. These descriptions will include behaviors linked to each domain targeted by the interventions, which includes characteristics of these behavior changes. The cost of intervention delivery will be estimated for the two arms.

We will also assess whether intervention adherence varies between strata based on whether or not participants were enrolled prior to the COVID19-related pause in assessments.

4.6 Safety Analysis

Safety will be assessed by summarizing and analyzing adverse events (AE) during the intervention period. Treatment-emergent adverse events (TEAE) will be defined as events that first occurred or worsened on or after randomization.

An overview of AEs, including the number and percentage of participants who died, suffered serious adverse events (SAE), discontinued due to AEs, and who suffered TEAEs will be provided. A comparison between intervention arms will be performed using a Fisher's Exact test. Summaries of AEs by system organ class will be provided for: (i) pre-existing conditions, (ii) TEAEs, and (iii) SAEs. Discontinuations due to AEs will also be listed.

Safety assessment proceeds uninterrupted by the COVID19-related pause. Because intervention delivery was altered during the pause, we will separately report AEs that occurred during the pause from those that occurred during normal follow-up.

4.7 Interim Analysis

Trial investigators considered whether plans for interim testing towards efficacy or futility (i.e., early discontinuation of the trial) should be pre-specified but have decided against prescribing interim testing and formal stopping rules to guide deliberations of the POINTER Data and Safety Monitoring Committee (DSMB). This decision was based on (i) the relatively short (e.g., 2 year) planned follow-up, (ii) the importance of paralleling the FINGER trial design, (iii) the potentially diminished impact of the trial on health care guidelines if follow-up is curtailed, and (iv) the expectation that the full planned duration of the trial is necessary to meet secondary objectives.

An independent, external DSMB will perform regular monitoring of conduct (i.e., likelihood to meet objectives) and safety over the entire duration of the study.

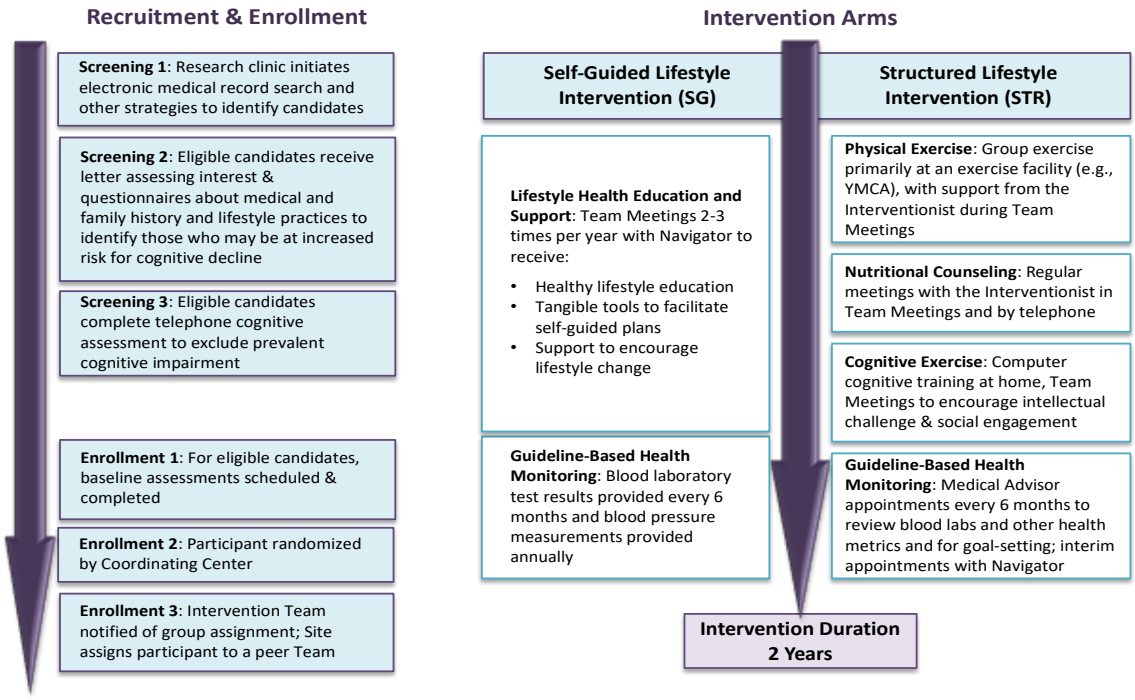
5 INTERVENTIONS AND IMPLEMENTATION

5.1 Overview

U.S. POINTER builds on lessons learned from FINGER and will assess the cognitive effects of a 2-year multi-region and community-based program comparing a highly structured lifestyle intervention to a self-guided lifestyle intervention in 2000 cognitively normal older adults who are at risk of cognitive decline and dementia due to well-established factors such as age, sedentary lifestyle, an unhealthy diet, suboptimum cardiometabolic health status, race/ethnicity, and family history of memory impairment. The Structured Lifestyle Intervention (STR) will consist of moderate-high intensity aerobic exercise and resistance training completed primarily at a participating exercise facility such as the YMCA and frequently in group exercise classes, regular telephone and in-person counseling sessions to support adherence to the MIND diet, computer-based cognitive training and regular facilitated group meetings to encourage intellectual and social engagement and challenge. STR participants will also meet with a Medical Advisor every 6 months to review blood pressure, weight, and blood laboratory measurements and for guideline-based health coaching and goal-setting to support self-management of cardiometabolic health, and with another member of the Intervention Team for interim health monitoring and coaching. The individual components of the Structured Lifestyle Intervention will be rolled out in waves over the first 4 months of the intervention to acclimate the participant to the various activities and expectations. The Self-Guided Lifestyle Intervention (SG) will include annual guideline-based health monitoring and 2-3 group meetings per year to provide lifestyle health education, tools and resources, and support to encourage a healthier lifestyle. Randomization to STR or SG will follow a 1:1 schedule, with stratification by site within a geographical region to maximize cost-efficiency of intervention delivery. Four to seven sites will participate in the trial. Each site will include a research clinic, a Clinical Network, 'Navigators' to deliver participant support, and individuals with intervention-relevant expertise (physical exercise, nutrition, cognitive aging, health education) to assist with STR intervention delivery (referred to as 'Interventionists'). Once randomized, participants assigned to the

same intervention arm will be placed in groups of approximately 10-15 individuals that will progress through the intervention together as a group, referred to as a 'Team.' Each Navigator will be assigned to work only with STR Teams or only with SG Teams, with no cross-over in assignment for the duration of the study (i.e., a Navigator assigned to a SG Team will always work only with SG Teams). This separation of Navigators by intervention arm assignment will help manage intervention-specific messaging during participant interactions. At each site, potential participants will be assessed for eligibility using a sequential process that includes contact via mail, phone, or in person to ascertain interest and obtain additional information about medical and family history and lifestyle practices, and a telephone cognitive screen to exclude low performers. The Clinical Network electronic medical record (EMR) will be used to identify potential participants that meet the inclusion criteria in targeted regions. Other grassroots community engagement strategies will also be employed in parallel to identify potential study candidates. A global cognitive composite score will serve as the primary outcome. At each site, the research clinic will be responsible for screening, the baseline outcomes assessment, and masked outcomes assessments at Months 6, 12, 18, and 24. Community partners will be responsible for intervention coordination and delivery, and adherence monitoring – in collaboration with POINTER's central team of experts charged with overseeing intervention delivery for the trial (Intervention Oversight Committee). Vanguard sites will initiate recruitment/enrollment and intervention delivery in advance of the remaining sites to gain information to optimize efficiency, adherence to the interventions, and utilization of community partners for intervention delivery. A schematic of the overall flow of participants from screening through randomization and intervention delivery is provided in **Figure 1.** Both interventions begin with the Intervention Initiation Team Meeting, scheduled to occur once sufficient numbers of participants (approximately 10 to 15) have been accrued to form a Team.

Figure 1. POINTER: Recruitment & Study Flow



5.2 Self-Guided Lifestyle Intervention (SG)

The health education, tools, medical support, and encouragement that participants randomized to the Self-Guided Lifestyle Intervention receive exceed that provided to older adults in the U.S. **Figure 2** outlines the participant contact schedule, which begins with the Intervention Initiation Team Meeting. In addition to this Initiation Team Meeting, other SG Team Meetings are held twice per year to provide general lifestyle health education information, tools and resources, and support to encourage a healthier lifestyle. SG participants will also receive results of blood laboratory testing and weight measurements every 6 months, and of blood pressure monitoring annually. Team Meetings will be facilitated by the Navigator.

Figure 2. Self-Guided Lifestyle Intervention: Participant Contact Schedule

Timeline		Year 1 Months												Year 2 Months											
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Intervention	Lifestyle Health Education & Support	X[1]		X			Y C			X			Y C			X			Y C			X			Y C
Team Meetings		1		1						1						1						1			
Health Monitoring							1						1						1						1
Clinic Outcomes Assessments (Post-Baseline)							1						1						1						1
Monthly Contact Totals		**1**	**0**	**1**	**0**	**0**	**2**	**0**	**0**	**1**	**0**	**0**	**2**	**0**	**0**	**1**	**0**	**0**	**2**	**0**	**0**	**1**	**0**	**0**	**2**

[1]Intervention Initiation Meeting in Week 1

X = Team Meeting
Y = Health Monitoring (e.g., blood tests, blood pressure, weight)
C = Clinic Visits for Outcomes Assessment

Contact Type	Year 1	Year 2	Total
Total Team Meetings	3	2	5
Total Health Monitoring Assessments	2	2	4
Total Clinic Outcomes Assessments	2	2	4
Total	**7**	**6**	**13**

5.2.1 Self-Guided Lifestyle Intervention: Team Meetings

Team Meetings for the Self-Guided Intervention arm provide an opportunity to share health-related information on a number of topics, identify and discuss participants' ideas and plans for initiating and maintaining a healthier lifestyle, and to support participants in their planning as needed. SG Team Meetings are conducted using a semi-structured format that allows for one-on-one and larger group interactions. These meetings are designed to support retention and participants' satisfaction with their assigned intervention arm through (i) interactive discussions, (ii) providing education that can be readily applied, (iii) positive reinforcement for success, and (iv) social cohesion.

5.3 Structured Lifestyle Intervention (STR)

5.3.1 Rollout of Intervention Components and Participant Contact Schedule

Figure 3 outlines the rollout and participant contact schedule for the Structured Lifestyle Intervention. To gradually acclimate participants to the various intervention activities, the first month of the intervention adoption phase will include weekly Team Meetings focused only on physical exercise, with

ongoing support after this initial period provided through weekly contact with the Navigator, monthly contact (at a minimum) with the Interventionist, and in group meetings. In the second month, the diet component is initiated, with counseling and training as the focus of the weekly meetings. Thereafter, ongoing support is provided through regular telephone calls with the Interventionist (call frequency: **Figure 3**) and during the regular Team Meetings. In the third month, the cognitive exercise component will be initiated, with dedicated related content and instruction provided during the weekly meetings. In the fourth month, the weekly meetings will include curricula focused on cardiovascular and metabolic health and training to encourage active self-management of these conditions.

During the Adoption Phase of intervention rollout (Months 0-4), Team Meetings are held weekly and focus on one intervention component per month. During the Transition Phase (Months 5 and 6), Team Meeting frequency is reduced to twice monthly. In the Maintenance Phase of intervention rollout (Months 7-24), Team Meetings are reduced to once per month. In each meeting, all intervention activities are discussed and assessed for adherence.

Figure 3. Structured Lifestyle Intervention: Participant Contact Schedule

		Adoption				Transition		Maintenance																	
Timeline		Year 1 Months (Weeks)												Year 2 Months											
		1 (1-4)	2 (5-8)	3 (9-12)	4 (13-16)	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Intervention Domain	Physical Exercise[1,2]	XXXX				XX OO	XX OO Y C	X O	X O	X O Y	X O	X O	X O Y C	X O	X O	X O Y	X O	X O	X O Y C	X O	X O	X O Y	X O	X O	X O Y C
	Nutrition[3]		XXXX	OO	OO																				
	Cognitive Exercise[4]			XXXX																					
	Medical Monitoring				XXXX																				

Team Meetings	4	4	4	4	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Telephone Calls to Review Diet			2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Health Coaching Appointments						1			1			1			1			1			1			1	
Clinic Outcomes Assessments (Post-Baseline)						1						1						1						1	
Monthly Contact Totals	**4**	**4**	**6**	**6**	**4**	**6**	**2**	**2**	**3**	**2**	**2**	**4**	**2**	**2**	**3**	**2**	**2**	**4**	**2**	**2**	**3**	**2**	**2**	**4**

[1]First meeting =Intervention Initiation; [2]Exercise 4 days/week primarily at a local YMCA; [3]MIND diet 7 days/week; [4]Includes cognitive training at home 4 days/week

X = Team Meeting
O = Telephone Call to Review Diet
Y = Health Coaching Appointment
C = Clinic Visits for Outcomes Assessment

Contact Type	Year 1	Year 2	Total
Total Team Meetings	26	12	38
Total Telephone Calls to Review Diet	14	12	26
Total Health Coaching Appointments	3	4	7
Total Clinic Outcomes Assessments	2	2	4
Total	**45**	**30**	**75**

Additional participant contact during the study includes regular telephone calls with the Navigator and/or the Interventionist to review dietary intake and to address challenges as needed (not itemized in Figure 3).

