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

Short Study Name:

POINTER-zzz

Protocol Version 1.1
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ABBREVIATIONS

AB	**AMYLOID BETA**
AD	**ALZHEIMER'S DISEASE**
AE	**ADVERSE EVENT**
AHI	**APNEA-HYPOPNEA INDEX**
ANCOVA	**ANALYSIS OF COVARIANCE**
BMI	**BODY MASS INDEX**
BWH	**BRIGHAM AND WOMEN'S HOSPITAL**
CPAP	**CONTINUOUS POSITIVE AIRWAY PRESSURE**
CVD	**CARDIOVASCULAR DISEASE**
DSMB	**DATA SAFETY AND MONITORING BOARD**
FINGER	**FINNISH GERIATRIC INTERVENTION STUDY TO PREVENT COGNITIVE IMPAIRMENT AND DISABILITY**
HIPAA	**HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT**
ITT	**INTENT TO TREAT**
MCI	**MILD COGNITIVE IMPAIRMENT**
ODI	**OXYGEN DESATURATION INDEX**
PET	**POSITRON EMISSION TOMOGRAPHY**
SAE	**SERIOUS ADVERSE EVENT**
SPO_2	**OXYHEMOGLOBIN SATURATION**
SD	**STANDARD DEVIATION**
SDB	**SLEEP DISORDERED BREATHING**
SG	**SELF-GUIDED**
STR	**STRUCTURED**
T2D	**TYPE 2 DIABETES**
WHISPER	**WOMEN'S HEALTH INITIATIVE SLEEP HYPOXIA EFFECTS ON RESILIENCE STUDY**

PROTOCOL SYNOPSIS

STUDY TITLE	POINTER-zzz: Sleep Ancillary to U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk of Alzheimer's Disease
STUDY NAME	U.S. POINTER Sleep Ancillary Study
ABBREVIATED STUDY NAME	POINTER-zzz
PRINCIPAL INVESTIGATORS	MPI: Kathleen Hayden, PhD; Laura Baker, PhD
STUDY SPONSOR	National Institute on Aging
STUDY DESIGN	Ancillary study to the U.S. POINTER lifestyle intervention trial that adds in-home objective sleep assessments in approximately 700 older parent trial participants at baseline, and at Months 12 and 24.
DURATION OF STUDY PARTICIPATION	At least 24 months (duration of the parent trial)
SUMMARY OF KEY SLEEP ASSESSMENTS	1. Sleep Questionnaires: records rest/wake times, and use of sleep medications, alcohol, tobacco, caffeine on nights that sleep assessments are conducted. 2. WatchPAT™: wrist-worn device that captures continuous overnight measurement of oxygen desaturation, pulse tonometry and heart rate using finger pulse oximetry. Key measurements include the apnea-hypopnia index (AHI) and the oxygen desaturation index (ODI). 3. ActiGraph Link™: measures total rest-wake activity using triaxial accelerometry for 6 days and nights, Key measurements include sleep duration, sleep latency, and sleep fragmentation.
INCLUSION/ EXCLUSION CRITERIA	• All participants must be enrolled in the parent trial. • Hearing ability must be adequate to complete a telephone interview.
PRIMARY OUTCOME MEASURES	• Oximetry: 4% ODI • Actigraphy: Sleep fragmentation (assessed with K_{RA} metric to quantify minute-to-minute rest-activity transitions during sleep)
SECONDARY OUTCOME MEASURES	• 3% ODI • 3% and 4% AHI • Blood oxygen desaturation below 90% (mean level, % time) • Total sleep-wake time (using Cole-Kripke algorithm) • Total sleep duration (mean, SD, midpoint) • Wake time after sleep onset (min)

1 INTRODUCTION

One-third of Americans are currently projected to be obese,[1] and one-third are projected to have type 2 diabetes (T2D) by 2050;[2] while over 66% of Americans aged 60+ currently have hypertension.[3] Together, sedentary behaviors, obesity, depression, and cardiometabolic disease (e.g., obesity, diabetes, and hypertension) account for a substantial amount of Alzheimer's disease (AD) risk. Lifestyle modification targeting these conditions has the potential to prevent >30% of AD cases.[4] This estimate does not include the added AD risk associated with sleep disordered breathing (SDB). Today, over 60% of older adults (aged 50-70 years) have at least mild SDB.[5] Sleep disturbance is both a symptom and a consequence of cognitive impairment.[6,7] The risk of cognitive impairment may be reduced and cognitive decline may be attenuated through improved sleep.[8] A 2017 meta-analysis of sleep studies suggests that individuals with sleep disturbances have an estimated risk for AD that is 1.55 times higher than those without sleep disturbances, and the population attributable risk for AD due to poor sleep is as high as 15%.[9] This report likely underestimates the true problem given that many of the included studies in the meta-analysis relied on self-report rather than objective sleep measures. POINTER-zzz, the Sleep Ancillary study to the large-scale randomized controlled trial, U. S. Study to PrOtect Brain Health through Lifestyle INTErvention to Reduce Risk (U.S. POINTER), will test whether intensive lifestyle modification can improve sleep in older adults at-risk for cognitive decline and AD, and will examine whether intervention-related improvements in cardiometabolic health and sleep predict 2-year improvements in cognitive function.

1.1 U.S. POINTER Parent Trial Summary

U.S. POINTER was launched to test the generalizability of the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) findings in a geographically and racially diverse cohort of Americans. U.S. POINTER, uses a similar multimodal intervention approach that has also proven successful for cardiovascular disease and diabetes prevention. The parent study will investigate whether random assignment to a Self-Guided (SG) versus a Structured (STR) lifestyle intervention influences cognitive trajectory over 2 years in 2000 older adults (age 60-79 yrs). POINTER participants are cognitively normal but *at-risk* for cognitive decline and dementia due to factors such as sedentary lifestyle, poor diet, suboptimum cardiovascular health, and family history of significant memory impairment. Participants assigned to the SG arm attend facilitated group meetings 2-3 times per year for education and support, and complete blood testing every 6 months and an annual physical exam. Participants assigned to the STR arm complete a more intensive lifestyle intervention that includes structured physical and cognitive exercise programs, a modified Mediterranean diet, and frequent physical exams, blood testing, and health coaching for cardiometabolic risk management. Intervention effects on 2-year trajectories of a global cognitive composite score and other outcomes are assessed at 6-month intervals.

1.2 U.S. POINTER Sleep Ancillary Study Summary

POINTER-zzz adds in-home objective sleep assessments to the parent trial to examine the effects of lifestyle modification and cardiovascular risk management on sleep disturbances that have been linked to cognitive decline and AD and that may improve with the POINTER intervention. In older adults, chronic sleep disturbances marked by SDB and sleep fragmentation are associated with impaired