5.3.2 Structured Lifestyle Intervention: Navigators and Interventionists

Community partners will play a central role in intervention delivery for POINTER. Once randomized, each participant will be assigned to an Intervention Team, which will include a Navigator, an Interventionist, and a clinician Medical Advisor. Navigators will assist participants with coordination of their intervention activities and addressing related challenges as needed on a weekly basis. The Navigators will also work with participants to support adherence, providing accountability and ongoing encouragement. Interventionists have expertise in physical exercise, nutrition, cognitive aging and/or health education, and the Medical Advisor will work with participants to review health metrics and to set goals aimed at improving overall health status.

To ensure consistency in intervention delivery, adherence monitoring, and quality of participant contact across staff members within and across sites, Interventionists, Navigators, and Medical Advisors will undergo training and certification prior to participant contact, and re-certification on an annual basis or when requested by the Intervention Oversight Committee. The training program includes guided instruction to facilitate effective use of self-management strategies founded on social cognitive theory concepts (e.g., self-regulation, behavioral rehearsal) and motivational interviewing when working with participants to foster behavior change. Site visits will be conducted to ensure consistency and standardization of protocol implementation over time.

5.3.3 Structured Lifestyle Intervention: Team Meetings

The Team Meetings, led by the Navigator and/or the Interventionist, are designed to facilitate behavior change that can be sustained over time, and encourage intervention adherence and retention. For the STR arm, this goal is accomplished by (i) facilitating communication between participants and Navigator/Interventionist, (ii) providing education relative to each intervention component to participants, (iii) teaching self-regulation skills (e.g., goal setting, problem solving, coping with challenges to adherence), (iv) providing positive reinforcement for success and identifying barriers and plans to resolve, (v) leveraging social and group processes, such as group cohesion and social problem solving, and (vi) promoting independent behavioral maintenance (e.g., long-term physical activity and adoption of a healthy diet).

The Team Meetings are conducted using a semi-structured format. This format allows for some individual contact as the group facilitator reviews participants' self-monitoring records, group processes through open discussion of progress toward behavioral goal attainment, and education regarding a specific intervention component. The design and format of the Team Meetings are based on social cognitive theory and cognitive behavioral therapy.

5.3.4 Structured Lifestyle Intervention: Physical Exercise

5.3.4.1 Collaboration with Community Exercise Facilities (YMCA)

POINTER is partnering with local community-based exercise facilities such as the YMCA to provide participants access to appropriate facilities in geographical regions where the study is conducted. Exercise facility staff maintain certifications to keep current with latest knowledge about fitness, health wellbeing, relationship building, and practices of these skills, and have experience providing exercise prescriptions and supervising older adult exercisers. Response to emergent serious or life-threatening medical events that occur while the participant is exercising at the YMCA or any other exercise facility will follow standard protocols that apply to the management of these events for any member of the facility. This collaboration with the local exercise facility will leverage an existing and well-established

community resource that could contribute to the sustainability of the POINTER intervention in the future if the trial results are positive.

5.3.4.2 Description of Physical Activity Program

The exercise component of the Structured Lifestyle Intervention includes a regimen of aerobic exercise, resistance training, and stretching, balance, and range of motion activities (**Table 2**). Aerobic exercise is performed at moderate/high levels of cardiorespiratory intensity, defined as 70-80% of heart rate reserve (HRR: 220-age-resting HR) for 30-40 minutes, 4 times per week, at an intensity of 6-8 on the modified Ratings of Perceived Exertion (RPE) scale that ranges in value from 0 (minimal to no effort) to 10 (maximal effort possible). Resistance training is performed using weight machines, free weights, and/or resistance bands for 20 minutes 2 days per week. Upper and lower body exercises are performed at an intensity of 4-6 on the RPE scale. A variety of stretching, balance, and range of motion activities are performed for 15 minutes 2 days per week at a low level of exertion (i.e., 2-3 RPE).

Table 2. Structured Lifestyle Intervention: Physical Activity Regimen

Exercise Type	Frequency (days/week)	Duration (minutes/session)	Intensity
Aerobic Exercise	4	30-35 (plus time for warm-up and cool-down)	70-80% HRR; RPE 6-8
Resistance Training	2	15-20	RPE = 4-6
Stretching, Balance, Range of Motion	2	10-15	RPE = 2-3

STR participants are provided with flexibility in the design of their exercise programs. Although they are encouraged to attend a minimum of 2 group classes per week at a participating exercise facility such as the YMCA, they are also permitted to use the facility's aerobic and resistance training equipment (e.g., elliptical trainer, treadmill, weight machines). Once a participant is comfortable with the physical activity program, the Interventionist may approve home exercise once per week.

At the YMCA or other participating exercise facility, group exercise is performed in approved group exercise classes designed for older adults. Many of the approved classes include aerobic training, resistance exercises and stretching/balance activities, thus meeting the study's physical activity requirements.

The Navigator and Interventionist assist participants in identifying appropriate classes to attend and how to meet the POINTER exercise goals, address participant questions and concerns, ensure adherence logs are completed correctly, and provide ongoing encouragement and accountability. Participant experiences with the exercise program are discussed at group meetings where challenges can also be addressed. Additional support is provided through one-on-one meetings between the participant and Navigator and/or Interventionist as needed.

5.3.4.2.1 Physical Activity Program: Aerobic Exercise

At the YMCA or other participating exercise facility, standard well-established principles for exercise safety are used to ensure member safety. The duration and intensity of the aerobic exercise is implemented in a ramped fashion such that intensity begins at a low level and gradually increases over time until the target intensity and duration are achieved. Participants assigned to the Structured

Lifestyle Intervention will be provided with wrist-worn Fitbit devices that provide continuous HR readings. For participants taking a HR-lowering medication, they will be trained to rely more on the RPE scale to assess exercise intensity.

Although the algorithm used to identify target HR for the aerobic training component will be appropriate for the majority of older adults, the targets may require slight adjustments by the Interventionist to meet specific needs of participants. Adjustments to the target HR algorithm will be regularly reviewed by the central Intervention Oversight Committee to ensure that study goals are met.

5.3.4.2.2 Physical Activity Program: Resistance Training

Resistance training can be performed in group exercise classes and includes upper and lower body exercises. Hand-held weights, elastic tubing with handles, and/or exercise balls are used for resistance, and chairs are often used to provide support.

5.3.4.2.3 Physical Activity Program: Stretching, Balance, Range of Motion

Stretching, balance, and range of motion exercises can be performed in group classes that include these elements in the programming, in classes that target these elements (e.g., stretching, easy yoga, or tai chi classes), or independently. The goal of these activities is to increase flexibility, mobility and stability.

5.3.4.2.4 Physical Activity Program: Tailoring to Meet Participant Needs

In the event that participants are unable or unwilling to engage in group exercise classes, the Intervention Team will assist in designing an individualized exercise program that targets the prescribed exercise dose. The Intervention Team will work with participants to ensure the appropriate activities are performed to meet study goals.

5.3.4.3 Physical Activity Program: Safety

While completing the physical activity component of the intervention, participants will be instructed as to best-practice guidelines including warm-up and cool-down activities, positioning and shifting of body weight, proper form, safety around exercise equipment, exercise dose (intensity, duration, frequency), and attire to minimize risk of discomfort and injury. Physical activities will be gradually increased in intensity and duration in the initial stages of the exercise intervention to reduce likelihood of injury and to promote self-efficacy regarding the participant's ability to safely and successfully follow the POINTER exercise program. Regular interaction with the Interventionist will provide numerous opportunities for (i) encouragement, (ii) minor adjustments to the routine or program as needed, and (iii) discussions about participant successes and challenges and the importance of adhering to the POINTER protocol.

5.3.4.4 Physical Activity Program: Adherence

Well-established behavioral management strategies will be used to support a positive exercise environment and high adherence to the exercise component of the intervention. The goal in POINTER will be for participants to complete at least 75% of their exercise sessions (i.e., 3 sessions per week). Adherence will be assessed using several strategies, including attendance records provided by the exercise facility (i.e., membership card electronic scan), Fitbit data, and entries in participants' Personal Activity Logs. The Personal Activity Logs are completed to track type of activities completed, duration of exercise, and indices of exercise intensity. The Navigator and/or Interventionist will review these logs with the participant and discuss challenges and goals for the coming weeks.

5.3.5 Structured Lifestyle Intervention: Diet

The diet intervention will involve nutritional counseling to encourage adherence to the MIND diet.

5.3.5.1 Description of the MIND Diet

The MIND diet is a hybrid of the Mediterranean and DASH diets but with selected modifications based on the most compelling evidence in the diet-dementia field. The two diets have the same basic components, such as emphasis on natural plant-based foods and limited animal and high saturated fat foods. The MIND diet uniquely specifies green leafy vegetables and berries as well as food component servings that reflect the nutrition-dementia study findings. Among the different types of vegetables, the green leafy variety has been identified as having the strongest protective associations against cognitive decline.

The Interventionist instructs participants on how to incorporate these foods into their dietary plan, the components of which are listed in **Table 3**. Total fat for the MIND diet is ad libitum as long as most of it comes from fatty fish, olive oil, and nuts. For safety, there is no diet recommendation for wine (or alcohol) consumption in POINTER.

Table 3. The MIND Diet

2 T per day extra virgin olive oil	≤4 weekly servings of sweets, including pastries and candy bars
≥3 daily servings of whole grains	≤2 1-oz servings per week whole fat cheese
≥3 weekly servings of legumes	1+ fish and 2+ poultry (white meat, skinless) servings per week
≤3 weekly servings of red and processed meat	5 1-oz servings of nuts per week
≤1 pat (tsp) per day butter, cream, margarine	2+ daily servings of vegetables (1 green leafy)
≤1 weekly fast food meal; fried food	1 daily serving berries (1/2 c blueberries, strawberries, blackberries, raspberries)

5.3.5.2 MIND Diet Program: Adherence

A multi-pronged strategy to maintain dietary compliance is used that includes: (i) personalized diet guidelines and strategies, (ii) multiple adherence aids, (iii) group motivation strategies, and (iv) frequent monitoring and check-ins. The Interventionist provides intensive counseling and nutrition education to participants including instructions, meal and snack ideas, and recipes for foods to incorporate into the diet, ways to prepare these foods, and behavioral strategies to encourage adherence to the diet.

During the first Team Meeting focused on diet (Month 2), the Interventionist describes the goals of the diet intervention component and specifics of the diet plan. A primary focus of these meetings is to discuss specific and reasonable personal goals for dietary changes that are documented in a behavioral contract between the participant and Intervention Team (Interventionist and Navigator). Participants are trained in the daily use of a refrigerator chart and/or a phone/tablet app to track their consumption of key food items, and to encourage self-monitoring and adherence to meal plans. These records are reviewed by the Intervention Team to document achievements. Adherence is assessed by the Interventionist on regular phone calls using the Personal Activity Log and the refrigerator chart to

generate a dietary compliance score. In addition, change in diet is assessed as an outcome at clinic visits (for both intervention arms) using the Rush Food Frequency Questionnaire.

5.3.6 Structured Lifestyle Intervention: Cognitive Exercise

5.3.6.1 Cognitive Exercise Program: Computer-Based Cognitive Training

The computer-based cognitive training (CCT) program used in POINTER, BrainHQ provided by Posit Science, represents a collaboration motivated by the results of the large Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) that provided moderate strength evidence that cognitive training can improve long-term cognitive function[83] and help maintain independence in instrumental activities of daily living[120] in adults with normal cognition. CCT will be initiated for participants in the STR arm in Month 3, after rollout of the physical activity and diet intervention components (see **Figure 3**). The Team Meetings will provide CCT instruction and orientation, and the curricula will include materials to help participants relate CCT activities to real-life cognitive challenges.

The BrainHQ program designed for POINTER is web-based (can be accessed from any computer or tablet) and targets 4 cognitive functions affected by aging and AD: speed of processing, working memory, other executive functions, and episodic memory. The CCT program includes an extensive set of engaging tasks that are (i) easy to complete, (ii) adaptive in difficulty to maintain high levels of accuracy, and (iii) presented in a rotating sequence across training sessions to provide varied experiences and minimize boredom. Participants will be asked to complete CCT at least three times per week through Month 24.

5.3.6.2 Cognitive Exercise Program: Facilitated Intellectual and Social Stimulation

CCT will be supplemented by facilitated Team Meetings where information about the importance of intellectual and social stimulation is shared and discussed. The curricula will be based on educational information provided by the Alzheimer's Association, the NIA, BrainHQ, AgeWISE (Aging Well through Interaction and Scientific Education Program: an evidence-based 12-week program for older adults focused on successful brain aging),[121] and other similar materials and programs.

As part of this group experience, the Navigators also work with participants at each meeting to set personal goals to increase intellectual and social stimulation in the coming weeks. During the subsequent Team Meeting, participants report back to the group about their experiences completing this exercise.

5.3.6.3 Cognitive Exercise Program: Adherence

CCT completion per participant is automatically tracked through the software provider's portal and this information is accessible to POINTER in real time. Navigators and Interventionists will reference completion reports during their regular meetings with participants to discuss successes and challenges and to encourage continued adherence. Intellectual and social stimulation is also assessed as an outcome with the Cognitive Activity Questionnaire.

5.3.7 Structured Lifestyle Intervention: Health Coaching

The guideline-based health coaching component of the STR arm is based on evidence-based health guidelines promoting collaborative self-monitoring and care that includes Intervention Team health coaching to reduce cardiovascular and metabolic risk factors in older adults.

5.3.7.1 Health Coaching Program: Monitoring Visits with Clinician

Participants will meet with a Medical Advisor every 6 months (outside of the research clinic and following each of the clinic outcome assessment visits) to obtain a blood pressure measurement and to review health metrics obtained at the last clinic visit (when available) for BMI, waist circumference, fasting glucose, hemoglobin A1c (HbA1c), lipids and blood pressure. During this appointment, the Medical Advisor will also work with the participant to set goals for the subsequent months aimed at improving risk factor status by achieving guideline-based goals for each of these metrics. Any emergent health conditions requiring medical treatment will be referred to the participant's primary care provider (PCP) for management.

5.3.7.2 Health Coaching Program: Monitoring Visits with Navigator

The Navigator will meet with participants between Medical Advisor appointments outside of the research clinic to review recent blood pressure measurements (recorded by participants using a community facility such as a pharmacy, fire station, or the YMCA) and blood test results and other health metrics obtained at the last research clinic visit and Medical Advisor appointment. This appointment will also be used to discuss participant progress toward reaching health goals. The Navigator will work with the participant and collaborate with the Interventionist and Medical Advisor as needed, to address challenges and barriers in achieving these goals.

5.4 Travel Away from the Home Region

For planned travel, total time away must be no more than a total of 3 months over the course of the study, and no more than 1 month at any one time if the participant is to be considered for enrollment. Participants must be willing to continue intervention activities (with the exception of Team Meetings) if travelling out of the area for more than 1 week. For all planned absences, the Intervention Team will meet with the participant to develop an acceptable plan for continued intervention activities and communication with the Navigator.

5.5 Temporary Intervention Discontinuation

Situations may arise that will warrant temporary discontinuation of the intervention for a participant. When these events occur, the Intervention Team, in collaboration with the Intervention Oversight Committee, will develop a plan to keep the participant engaged in the study while 'on hold' and to reengage the participant once the situation has resolved. The decision to remove a participant from the study in the event of a prolonged Temporary Intervention Discontinuation will be made by the site PI and the trial PIs, with final approval by the Coordinating Center, on a case-by-case basis.

A participant will be classified as being medically 'on hold' if participants report a hospitalization, injury or other health issue. Participants who are withdrawn from the physical activity component of the intervention as per PCP orders, will not be considered 'on hold' from the intervention, but rather will be expected to continue engagement in other intervention components. If a participant is 'on hold,' the Navigator will obtain regular updates from the participant about his/her status and expected schedule for resuming the physical activity component of the intervention.

Restart of physical exercise following soft tissue injuries (that do not involve surgery) can occur when the participant self-reports an ability to continue the intervention. Restart following other medical complications will require prior approval by the Study Clinician. The site PI may choose to obtain the participant's PCP approval for re-start as well.

All reported health events will be documented on an Adverse Event Form and reviewed by a Study Clinician.

5.6 Reasons for Temporary Discontinuation

Reason(s) for temporary intervention discontinuation will be captured in the appropriate CRF and coded as follows:

- **Adverse experience**: The participant has experienced an AE that, in the opinion of the investigator, requires temporary intervention discontinuation; this may include abnormal laboratory values.
- **Safety risk**: Any participant who is deemed a safety risk by the investigator due to a temporary condition.
- **Investigator judgment** that it is in the participant's or study's best interest to temporarily discontinue the intervention until ongoing personal or medical issues no longer interfere with participation, including unanticipated prolonged travel or medical issues (e.g., surgery, accidents, development of new medical conditions), and family matters.
- **Intervention Oversight Committee's judgment** that it is in the participant's or study's best interest to temporarily discontinue the intervention until ongoing personal or medical issues no longer interfere with participation, including unanticipated prolonged travel or medical issues (e.g., surgery, accidents, development of new medical conditions), and family matters.

5.7 Masking

5.7.1 Coordinating Center

The POINTER Coordinating Center (CC) is divided into two distinct entities: the Administrative and Clinical Operations CC and the Data CC. Investigators and staff within the Administrative and Clinical Operations CC will be masked to outcomes data. Investigators and staff within the Data CC will be unmasked to intervention assignment and outcomes.

5.7.2 Intervention Oversight Committee

The Intervention Oversight Committee is comprised of Steering Committee members with expertise in the areas of exercise, diet, and cognition. This team will be unmasked to intervention assignment so that it may regularly review adherence of all trial participants and assist unmasked study personnel with intervention-specific challenges as they arise.

5.7.3 Site

At the research clinic, all examiners, the neuropsychologist, and personnel responsible for outcomes data entry will be masked to intervention assignment and unmasked to outcomes data. Other site personnel that may be intentionally or inadvertently exposed to intervention group assignment as a result of their role or responsibilities in the study (e.g., Study Clinician, Intervention Director, Assistant Intervention Director, Project Manager) may be unmasked to intervention assignment but will remain masked to outcomes data. All site community partners, including the Alzheimer's Association Chapter Lead, Interventionists, and Navigators are unmasked to intervention assignment but will remain masked to outcomes data.

Unmasked personnel will not discuss a participant's intervention or progress with masked personnel,

and masked personnel will not have access to intervention-related data, including adverse events or adherence information. Participants will be reminded by unmasked personnel at the start of every in-person clinic visit to 'keep the secret' and refrain from sharing any information about their assigned intervention with the Examiners.

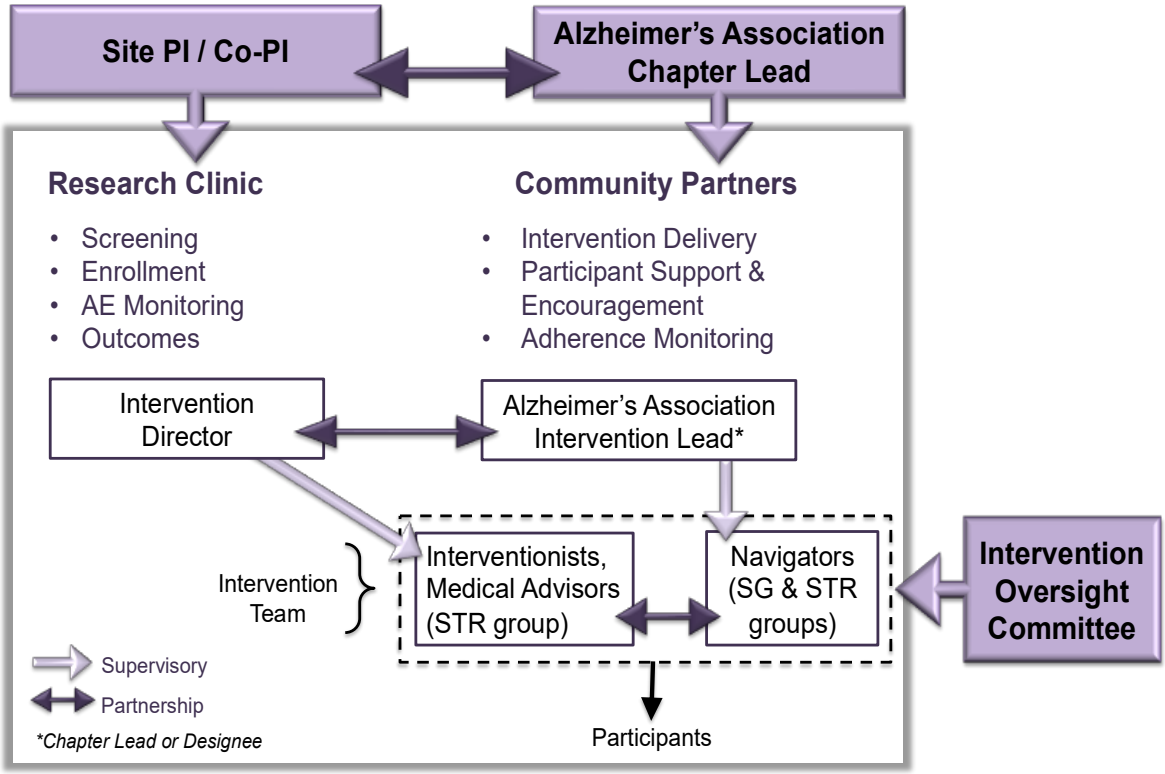
Decisions regarding breaking the mask for clinic personnel must be made in consultation with the Coordinating Center. If masking is broken for an examiner or for other personnel involved in outcomes assessment or data entry, the site PI must notify the Coordinating Center. In the event of unmasking of an examiner or of other personnel involved in outcomes assessment or data entry, an alternate plan for assessment of cognitive outcomes at future clinic visits may be required by the Coordinating Center.

5.8 Feasibility and Sustainability of Intervention Delivery in a Community

5.8.1 Infrastructure to Support Intervention Delivery and Oversight

One aim of POINTER is to identify and develop an integrated community partnership network for intervention delivery. **Figure 4** provides a schematic of this infrastructure for POINTER. The community partnership in POINTER will include the local chapter of the Alzheimer's Association that will identify and oversee the Navigators, and the Interventionists and Medical Advisors who will provide expert content input and work closely with the Navigators to provide support of participants. The research clinic's Intervention Director will serve as the liaison between the clinic and the community partners and will provide oversight of the Interventionists and Medical Advisors, in collaboration with the Study Clinician.

Figure 4. Intervention Delivery and Oversight



5.8.2 Assessment of Sustainability

The Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) model will be used to evaluate the effectiveness and sustainability of the community partnership component of POINTER (**Table 4**). This evaluation will utilize data collected during screening and enrollment, adherence monitoring, and outcomes assessments. In addition, the community partners will track information regarding intervention delivery logistics (time, place) and intervention infrastructure sustainability (e.g., staff feedback and retention rates) that will further inform this assessment.

The RE-AIM model was developed to provide a strategy for reporting and evaluating external validity, potential public impact, and sustainability of behavioral health interventions.

Table 4. RE-AIM Assessment in U.S. POINTER

Dimension	Conceptual Definition	Metrics
Reach	Proportion and representativeness of individuals who participate in the intervention	• Number of exclusions • Frequencies of reasons for exclusions • Number of potential participants contacted • Randomization rate: # randomized/# potential participants contacted • Statistical tests comparing differences between eligible and ineligible participants in basic demographics and screening measures
Efficacy	Degree to which participants' behavior changes	• Changes in consumption of MIND diet foods • Changes in physical activity • Changes in cognitive training skills and cognitive activity • Changes in health metrics (e.g., cholesterol, BP)
Adoption	Characteristics of intervention settings and staff that support delivery	• Description of intervention locations • Description of Interventionists and Navigators • Methods to identify Intervention Teams • Intervention Team success (mean adherence of their participants)
Implementation	Level of fidelity to the intervention protocol, and needed resources (cost, time)	• % attendance at Team Meetings • % physical activity sessions completed • % CCT sessions completed • % telephone contacts completed • % health monitoring/coaching visits completed
Maintenance	Level of sustained use of the intervention at the organizational and individual levels	• Organizational Level: Retention of Intervention Team members at the end of the trial; Satisfaction ratings of Intervention Team members at the end of the trial • Individual Level: Changes in participant outcomes at 24 months; study retention; satisfaction ratings of participants at 24 months

6 STUDY POPULATION

Approximately 2000 adults will be enrolled in POINTER, which is designed as a traditional clinical trial

to demonstrate efficacy, not effectiveness, with exclusion and inclusion criteria to enhance safety, adherence and risk for cognitive decline, and to identify health targets for the interventions. To determine eligibility, all participants will undergo a multi-step screening process prior to enrollment.

6.1 Exclusion & Inclusion Criteria

The Coordinating Center must approve any requested exceptions regarding possible exclusionary medications, medical conditions, laboratory tests or cognitive function assessments.

6.1.1 Exclusion Criteria

1. Age <60 or ≥80 years
2. Any significant neurologic disease, including any form of dementia, mild cognitive impairment, Parkinson's disease, Huntington's disease, normal pressure hydrocephalus, progressive supranuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, or history of significant head trauma with persistent neurologic sequelae or known structural brain abnormalities
3. History of major depression within the last 6 months
4. History of bipolar disorder or schizophrenia as per DSM V criteria
5. History of alcohol or substance abuse or dependence within the past 2 years, as per DSM V criteria
6. Current or past use of medications for memory impairment or AD (e.g., cholinesterase inhibitors, memantine)
7. Current daily use of systemic corticosteroids
8. Current use of 3 or more doses of narcotics/week. Use of intermittent narcotics should be stopped 48 hours prior to clinic visits/cognitive testing. Tramadol is allowed as long as the dose remains stable for 3 months.
9. Use of psychoactive medications, including benzodiazepines, tricyclic antidepressants, antipsychotics, mood-stabilizers, psychostimulants, anti-parkinsonian medications, anticonvulsant medications or medications with significant central anticholinergic activity are allowed as long as the medication is NOT used to treat an exclusionary medical condition.
10. Significant cardiovascular disease (including NYHA Class III or IV congestive heart failure, clinically significant aortic stenosis, history of cardiac arrest, or uncontrolled angina)
11. Serious conduction disorder (e.g., 3rd degree heart block), uncontrolled arrhythmia, or new Q waves or ST-segment depressions (>3 mm) on ECG (treated atrial fibrillation for more than 1 year or occasional premature ventricular contractions on ECG are <u>not</u> exclusions)
12. Myocardial infarction, major heart surgery (i.e., valve replacement, bypass surgery, stent placement, angioplasty), deep vein thrombosis, or pulmonary embolus in the past 6 months
13. Large vessel stroke in the past 2 years
14. History of TIA or small vessel stroke in the last 6 months; TIA occurring more than 6 months ago with residual effects
15. Current use of insulin to treat type 2 diabetes
16. Lung disease requiring either regular use of corticosteroids or the use of supplemental oxygen; intermittent use of corticosteroids or supplemental oxygen to treat chronic

obstructive pulmonary disease exacerbation is allowed; use of inhaled steroids for asthma is allowed

17. End stage renal disease (e.g., requiring dialysis or as per clinician discretion)
18. Clinically significant abnormalities in laboratory blood tests as per judgment of the site Study Clinician
19. History within the last 2 years of treatment for primary or recurrent malignant disease, excluding non-melanoma skin cancers, resected cutaneous squamous cell carcinoma in situ, basal cell carcinoma, cervical carcinoma in situ, or in situ prostate cancer with normal prostate-specific antigen post-treatment; long-term endocrine therapy for breast cancer is allowed (e.g., tamoxifen, anastrozole)
20. History of hip fracture, joint replacement, or spinal surgery in the last 6 months
21. Currently receiving physical therapy or cardiopulmonary rehabilitation
22. History of a malabsorptive bariatric procedure (gastric bypass, biliopancreatic diversion); other bariatric procedures involving restriction (i.e., sleeve, band) are not exclusionary
23. Resides in an assisted living facility or nursing home
24. Receives hospice care
25. Site PI/Study Clinician discretion regarding medical status, appropriateness of participation or concern about intervention adherence

6.1.2 Inclusion Criteria

1. Sedentary (not a regular exerciser, determined using the POINTER Physical Activity Questionnaire)
2. Low MIND Diet score (determined using the MIND Diet Screener)
3. No cognitive impairment as per TICSm score $\geq$32 (includes adjustments for demographics such as age, education and race), the Clinical Dementia Rating Scale (CDR $\leq$0.5), and the CDR-Sum of Boxes (CDR-SB $\leq$1)
4. Risk Score for cognitive decline $\geq$2, using the following scoring algorithm:
   - **1 pt:** Suboptimum cardiovascular health (treated or untreated): systolic BP $\geq$125 mmHg ~OR~ LDL cholesterol $\geq$115 mg/dL~OR~ glycated hemoglobin (HbA1c) $\geq$6.0%
   - **1 pt:** First degree family history (mother, father, sister, brother) of memory impairment
   - **1 pt:** Race and ethnicity: African American/Black, Native American, or Hispanic/Latinx
   - **1 pt:** Older age: 70-79 years
   - **1 pt:** Sex: male
5. Lives in a region where the POINTER interventions will be delivered
6. Does not plan to travel outside of the home geographic area for an extended period of time during study participation
7. Capacity to complete physical exercise
8. Willing to complete all study-related activities for at least 24 months
9. Willing to be randomized to either lifestyle intervention group

In addition, participants will be asked to identify a friend or family member with whom they have weekly

contact who is willing to serve as a study partner to answer questions during clinic visits or by telephone. Although identification of a study partner is encouraged, it is not mandatory for study participation.

6.2 Recruitment and Screening

Recruitment to identify potential participants and screening to determine eligibility will be completed using a sequential process:

- **Screening 1**: A targeted search will be conducted using the participating clinical network's EMR to identify study candidates that are 60-79 years old, do not meet exclusion criteria (**Section 6.1.1**) within the limitations provided by the EMR, and live within the targeted geographical region for a given wave of recruitment. Patients from racial and ethnic minority groups will be prioritized in this search. As needed, additional partners within the Clinical Network will be engaged at a site to increase the pool of potential participants. Although the primary recruitment approach for Screening 1 will be through the EMR, sites will simultaneously use other strategies to engage targeted groups through community presentations and networking. Recruitment will also benefit from perpetual widespread national and local efforts by the Alzheimer's Association (the sponsor) to increase publicity about the study through their website, newsletters, eNotifications, and invited articles/editorials.

- **Screening 2**: Eligible study candidates will first receive a letter from the site PI or other institution or Clinical Network authority that briefly describes the study, and a recruitment postcard to help study candidates decide whether to participate in the screening process for POINTER. If a study candidate indicates interest (via return postcard, phone call, or electronic communication), a packet of questionnaires will be mailed (or a link sent via email for online completion) to identify those who meet other eligibility criteria. Completed questionnaires will be returned to the research clinic via mail (or online).

- **Screening 3**: Screening 2-eligible study candidates will complete the TICSm, a brief validated telephone-administered cognitive screening test to exclude very low performers who may have a significant cognitive impairment.[122]

Study candidates who continue to meet eligibility criteria after completing Screening 3 will be scheduled for the baseline visit.

6.3 Inclusion of Women and Minorities

No study candidate will be excluded for reasons of sex, race, or ethnic group. There are currently no studies that definitively support or negate differences in response to an intensive multidomain lifestyle intervention within these subgroups. POINTER will target to enroll 50% women, and 23% from racial/ethnic minority groups, which reflects the demographics of the U.S. population as reported by the Census Bureau in 2016.

7 DESCRIPTION OF RESEARCH CLINIC STUDY VISITS

The planned schedule of events for study visits conducted at the research clinic is provided in Appendix 1; additional details, including visit windows, are provided in the Manual of Procedures.

Follow-up was "paused" from March 23, 2020 until July 13, 2020 due to the COVID-19 pandemic. This interval of time is censored from the schedule of outcome assessments, with follow-up restarting at the

end of this pause and schedules adjusted for participants who were enrolled prior to the pause to reflect this censoring.

7.1 Baseline

Participants can be excluded during the baseline visit if eligibility criteria are not met. The baseline assessment should be completed over two separate days and flexibility remains for each site to adjust clinic flow as necessary. Baseline procedures include:

- Informed Consent
- Demographics review
- Medical history review
- Medication review
- Review of inclusion/exclusion criteria to confirm eligibility
- Brief physical examination, vital signs, weight, waist circumference, height
- Brief neurological examination
- Electrocardiogram (ECG)
- Blood collection for APOE4 and extraction of DNA for storage
- Fasted blood collection for clinical labs: hemoglobin A1c, lipid panel, comprehensive metabolic panel (CMP, includes glucose), and hemoglobin/hematocrit (only if hemoglobin/hematocrit results are not available within 6 months of the baseline visit)
- Fasted blood collection for banking
- Cognitive assessment: Part 1
    - Primary Outcome: POINTER mNTB (FCSRT, SR, VPA, Number Span, Word Fluency, DSST, TMT)
    - MMSE
- CDR
- Study partner to provide verbal consent and complete questionnaires (when available; in person, by telephone, or online)
    - Subjective Concerns: Cognitive Function Instrument
    - Functional Status: IADL, ECog
- Participant questionnaires
    - Subjective Concerns: Cognitive Function Instrument
    - Functional Status: ECog
    - Mood: GDS
- Cognitive assessment: Part 2 (administration of Part 1 must always precede Part 2, preferably on different days)
    - Cogstate Battery (C-3) Practice
    - Cogstate (C-3) Battery
    - DCT Clock Drawing
    - BrainHQ Assessment
- Self-administered questionnaires
    - Sleep: Sleep Questionnaire
    - Lifestyle: Physical Activity Questionnaire, Sitting Habits Questionnaire, Rush Food Frequency Questionnaire, Cognitive Activity Questionnaire
    - Health-Related Quality of Life: 36-Item Short Form Health Survey, EuroQol 5-Item Health Questionnaire
- Functional assessment
    - 400m Walk Test (with BP and HR measurements)
    - Short Physical Performance Battery

- Confirm receipt of signed PCP Authorization Letter for study participation
- Randomization
    - Eligible participants will be randomized to either the Self-Guided Lifestyle Intervention or the Structured Lifestyle Intervention by the Data CC using a real-time web-based randomization system.
    - The participant will be asked to sign a document indicating his/her willingness to complete the assigned intervention for the duration of the trial
    - Participants will be instructed to 'keep the secret' about intervention group assignment from all other clinic staff; the importance of keeping this secret to avoid implicit bias will be discussed.

Once an individual is randomized, he/she is a U.S. POINTER trial participant. Follow-up for intervention-related safety begins at this point. All participants will be asked to follow the same schedule for assessments, even if they drop out of the intervention. This assessment schedule is based on the date of their Intervention Initiation Team Meeting, which should occur within approximately 2 months of randomization. If a participant does not attend his/her assigned Intervention Initiation Team Meeting, the participant's assessment schedule will be based on the date the participant's assigned Team completes their Intervention Initiation Team Meeting.

7.2 Month 6

The Month 6 assessment should be completed 6 months from intervention initiation (i.e., Intervention Initiation Team Meeting), and the recommendation is to complete these procedures in a single appointment. Month 6 procedures are expected to take approximately 2 hours to complete, and include:

- Unmasked intake interview
- Adverse event query
- Medication review
- Non-fasted blood collection for clinical labs: hemoglobin A1c and lipid panel
- Weight
- Cognitive assessment
    - Primary Outcome: POINTER mNTB (FCSRT, SR, VPA, Number Span, Word Fluency, DSST, TMT)
    - MMSE
    - DCT Clock Drawing
    - BrainHQ Assessment
- Participant questionnaires
    - Mood: GDS
    - Sleep: Sleep Questionnaire
    - Lifestyle: Physical Activity Questionnaire, Sitting Habits Questionnaire, Rush Food Frequency Questionnaire, Cognitive Activity Questionnaire

7.3 Month 12

The Month 12 assessment should be completed 12 months from intervention initiation, and the recommendation is to complete these procedures over 2 separate appointments to minimize participant fatigue due to cognitive testing. Month 12 procedures include:

- Unmasked intake interview
- Adverse event query

- Medication review
- Vital signs, weight, waist circumference
- Fasted blood collection for clinical labs: hemoglobin A1c, glucose, lipid panel
- Fasted blood collection for banking
- Cognitive assessment: Part 1
    - Primary Outcome: POINTER mNTB (FCSRT, SR, VPA, Number Span, Word Fluency, DSST, TMT)
    - MMSE
- CDR
- Study partner questionnaires (when available; in person, by telephone, or online)
    - Subjective Concerns: Cognitive Function Instrument
    - Functional Status: IADL, ECog
- Participant questionnaires
    - Subjective Concerns: Cognitive Function Instrument
    - Functional Status: ECog
    - Mood: GDS
- Cognitive assessment: Part 2 (administration of Part 1 must always precede Part 2, preferably on different days)
    - Cogstate (C-3) Battery
    - DCT Clock Drawing
    - BrainHQ Assessment
- Self-administered questionnaires
    - Sleep: Sleep Questionnaire
    - Lifestyle: Physical Activity Questionnaire, Sitting Habits Questionnaire, Rush Food Frequency Questionnaire, Cognitive Activity Questionnaire
    - Health-Related Quality of Life: 36-Item Short Form Health Survey, EuroQol 5-Item Health Questionnaire
- Functional assessment
    - 400m Walk Test (with BP and HR measurements)
    - Short Physical Performance Battery

7.4 Month 18

The Month 18 assessment should be completed 18 months from intervention initiation and should follow the same procedures outlined for the Month 6 assessment.

7.5 Month 24

The Month 24 assessment should be completed 24 months from intervention initiation and should follow the same procedures outlined for the Month 12 assessment. Note that the fasted blood collection at this assessment, however, will include the CMP (includes glucose) rather than the stand-alone glucose measurement. In addition, the Intervention Director, the Study Clinician, or another designated trained staff member will meet with participants to review their achievements in the study and all lab results, to obtain feedback about their experiences, and to discuss their plan to support sustainable healthy lifestyle practices after exiting the study.

8 ADJUDICATION OF COGNITIVE STATUS TO IDENTIFY MCI, AD AND OTHER DEMENTIAS

Following enrollment, cognitive status will be adjudicated to identify MCI, AD and other dementias according to standard guidelines[123,124] by one or more experts using all available data. Participants with

adjudicated dementia are expected to be very low in number over the 2-year intervention period. Participants showing significant cognitive decline at the end of the trial will be contacted to alert them that their performance was poorer than expected given their age and education, and to recommend follow-up with their PCP.

9 PERMANENT INTERVENTION DISCONTINUATION

The POINTER study team at each site will make every effort to maximize participant retention. If a participant expresses a desire to stop the intervention, the Coordinating Center will be notified.

If participation in the intervention is permanently discontinued, the participant will still be asked to attend his/her scheduled assessment visits at 6-month intervals and to report any adverse events throughout the planned follow-up period. It will be emphasized to participants that whether or not they adhere to their assigned intervention, they still can provide valuable data to the study if they are willing to undergo the planned assessments.

9.1 Reasons for Permanent Intervention Discontinuation

Reason(s) for permanent intervention discontinuation will be coded as follows:

- Perceived lack of efficacy by participant
- Adverse experience by participant that, in the opinion of the investigator, requires permanent discontinuation; this may include emergent medical conditions
- Participant becomes a safety risk
- Participant is unwilling or unable to participate
- Investigator judgment that it is in the participant's best interest to permanently discontinue participation in the intervention
- The medical safety team determines that it is in the participant's best interest to permanently discontinue participation in the intervention

10 STUDY WITHDRAWAL

Participants may withdraw informed consent at any time during the trial, personally or through their designated representative. The clinical site PI must document the reason for the withdrawal.

If participants are not willing to continue with the planned assessments, an Early Discontinuation Visit should be completed as soon as possible just prior to or immediately following intervention discontinuation. The Early Discontinuation Visit includes all Month 24 assessments for collection of primary and secondary outcomes. Alternatively, if an in-person Early Discontinuation Visit cannot be completed, site personnel should attempt to complete as many of the Month 24 procedures as possible, with accommodations for off-site data collection (including in-home visits) as permitted.

Reason(s) for study withdrawal:

- Participant is unwilling or unable to participate
- Participant enrolls in another intervention trial
- The medical safety team determines that it is in the participant's best interest to withdraw from study
- POINTER is terminated
- Lost to follow-up: participant could not be recalled to the clinic for follow-up assessments

- Death

11 STUDY-SPECIFIC INSTRUMENTS

11.1 Screening Instruments

11.1.1 Medical History

The Medical History Questionnaire is completed at Screening 2 to identify study candidates who meet medical eligibility requirements for enrollment.

11.1.2 Family History of Memory Impairment

The Family History of Memory Impairment Questionnaire is completed at Screening 2 to identify study candidates with a first degree relative (biological mother, father, sibling) who had signs of or was diagnosed with a memory impairment. First-degree family history of memory impairment is one of the cognitive decline risk enrichment variables that is used to calculate Risk Score for eligibility determination.

11.1.3 Physical Activity Screener

The Physical Activity Questionnaire is completed at Screening 2 to identify study candidates who are largely sedentary. Candidates who adhere to a sedentary lifestyle are at increased risk for cognitive decline. Participants who engage in regular moderate to high intensity aerobic exercise will be excluded from participation in the trial.

11.1.4 MIND Diet Screener

The MIND Diet Screener is used to quantify consumption of 9 foods believed to be important for protection against cognitive decline and those thought to be harmful to brain health. To be eligible for enrollment, participants must obtain a low score using this Screener.

11.1.5 Telephone Interview for Cognitive Status – Modified

The Telephone Interview for Cognitive Status-modified (TICSm) is administered as part of Screening 3 to assess cognitive eligibility for enrollment in POINTER. This test of global cognitive function,[125,126] assesses orientation, attention, language, immediate and short delay word recall, psychomotor skills, and abstraction. Long delay recall 15-20 minutes after encoding the word list is also assessed. The TICSm has been previously validated for administration to older adults[125-129] and used in large-scale epidemiological studies of cognitive impairment.[130] The TICSm correlates highly with other measures of global cognitive function, including the MMSE (r =0.86), the Clinical Dementia Rating scale (r =-0.75), and comparable neurocognitive tests administered face-to-face.[127,131-133] The TICSm has excellent sensitivity (0.87) and specificity (0.89) to differentiate older adults with and without dementia[134] and to identify MCI.[122,135]

11.2 Cognitive, Clinical and Behavioral Outcomes Assessments

11.2.1 Cognitive Assessments

Cognitive performance is measured using a modified version of the Neuropsychological Test Battery for POINTER. **Table 5** lists the constituent tests of the Neuropsychological Test Battery modified for POINTER on which the primary cognitive composite score will be based, and other experimental tests to be administered in the study. For memory tests that are most susceptible to practice effects (FCSRT, SR), alternate versions are administered across assessment visits. The primary outcome will be assessed at baseline and at Months 6, 12, 18 and 24. Other than the MMSE, the DCTClock and the BrainHQ Assessment, which will be administered every 6 months, experimental cognitive outcomes will be assessed at baseline, and at Months 12 and 24.

Table 5. U.S. POINTER Cognitive Tests

Outcomes	Cognitive Domain	Tests
Primary Composite (PmNTB)	**Memory**	Free and Cued Selective Reminding Test (FCSRT)
		Immediate and Delayed Story Recall (SR)
		Immediate and Delayed Visual Paired Associates (VPA)
	Executive Function	Number Span Backward, Sequencing
		Word Fluency by Letter (F, A, S)
		Word Fluency by Category (Animals, Vegetables, Fruits)
		Trail-Making Test, Condition B (Trails B)
	Processing Speed	Trail-Making Test, Condition A (Trails A)
		Digit Symbol Substitution (DSST)
Secondary / Experimental	**Global**	Mini-Mental Status Exam (MMSE)
		Cogstate Test Battery (C3) Summary Score
		Digital Cognition Technologies Clock Drawing (DCTClock) Summary Score
		BrainHQ Assessment Summary Score
	Memory *(plus PmNTB tests listed above)*	Cogstate One-Card Learning (OCL)
		Cogstate Face Name Associative Memory Exam (FNAME)
		Cogstate Behavioral Pattern Separation of Objects (BPSO)
	Executive Function & Processing Speed *(plus PmNTB tests listed above)*	Cogstate Detection (DET) and Identification (IDN)
		Cogstate One Back (OBK)
		Digital Cognition Technologies Clock Drawing (DCTClock) Component Scores
		BrainHQ Assessment Component Scores

Examiners will be trained and certified by the site neuropsychologist or cognitive specialist. High integrity and consistency of test administration procedures will be ensured through random review of recorded assessments and annual re-certification.

11.2.1.1 Free and Cued Selective Reminding Test

The FCSRT[136,137] is a 16-item word list with visual and auditory presentation that uses semantic cueing

to facilitate encoding and retrieval. Pictured items are learned four at a time with their respective semantic categories. The FCSRT has been shown to be sensitive to progressive memory decline in community samples[138] and associated with biomarker abnormalities.[139] The test ranges in score from 0 to 48 for Free Recall and 0 to 48 for Total Recall. The outcome of interest is sum of Free and Total Recall; higher scores reflect better performance.

11.2.1.2 Story Recall

SR (immediate and delayed) is based on a subtest from the Wechsler Memory Scale-Revised (WMS-R) that assess episodic memory.[140] In the modified version used in POINTER, free recall of 1 short story consisting of 25 bits of information will be elicited immediately after the story is read aloud to the participant and again after a 20-minute delay.[141] The total bits of information from the story that are recalled immediately (maximum score =25) and after the delay (maximum score =25) are recorded. Immediate and delayed recall will be used in the composite with a higher score indicating better performance.

11.2.1.3 Visual Paired Associates

VPA is adapted from the WMS-R and measures visual memory.[140] Six color-figure pairs will be shown to the participant over the course of 3 learning trials (total scores for the learning phase range from 0 to 18). After a 30-minute delay, the figure is presented alone and the participant recalls the corresponding color. Delayed recall scores range from 0 to 6.

11.2.1.4 Word Fluency by Category

This task assesses word fluency by category, and thus involves planning, organization, and cognitive flexibility. Participants are asked to generate as many words as possible in 60 seconds that belong to a given semantic category (e.g., animals, vegetables, fruits). Total score is the number of words generated per category, and higher values indicate better performance. Reduced word fluency is associated with early changes in cognitive function and progression of cognitive decline,[142] and was sensitive to the effects of aerobic exercise in preliminary studies focused on slowing cognitive decline in adults at increased risk for dementia.[10,114]

11.2.1.5 Word Fluency by Letter

This task is also a measure of verbal fluency and is similar to Category Fluency except that participants are asked to generate as many words as possible in 60 seconds that begin with a specific letter of the alphabet. Total score equals total words generated across three trials of different letters (i.e., F, A, S).

11.2.1.6 Number Span

Number Span measures simple attention and working memory.[143] This task requires the participant to repeat a series of single-digit numbers of increasing span length, first in the same order as presented by the examiner (Number Span Forward, administered for practice), in the reverse order (Number Span Backward), and subsequently in the correct numeric sequence (Number Span Sequencing). Largest span of digits correctly repeated per condition (i.e., Forward, Backward, Sequencing), and total number of correct responses across all 3 conditions are recorded.

11.2.1.7 Trail-Making Test

The TMT consists of 2 conditions: Trails A and Trails B.[144] Trails A consists of 25 circles numbered 1

through 25 distributed over a white sheet of paper, and the participant is instructed to draw a line to connect the circles in ascending numerical order as quickly as possible (150 second maximum). Trails B consists of 25 circles containing either numbers (1 through 13) or letters (A through L) that are randomly distributed across the page, and participants are instructed to connect the circles in alternating and ascending order (e.g., 1 to A; 2 to B). Time to complete Trails B is a sensitive measure of executive function and working memory, and the effects of lifestyle interventions.[10,114] Longer time to complete Trails B is associated with poorer performance.

11.2.1.8 Digit Symbol Substitution Test

The DSST[144] is based on a subtest from the Wechsler Adult Scale of Intelligence-*Revised* (WAIS-R). The test consists of 110 small blank squares presented in 7 rows with 1 of 9 numbers (1-9) randomly printed directly above each blank square. A legend is printed above the rows of blank squares, at the top of the page. The legend pairs each of the numbers with an abstract symbol. Following a few practice trials, the participant is asked to reference the legend and fill in the blank squares with the appropriate matching symbol in consecutive order from left to right across each row as quickly as possible for 90 seconds. This test engages multiple abilities including attention, psychomotor speed, visual scanning and tracking, and working memory. Number correct is recorded (maximum score =110) with higher scores reflecting better performance.

11.2.1.9 Cogstate (C-3) Battery

The Cogstate battery of tests is administered using a touchscreen tablet for stimulus display and response collection.

11.2.1.9.1 Detection, Identification, One Back, and One-Card Learning[145]

Performance on DET and IDN are used to adjust OBK and OCL performance for simple and choice reaction time. OBK is a test of attention and working memory. In this task, a playing card is presented face up in the center of the screen and starting with trial 2, the participant must decide whether it is identical to the card presented in the previous trial by responding with a finger touch. OCL is a test of short-term memory that is sensitive to early changes associated with AD.[146,147] In this task, a playing card is presented in the center of the screen and starting with trial 2, the participant must decide whether or not the same card was seen before in this task by responding with a finger touch.

11.2.1.9.2 Face Name Associative Memory Exam

The FNAME pairs 12 pictures of unfamiliar faces with 12 common first names, and engages memory networks, including the hippocampus and default network regions as per fMRI findings.[148-150] During the learning phase, participants are instructed to rate each face-name pair on whether the name ‘fits’ with the face: ‘fits’ or ‘doesn’t fit.’ During delayed recall, participants are asked to identify the face previously seen amongst 2 distracters, identify the first letter of the correct name associated with each face, and subsequently, to select the correct name per face from 3 options presented on the screen. Accuracy is recorded for each task, and maximum score per task is 12. Test performance is sensitive to physical activity in older adults.[151]

11.2.1.9.3 Behavioral Pattern Separation of Objects

The BPSO[152] displays pictures on the screen of common objects interspersed with highly similar “lures” that vary in levels of mnemonic and visual similarity with target items. During encoding, participants indicate whether pictures were of “indoor” or “outdoor” objects by touching a ‘button’ on the screen.

During the test phase, participants view objects that include exact replicas of previously viewed objects, similar but not identical objects, and new objects, and are asked to judge whether each object is "old," "similar," or "new" using a 'button' press. Higher accuracy reflects better separation of the visual patterns, and thus better memory. The BPSO robustly activates the hippocampus in fMRI studies, and is sensitive to early dysfunction in the hippocampus in aging,[153,154] and to therapeutic effects in adults with amnestic MCI.[155,156]

11.2.1.10 Digital Cognition Technologies Clock Drawing

DCTClock assesses cognition via novel software that processes information from a commercially available digital pen. This software captures nuances in cognitive performance (i.e., mental speed/efficiency, decision-making time and planning/organization) by providing a measurement tool to quantify the different cognitive processes used for task completion, even if the task is completed correctly. Outcomes for this measure have been developed using machine learning techniques to identify the relevant variables from over 700 metrics with high sensitivity and specificity to subtle cognitive deficits. Performance on this task is sensitive to PET amyloidosis, PET tau deposition, and hypometabolism in AD-associated regions in cognitively asymptomatic older adults.[157] The test includes command drawing and copy of a clock.

11.2.1.11 BrainHQ Assessment

The BrainHQ Assessment is administered using a touchscreen tablet or computer for stimulus display and response collection. The assessment takes 10-15 minutes to complete and includes 4 tests of executive function focused on selective and sustained attention, and cognitive flexibility. The tests, which will be administered to all participants during clinic visits, are similar to those completed as part of the cognitive training component of the STR intervention. The results of this assessment will be used to quantify magnitude of the cognitive training effect in the POINTER intervention.

11.2.1.12 Mini-Mental Status Exam

The MMSE[158,159] is a brief, frequently used screening instrument of global cognition. The MMSE evaluates orientation, memory, attention, concentration, naming, repetition, comprehension, and ability to create a sentence and to copy 2 overlapping pentagons. The MMSE is scored as the number of correctly completed items (maximum =30 points) with a lower score indicative of poorer performance and greater cognitive impairment.

11.2.2 Clinical and Behavioral Assessments

11.2.2.1 Clinical Dementia Rating Scale – Sum of Boxes

The CDR[144] is a clinical scale that rates the severity of dementia as absent, questionable, mild, moderate, or severe (CDR score of 0, 0.5, 1, 2, or 3, respectively). The score is based on interviews with the participant and study partner, using a structured interview that assesses 6 domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The ratings of degree of impairment for each of the 6 domains are synthesized into one global rating of dementia (ranging from 0 to 3), with more refined measure of change available with the Sum of Boxes. Scores across the 6 domains will be summed to obtain the Sum of Boxes score. Different masked examiners should administer the CDR and the POINTER cognitive battery. Although participants will be encouraged to identify a study partner who can answer questions about the participant in person or by telephone, a study partner will not be required. For participants without an identified study partner, CDR administration will be modified to exclude questions requiring study partner input.

11.2.2.2 Instrumental Activities of Daily Living

The Lawton-Brody IADL is a commonly used scale in clinical practice and research that assess a person's functional ability to complete tasks such as shopping, food preparation, transportation, and managing finances.[160] The scale is completed by the study partner (when available) at the clinic visit, by telephone, or online.

11.2.2.3 Everyday Cognition

The ECog is a validated scale developed to assess everyday functional status as it relates to memory, language, visuospatial abilities, planning, organization and divided attention in older adults.[161] The short form of the instrument will be used in POINTER. The scale is provided as a questionnaire that is completed by the participant and by the study partner (when available). The study partner can complete the questionnaire in person (at the clinic visit), by telephone, or online.

11.2.2.4 Cognitive Function Instrument

The Cognitive Function Instrument (CFI) is validated self-report questionnaire developed to detect early changes in cognitive abilities in individuals without clinical symptoms.[162,163] The CFI includes 14 questions that the participant and study partner (when available) complete that queries presence of mild cognitive difficulties often reported by older adults.[164] The study partner can complete the questionnaire in person (at the clinic visit), by telephone, or online.

11.2.2.5 Short Form Health Survey

The SF-36 is a well-validated, commonly used self-administered survey of health status that includes questions about mood, pain, physical functioning, and overall health.[165]

11.2.2.6 EuroQol-5D

The EQ5D is a brief questionnaire about health-related quality of life that queries 5 dimensions of everyday experience (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) that are each rated using a 5-point scale (no problems/slight problems/moderate problems/severe problems/extreme problems). The EQ5D is a well-validated instrument that provides a single index for overall health status.[166]

11.2.2.7 Geriatric Depression Scale

The GDS is a well-validated, self-administered questionnaire used to assess mood in geriatric populations.[167]

11.2.2.8 Sleep Questionnaire

Sleep quality will be assessed at baseline, and at Months 6, 12, 18, and 24 during the clinic visit using the Sleep Questionnaire that consists of 2 brief validated instruments: the Pittsburgh Sleep Quality Index and the Insomnia Severity Index.[168,169] The Sleep Questionnaire includes questions about sleep/wake times, difficulties falling or staying asleep, behaviors that occur while sleeping (e.g., breathing difficulties, restless legs), and use of sleep-aid medications.

11.2.2.9 Lifestyle Questionnaires

11.2.2.9.1 Physical Activity Questionnaire

The Physical Activity Questionnaire is completed by all participants during clinic visits at baseline, and Months 6, 12, 18, and 24 to collect information about frequency, type, and intensity of physical activities completed in the last 6 months.

11.2.2.9.2 Sitting Habits Questionnaire

The Sitting Habits Questionnaire is completed by all participants during clinic visits at baseline, and Months 6, 12, 18, and 24 to collect information about time spent sitting on a typical day of the week (e.g., sitting while watching television or reading, sitting at a desk).

11.2.2.9.3 Rush Food Frequency Questionnaire

Participants complete the Rush FFQ during clinic visits at baseline, and Months 6, 12, 18, and 24. The FFQ queries usual intake frequency of foods and vitamin supplements as well as specific brands of multivitamins, margarine, vegetable oil, and cereals. Compared to other dietary questionnaires, this simplified version has fewer food items per page, non-quantitative portion sizes (e.g., 1 slice), and fewer and shorter response options listed directly below each food item.

11.2.2.9.4 Cognitive Activity Questionnaire

The Cognitive Activity Questionnaire is completed by participants during clinic visits at baseline, and Months 6, 12, 18, and 24. The questionnaire queries types and frequency of various intellectual and social activities completed over the past 6 months.

11.2.2.10 400 m Walk Test

For this test, participants will be instructed to walk as quickly as possible to complete 10 laps, totaling 400 m. Blood pressure and heart rate measurements are obtained as part of this test as well. Safety precautions will be taken while administering this test by monitoring physical signs and symptoms of fatigue or discomfort, and by applying standardized stopping criteria.

11.2.2.11 Short Physical Performance Battery

Physical function will be evaluated using the well-validated Short Performance Physical Battery (SPPB).[170,171] The SPPB incorporates testing of gait speed, ability to move from a sitting position to standing, and tests of balance. Total score ranges from 0 to 12 with higher scores indicating better performance.

11.2.2.12 Deficit Accumulation Frailty Index

Deficit accumulation frailty indices are measures of overall health status that also reflect biologic aging.[172,173] They are computed as the fraction of age-related deficits (based on disease, clinical biomarkers, function, behaviors) that are evident in an individual. The specific components used to compute a frailty index vary and depend on the available data, however it is recommended that at least 30 components be included. There is emerging evidence that increases in deficit accumulation indices over time can be slowed by multidomain lifestyle interventions and that they may also be predictive of response to intervention.[174,175]

11.3 Health Care Utilization

The use of medical resources (i.e., number and type of hospitalizations, ambulatory visits, procedures) will be assessed from participants' self-report. The cost per type of hospitalization, outpatient encounter, etc., will be estimated using available U.S. data, aggregated to estimate total direct medical costs for each intervention arm. Participants will bring all prescription medications to clinic visits to be recorded, and then classified by the Coordinating Center. Health care utilization costs will be estimated using the Healthcare Cost and Utilization Project Nationwide Inpatient Sample, the National Physician Fee Schedule, the National Home Health Utilization statistics, the Medicare Skilled Nursing Facility Prospective Payment System, and national averages on medication costs.

11.4 Tracking Intervention Adherence

11.4.1 Personal Activity Log

Participants assigned to the Structured Lifestyle Intervention will track intervention activities by completing a Personal Activity Log (PAL), which will be reviewed by the members of the Intervention Team. PAL entries will include frequency, type, and duration of physical activity completed, and achieved HR; a daily checklist of foods consumed; and a log of CCT and other intellectual/social challenge activities completed.

11.4.2 Additional Physical Activity Tracking Mechanisms

11.4.2.1 Fitbit

A wristband style Fitbit will be provided to participants randomized to the Structured Lifestyle Intervention. Participants will be instructed to wear the Fitbit for the duration of trial participation. The Fitbit tracks total steps and heart rate, which will be uploaded regularly from Fitbit cloud-based storage to a POINTER database.

11.4.2.2 Rating of Perceived Exertion

Participants assigned to the Structured Lifestyle Intervention will provide ratings of perceived exertion while engaging in physical exercise. The RPE (modified Borg scale) is a validated and accepted supplemental method for assessing exercise intensity in older adults. The rating scale ranges from 1 to 10 (1 =very mild, to 10 =very, very hard), and participants are trained to self-assess their physical effort using this tool.

12 STUDY–SPECIFIC PROCEDURES

12.1 Safety Assessments

12.1.1 Physical Examination

A brief physical examination will be performed by a medically qualified professional at baseline, which will include a review of major body systems and measurement of vital signs.

12.1.2 Electrocardiogram

A standard 12-lead resting ECG will be performed at baseline. The ECG report will be reviewed, signed, and dated by the Study Clinician. Those with clinically significant ECG findings will be referred

for follow-up as deemed appropriate by the Study Clinician and may be excluded from further participation in the study.

12.1.3 Clinical Laboratory Evaluation

At each of the clinic visits, routine laboratory samples will be analyzed using the local (site) laboratory. Lab reports will be reviewed, signed and dated by the Study Clinician. If a value is outside of the laboratory's normal range, the Study Clinician will indicate if it is clinically significant. If clinically significant, lab tests may need to be repeated and/or follow-up with the participant's PCP may be required. At months 6, 12, 18 and 24, although lab reports will be reviewed by the Study Clinician there should be no discussion of results with participants during clinic visits unless PCP follow-up is required. Test results will be mailed to participants.

Clinical laboratory assessments:

- Fasting glucose and hemoglobin A1c
- Lipid panel
- Comprehensive Metabolic Panel (baseline, Month 24)
- Hemoglobin/hematocrit (only at baseline if test results are not available within 6 months of the baseline visit)

12.2 Blood Collection and Banking

12.2.1 Genetic Samples and Storage for Future Use

At baseline, APOE genotyping will be performed by the Biomarker Core of the Alzheimer's Therapeutic Research Institute (ATRI) at the University of Southern California from specimens collected for banking. Participants will be asked to consent to optional DNA banking for future research studies. DNA extraction and APOE genotyping will be performed using established Biomarker Core processing protocols of the ATRI.

12.2.2 Blood Collection for Future Biomarker Analyses and Banking

At each of the baseline, Month 12 and Month 24 clinic visits, blood will be collected after a 10-hour overnight fast. Samples will be shipped to the ATRI Biomarker Core for extraction and storage of plasma for future biomarker analyses.

13 PERSONNEL REQUIREMENTS

Personnel roles and requirements to carry out the protocol are listed below. Additional details are provided in the Manual of Operating Procedures.

13.1 Clinic Personnel

- **Site Principal Investigator:** The site PI is responsible for the overall conduct of the study at the site. The PI will perform or supervise the evaluation of all participants and ensure adherence to the protocol. The PI will supervise clinic personnel and ensure that the examiners maintain a high level of skill and accuracy in conducting assessments. The PI will remain masked to outcomes data, and unless the PI also serves as the Study Clinician, the PI will also remain masked to intervention assignment.

- **Personnel Unmasked to Intervention Assignment and Masked to Outcomes Data**

    - **Intervention Director:** The Intervention Director serves as the main liaison between the clinic and the community partners to assist in addressing study- or participant-related issues as they arise. The Intervention Director also supervises and provides ongoing support to field Interventionists.

    - **Assistant Intervention Director:** The Assistant Intervention Director will provide back-up support for the Intervention Director, assist with triage of adverse event reports, address participant-related issues as needed, and assist with recruitment and screening.

    - **Study Clinician:** The Study Clinician is responsible for the medical oversight of participants enrolled at the site, including initial assessments to confirm medical eligibility for enrollment, and safety monitoring and management of adverse events throughout the trial. Study Clinician qualifications will be approved by the POINTER Safety team.

- **Personnel Masked to Intervention Assignment and Unmasked to Outcomes Data**

    - **Examiners:** Examiners will be responsible for administering all outcomes assessments and maintaining the appropriate certifications.

    - **Neuropsychologist:** The Neuropsychologist will be responsible for training and certifying Examiners, overseeing cognitive test administration, and monitoring data integrity of cognitive outcomes.

    - All other clinic personnel involved in outcomes data collection will remain masked to intervention assignment.

13.2 Intervention Team

The Intervention Teams will be unmasked to intervention assignment and includes a Navigator for the SG group, and a Navigator, an Interventionist, and a Medical Advisor for the STR group. The Navigators will be identified by the Alzheimer's Association Chapter Lead, in collaboration with the research clinic team. Interventionists will be identified by the Intervention Director and other research clinic team members. The Medical Advisor will have the appropriate training and certifications to provide medical advice to older adults. The Intervention Teams will complete central training and certification procedures and will be re-certified on an annual basis.

14 SAFETY MONITORING

Participants will receive PCP authorization to enroll in the trial and will be monitored routinely for safety issues through interviews, vital signs, physical examinations and laboratory tests. Safety monitoring begins at the time of consent and will continue through study exit. An adverse event (AE) is defined as any untoward or unfavorable medical event that occurs during intervention delivery, intervention-related activities, or outcomes assessments at the clinic. This includes a clinically significant abnormal physical exam or laboratory finding, or presence of symptom or disease that is temporally associated with the participant's involvement in the study. In POINTER, sites will report all serious adverse events and adverse events as defined and described below.

14.1 Serious Adverse Events

14.1.1 Definition

A SAE is defined as per the Code of Federal Regulation Title 21 Part 312, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32, and includes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, or persistent or significant disability/incapacity. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs if they have the potential to jeopardize participant safety or to require medical or surgical intervention to prevent a more serious outcome listed above, such as an injurious fall resulting in a fracture that occurred while completing the physical exercise component of the intervention.

14.1.2 Reporting SAEs

SAEs due to any cause that occurs during the course of the study (i.e., after informed consent, regardless of study intervention exposure) that is reported by a participant must be recorded on an AE Report Form and entered on the study website within 72 hours of learning of the event and to the IRB within 7 days of learning (or as specified by local IRB reporting regulations). The Data CC will provide reports of SAEs for review by the Safety Committee and the DSMB, with masking maintained and in summary format (i.e., Group A, Group B).

14.2 Adverse Events

14.2.1 Definition

In POINTER, adverse events are defined as clinically relevant unfavorable or unintended health events (see Manual of Operating Procedures) that occur during intervention delivery, intervention-related activities, or outcomes assessments whether they resulted in hospitalization or met other criteria for reporting as SAEs. These events include but are not limited to: (1) worsening or change in nature, severity, or frequency of conditions or symptoms present at the start of the study; (2) participant deterioration due to primary illness; (3) intercurrent illness; and (4) physical incapacity to carry out the intervention. An abnormal laboratory value will only be reported as an AE if the investigator considers it to be an AE, if it leads to a need for medical care, or if it leads to the discontinuation or termination of the intervention. All AEs will be classified using MedDRA coding.

14.2.2 Reporting AEs

Potential AEs for study-related activities and interventions are described to each participant by trained clinic staff during the informed consent process and are queried at each clinic visit. Between clinic visits, participants are instructed to report the occurrence of relevant health events to unmasked clinic personnel or the Navigator.

- If a health event is reported to an unmasked clinic staff member, an AE Report Form is completed and reviewed by the Study Clinician.
- If a health event is reported to the Navigator, the Navigator documents the event using a web-based health event log, and an unmasked clinic staff member completes an AE Report Form for Study Clinician review.

At any time during the study, a noticeable change in medical condition or health status will be queried

during the clinic visit and/or by the Navigator and documented if applicable using the procedure described above. Examples of such noticeable changes may include skin rash or abrasion, gait disturbance, bone cast or splint, or bruising.

14.3 Follow-Up of SAEs and AEs

All AEs will be reviewed by the Study Clinician. Following questioning and evaluation, all AEs will be documented on the AE Report Form in accordance with central and local regulatory procedures. Expected and unexpected AEs will be rated for duration, seriousness, and causal relationship to the intervention. These ratings will also pertain to abnormal laboratory values deemed clinically significant by the Study Clinician.

The Study Clinician is obliged to follow participants with AEs until the events have subsided, the conditions are considered medically stable, or the participants are no longer available for follow-up. Participants who discontinue the study due to adverse experiences will be treated and followed according to established medical practice. SAEs and AEs will be reported as required to the DSMB.

14.4 Reporting of Unanticipated Problems, Adverse Events, Protocol Deviations

Any unanticipated problems, serious and unexpected AEs, or protocol deviations will be promptly reported by the site PI or a designated member of the research team to the central IRB, the POINTER Coordinating Center, the DSMB, and the Alzheimer's Association (sponsor) as appropriate.

14.5 Data and Safety Monitoring Board

An independent, external DSMB appointed by the sponsor will review the safety of all enrolled participants on an ongoing basis. The DSMB will work with the POINTER data analytic team and the medical monitor to identify the study-specific data parameters and format of the information to be regularly reported. The DSMB will initially be provided with data masked to intervention group assignment, but this group may request unmasked data if there is a safety concern. The DSMB and an Alzheimer's Association representative will meet in person or by conference call twice per year.

Additionally, the DSMB and the sponsor will be informed of the occurrence of any SAEs on a schedule specified by the DSMB. The DSMB and/or sponsor may at any time request additional information from the Coordinating Center.

Based on the review of safety data, the DSMB will make recommendations regarding the conduct of the study. These may include amending safety monitoring procedures, modifying the protocol or consent, terminating the study or continuing the study as designed.

15 DATA MANAGEMENT

15.1 Data Collection and Management Responsibilities

The POINTER Data CC is responsible for overseeing research clinic data collection and standardization, data management, data transfer, and QC analyses.

15.2 Clinical Data Management

15.2.1 Study Website Overview

All research clinics use a secure website to enter POINTER data collected from participants during clinic visits. Each research clinic staff member has a password-protected area on the home page through which data is entered. Documentation of the data entry system is maintained by the POINTER Data CC. Site-specific reports will be available on the website based on live data. All data are password protected and users are granted restricted access depending on their role in the trial.

15.2.2 Data Collection

Each research clinic maintains appropriate medical and research records for the study, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants. As part of participating in an Alzheimer's Association sponsored study, clinical records for the purposes of quality assurance reviews, audits, and evaluation of study safety, progress, and data validity are available as required. Data collection is the responsibility of the research clinic under the supervision of the research clinic PI. The research clinic PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Data are collected in multiple ways at all participant contacts, including electronic Case Report Forms (eCRF) or hard copy CRFs and automatically generated machine data. Research clinic staff are expected to review hard copy CRFs for accuracy and completeness and resolve any data issues prior to data entry. Clinical data (including AEs, concomitant medications, clinical laboratory result data) are entered into the POINTER website, a secure data capture system provided by the Data CC.

15.2.2.1 Data Entry, Verification, Quality Control, and Metadata

eCRFs will be developed that will closely resemble the paper CRFs. Those eCRFs will be used by the sites to enter the data from any paper CRF. During data entry, a variety of programmed error checks are performed for key variables, such as automatic range checks and logical consistency checks, to identify data that are inconsistent, incomplete, or inaccurate. When these edit checks fail, data may be flagged for further review or prevented from becoming part of the study database. At regular intervals, data queries are carried out on the computerized databases to perform consistency checks on key variables and other data. Metadata of the date, person, programmed edit check results, as well as the creation, modification, deletion, transfer, aggregation, and derivation of data are collected and documented.

15.2.2.2 Machine-Generated Data

Research clinic-generated measurements from instruments and devices (e.g., FitBit) will be uploaded to the central database. The Data CC is responsible for standardizing metadata captured for machine-generated data and evaluating the proper storage of these data in the central database. Data that are not readily abstracted by the research clinics for input into the eCRFs on the POINTER website are uploaded to the central database through the POINTER website, or through secure vendor portals and downloaded and integrated by the Data CC.

15.2.3 Randomization

POINTER uses an internet-based, web-based randomization procedure. An unmasked member of the research clinic team accesses the randomization application through the study website. Access to this application is password protected and its communications are encrypted. Once security requirements are satisfied and eligibility of the participant is verified, randomization will occur.

15.2.4 Participant Tracking

The POINTER website maintains a research clinic tracking system where all tools used to track various aspects of the study reside. This includes tools for tracking and monitoring recruitment, reporting and monitoring safety, monitoring adherence, and monitoring regulatory activities. The system includes a fully integrated tracking and notification system that advises research clinic staff about participant follow-up windows, and projects clinic and laboratory workload. Tracking a participant begins at screening and continues throughout the study by integrating participant follow-up data with a schedule of target dates for each of the participant contacts.

15.2.5 Security and Data Protection

Data security in the web-based data system uses 2048-bit encryption and Secure Socket Layer. Once data are uploaded to the POINTER central database, recovery from disasters such as natural phenomenon (water, fire, or electrical) is possible through the ability to reconstruct both the database management system and the data up to the last back-up through the use of nightly backups. This process ensures optimal recovery of data systems in the event of a disaster.

15.2.5.1 Research Clinic Data Security

Paper and/or electronic records for participants are stored at the research clinics. All records receive the same care as would ordinary medical records. Access to the data in any local POINTER database is controlled by a system of user identification names and passwords to ensure only authorized staff can enter. Each research clinic staff member is authorized before being given an ID and password to use the data system on the POINTER website.

15.2.5.2 Database Security

All data collected will be identified only by participant identification (PID) number and stored in a central POINTER database, with access via secure and encrypted website. Access to the website, privileges to various areas of the website, and to the data on the website is managed by the Data CC. Confidentiality of information within the database is protected through a variety of procedures and facilities:

1. The confidential nature of the data collected, processed, and stored is explained to all new personnel.
2. All access to data management team office space containing data is controlled through a single door, which is locked and only accessible by key or security badge.
3. All participant data uploaded to the central database is encrypted as described above.
4. All participant data stored on Wake Forest School of Medicine computers are likewise encrypted. In addition, all such databases are protected by passwords that must be supplied before the data can be accessed. Passwords are released only to data management team members who have a need to use the particular file and are changed on a regular schedule.
5. All printouts, plots, and reports containing individually identifiable data are produced on printers and plotters within data management team’s secure office space.

Protected Health Information (PHI) such as participant name, addresses, contact information and other identifiers of concern, if collected and data entered is securely stored separately from the main clinical data. Access to these data is limited to a few primary members of the Coordinating Center and only the PID will connect these data, if required.

15.2.6 Records Retention

Documents pertaining to the study should be retained for a minimum of 2 years after the formal discontinuation of POINTER. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed. It is the responsibility of study leadership to inform the PI when these documents no longer need to be retained.

16 ETHICS AND REGULATORY CONSIDERATIONS

16.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP) guidelines, as defined by the International Conference on Harmonization (ICH) Guideline, Topic E6, the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50) – Protection of Human Subjects and Part 56 – IRBs, HIPAA, State and Federal regulations and all other applicable local regulatory requirements and laws.

Study personnel involved in conducting this study will be qualified by education, training and experience to perform their respective task(s) in accordance with GCP.

No study document shall be destroyed without prior written agreement between the POINTER Coordinating Center and the site PI. Should the site PI wish to assign study records to another party or move them to another location, he/she may do so only with the prior written consent of the Coordinating Center.

16.2 Institutional Review Board

Multiple federal agencies have endorsed the use of a single centralized IRB (sIRB) review for multisite research. A single IRB provides a more consistent, efficient process, removes duplicative reviews, and provides for more consistent participant protections. The Wake Forest IRB will serve as the sIRB of record and be responsible for the review, approval and regulatory oversight of POINTER.

Each participating institution must provide all required documents for the review and approval of this protocol and associated informed consent documents and recruitment materials to the Wake Forest sIRB. Any amendments to the protocol or consent materials must be approved before they are placed into use. In the United States, only institutions holding a current US Federal-wide Assurance issued by OHRP may participate (http://www.hhs.gov/ohrp/assurances/).

Subsequent protocol amendments and, when warranted, changes to the informed consent document must be approved by the sIRB. Protocol and informed consent form amendments can be made only with the prior approval of the POINTER Coordinating Center. The investigator may not implement any protocol deviation without prior notification to the Coordinating Center and prior review and documented approval of the sIRB, except where necessary to eliminate an immediate hazard to study participants, or when change(s) involve only logistical or administrative aspects of the trial (ICH 4.5.4). The site PI shall notify the Coordinating Center and sIRB of deviations from the protocol or SAEs occurring at the site, in accordance with local procedures.

16.3 Informed Consent and HIPAA Compliance

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s) and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have IRB approval of the written ICF and any other written information to be provided to participants. Participants and their family members will be given ample opportunity to inquire about the details of the study. Prior

to enrollment in the trial, the written ICF must be signed and personally dated by the participant and by the person who conducted the informed consent discussion. Participants will be provided a copy of the signed ICF.

The informed consent will not only cover consent for the trial itself, but also for the genetic research, biomarker studies, and biological sample storage. The consent for storage will include consent to access stored data and biological samples for secondary analyses. Consent forms will specify that DNA and biomarker samples are for research purposes only; the tests on the DNA are not diagnostic in nature and participants will never receive results.

Consent forms will be developed by the POINTER Coordinating Center in collaboration with the trial leadership. The sample consent form provided to sites will include all of the required elements of informed consent required by the sIRB. The sample consent form will be sent to participating sites where it should be tailored to include site-specific information to meet local IRB regulations. Each site PI, under the guidance of the IRB, is responsible for ensuring that all applicable state laws are met with regards to judgment of competency and the consent form process. Each participating site must maintain IRB-approval, along with other required regulatory records and essential documents.

16.3.1 Participant Confidentiality | HIPAA

Information about study participants will be kept confidential and managed according to the requirements of HIPAA. HIPAA regulations require a signed HIPAA Authorization or informed consent form that includes HIPAA language informing the participant of the following:

- What PHI will be collected from participants in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for use of their PHI

In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. Each site PI, under the guidance of the IRB, is responsible for ensuring that all applicable HIPAA regulations and State laws are met.

16.4 Genetic Research and Storage of Genetic Material

The DNA is banked in locked freezers in the ATRI Biomarker Core laboratory. Sample tubes are bar-coded and linked to PID only and banked without personal identifiers. The presence of the sample is recorded into a computerized inventory database that is managed by ATRI and is encrypted and password protected.

Only DNA from consenting participants will be banked and used to facilitate future research on aging and dementia, particularly in the discovery of genetic polymorphisms that may influence risk of developing AD. Collection of DNA will permit AD investigators to probe genetic polymorphisms as predictors of outcome in future studies. The samples will be stored at ATRI as part of a national biospecimen resource for future investigations.

16.5 Storage of Biospecimen Samples

All biospecimens banked for future AD biomarker research will be shipped to the ATRI Biomarker Core.

Sample tubes will be bar-coded and linked to PID only and banked without personal identifiers. The presence of the sample will be recorded into a computerized inventory database that is managed by the ATRI Biomarker Core and is encrypted and password protected.

16.6 Study Monitoring

Data collection forms and source documents will be reviewed at regular intervals throughout the study to verify adherence to the protocol, completeness and accuracy of the data, and adherence to local regulations on the conduct of clinical research.

The monitoring visits will be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, compliance with regulatory requirements and continued adequacy of the clinical site and its facilities. The site PI will cooperate in the monitoring process by ensuring the availability of source and other necessary documents/records when requested and will promptly address any matters brought to his/her attention by the monitor.

16.7 Duality of Interest

In an environment where scientists may benefit directly or indirectly from commercial ties, the potential to influence scientific objectivity exists. Clinical trials are especially vulnerable to such influences, whether perceived or real. In these circumstances, a potential conflict of interest occurs when there is a divergence between an individual's private interests and his or her professional obligations to the research project, such that an independent observer might reasonably question whether the individual's professional actions or decisions, including the design, conduct, or reporting of the research are influenced or determined by considerations of personal gain, financial or otherwise. Allegations of conflicts of interest threaten the integrity of the scientific community. Policies that promote disclosure of potential conflicts of interest and propose means to manage those conflicts aim to protect the credibility and integrity of research investigators so public trust and confidence in the research results is preserved. The POINTER study team has developed a policy to address potential duality of interest and protect the integrity of decision-making within the trial. This document has been approved by the Executive Leadership and is available on the POINTER website.

17 AUDIT

In accordance with ICH GCP, representatives of Wake Forest University Health Sciences and/or the Alzheimer's Association may select this study for audit. The site PI and study staff are responsible for maintaining the site master file containing all study-related regulatory documentation that will be suitable for inspection at any time by the Coordinating Center, sponsor, its designees, and/or regulatory agencies. Inspection of site facilities (e.g., clinic and community facilities) to evaluate the trial conduct and compliance with the protocol may also occur.

18 PUBLICATION POLICY

The POINTER Emerging Science, Publications and Presentations Core will coordinate dissemination of data from this study. The Core, whose membership will be approved by the POINTER Executive Leadership, includes representation from the study team. The Core will solicit input and assistance from other investigators as appropriate and adhere to documented POINTER publication policies. A separate document outlining policies regarding publications and access to study data has been approved by the Executive Leadership and is available on the POINTER website.

19 ANCILLARY STUDIES

The POINTER study encourages the development of ancillary studies. These are studies that receive support from other funding mechanisms. An ancillary study's objectives are not duplicative of and do not interfere with the POINTER trial but use POINTER participants, samples, and data collected by POINTER. The policies governing ancillary studies are provided as a separate document that has been approved by the Executive Leadership and is available on the POINTER website.

20 SHARING OF FINAL RESEARCH DATA

Data from POINTER will be shared with other researchers pursuant to the 02/26/2003 “Final NIH Statement on Sharing Research Data” (**http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html**).

The NIH and the Alzheimer’s Association endorse the sharing of final research data to serve these and other important scientific goals. To protect participants’ rights and confidentiality, identifiers will be removed from the data before they are shared.

21 TRIAL ORGANIZATION

21.1 Sites

Each Site, which includes the research clinic, consists of an interdisciplinary team of clinical investigators who provide the expertise necessary for the successful implementation and completion of the POINTER protocol. Site responsibilities are listed below.

1. Recruit participants for the trial
2. Confirm eligibility of all participants
3. Implement the interventions in a systematic and standardized fashion consistent with the study protocol
4. Collect high quality data according to the study protocol
5. Make provisions to ensure the safety of trial participants
6. Collaborate in designing and monitoring of the study, including regular attendance at Steering Committee meetings
7. Collaborate in the analysis and dissemination of study results

21.2 Coordinating Center

The Coordinating Center has primary responsibility for overseeing intervention implementation, training and certification of staff for outcomes assessments, monitoring data quality, and analyzing data generated by the sites. Additional responsibilities of the Coordinating Center are listed below.

1. Financial management of the trial, including management of subcontracts with sites
2. Interface with the sIRB that will provide regulatory oversight
3. Prepare the protocol, forms, manuals, and intervention materials (with the aid of the Steering Committee and the Alzheimer’s Association)
4. Develop the study design and analytic plan
5. Work with the investigators in the development and pre-testing of forms and procedures, and assume responsibility for the reproduction and distribution of forms, hardware, and software associated with the data entry system
6. Collaborate in designing and overseeing implementation of the trial interventions
7. Ensure that all clinic staff and Navigators are properly trained and that certifications are

maintained for the duration of their involvement in the study
8. Regularly monitor site performance
9. Organize and oversee procedures to adjudicate cognitive status to identify MCI and dementia
10. Coordinate central resources
11. Manage quality control aspects associated with the collection and management of data
12. Summarize site performance at regular intervals for the Steering Committee and sponsor
13. Provide detailed reports regarding participant recruitment, data collection, and interim results to the Data and Safety Monitoring Board
14. Prepare, in collaboration with the research clinic investigators, manuscripts describing trial results

21.3 Alzheimer's Association

POINTER is sponsored by the Alzheimer's Association. The local Chapters of the Alzheimer's Association will participate in intervention delivery by providing the Navigators who will assist participants in carrying out their intervention activities. Association representatives participate in all phases of planning, scientific design, implementation and communication relating to POINTER, as well as in the general organization and management of the trial.

The Alzheimer's Association reserves the right to terminate or curtail the study (or an individual award) in the event of:

1. A major breach in the protocol or substantial changes in the agreed-upon protocol with which the Association does not agree;
2. Human subject ethical issues that may dictate a premature termination;
3. Substantial shortfall in recruitment and/or retention of participants.

21.4 Other Sponsors and Contributors

POINTER recognizes the important roles that partial sponsorship or other partnerships may play in supporting the development and conduct of the trial, which include the partnership with the YMCA and potential industry sponsors/contributors. A formal policy describing the rules that guide these relationships has been developed and approved by the Executive Leadership and is available on the POINTER website.

21.5 Steering Committee

The Steering Committee is the governing body that provides the leadership for POINTER and establishes scientific and administrative policy for the study. It holds the primary responsibility for developing the trial design and common clinical protocols, recommending appropriate procedures to manage the conduct and monitoring of study operations, review of ancillary studies, preparation of publications, and site-related conflicts that cannot be resolved locally or with Coordinating Center guidance, and reporting the study results. The Steering Committee is comprised of the Site Principal Investigators, core workgroup Chairs, the Principal Investigators of the Coordinating Center, representatives from the Alzheimer's Association, and representatives from the Executive Leadership. Executive level trial oversight by the Steering Committee is outlined in the Steering Committee Charter.

The Steering Committee for POINTER has a Chair and a Co-Chair, chosen from the Executive Committee.

21.6 Executive Committee

The Executive Committee includes all members of the trial's leadership, and others by invitation based on expertise and the needs of the Committee. The Executive Committee is convened to effect management decisions required between Steering Committee meetings, as needed, for efficient progress of the trial. The Executive Committee reports its actions to the Steering Committee on a regular basis. Meetings of the Executive Committee will generally be held by conference call according to a regular schedule. This Committee also develops timelines for the accomplishment of tasks, selects Committee members and chairs, presents information to the Data and Safety Monitoring Board, and develops Steering Committee meeting agendas.

21.7 Other Standing Committees

The POINTER Executive Committee will organize core workgroups and subcommittees of investigators and staff throughout the trial, as needed. Membership will be predicated on nomination from Principal Investigators and approval from the Executive Committee.

21.8 Central Resources

The POINTER study group will develop central laboratories, reading centers, recruitment cores, and repositories as needed for conduct of the study. Investigators and staff from these centers may participate in training and quality control activities but will not participate in policy issues or trial governance. Thus, while these individuals may be invited to attend Committee meetings, they will hold no rights to voting. Individuals from central resource centers may be invited to participate in the publication of POINTER data under the publications policy for the study.

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APPENDIX 1: SCHEDULE OF EVENTS FOR RESEARCH CLINIC STUDY VISITS

Visit	1	2	3	4	5
Visit Name / Month	**Baseline**	**Month 6**	**Month 12**	**Month 18**	**Month 24**
Informed Consent for Enrollment, HIPAA	X				
Review Inclusion & Exclusion Criteria	X				
Demographics Review	X				
Medical History Review	X				
Unmasked Intake Interview		X	X	X	X
Medication Review	X	X	X	X	X
Brief Physical Exam	X				
Vital Signs	X		X		X
Waist Circumference	X		X		X
Weight	X	X	X	X	X
Height	X				
Brief Neurological Exam	X				
Fasting Clinical Blood Labs					
Comprehensive Metabolic Panel (includes Glucose)	X				X
Glucose			X		
HbA1c, Lipid Panel	X		X		X
Hemoglobin/Hematocrit (if unavailable within 6 mos of baseline)	X				
Non-Fasting Clinical Blood Labs					
HbA1c, Lipid Panel		X		X	
12-Lead Resting ECG	X				
Blood Collection for APOE Genotyping and DNA Extraction and Storage	X				
Fasting Blood Collection for Banking	X		X		X
AE Monitoring at Clinic		X	X	X	X
POINTER Modified Neuropsychological Test Battery (Free and Cued Selective Reminding Test, Story Recall, Visual Paired Associates, Number Span, Word Fluency, Digit Symbol Substitution Test, Trail-Making Test)	X	X	X	X	X
Digital Cognition Technologies Clock Drawing	X	X	X	X	X

Visit	1	2	3	4	5
Visit Name / Month	**Baseline**	**Month 6**	**Month 12**	**Month 18**	**Month 24**
C-3: Cogstate Detection, Identification, One Back, One-Card Learning, Face Name Associative Memory Exam, Behavioral Pattern Separation of Objects	X		X		X
BrainHQ Assessment	X	X	X	X	X
MMSE	X	X	X	X	X
CDR	X		X		X
IADL	X		X		X
ECog (short form)	X		X		X
SF-36, EQ5D	X		X		X
Cognitive Function Instrument	X		X		X
GDS	X	X	X	X	X
Sleep Questionnaire	X	X	X	X	X
Lifestyle Questionnaires: Physical Activity, Sitting Habits, Rush Food Frequency, Cognitive Activity	X	X	X	X	X
400 m Walk Test	X		X		X
Short Physical Performance Battery	X		X		X
Obtain Signed PCP Authorization Letter	X				
Randomization	X				
Obtain Participant Feedback & Exit Interview					X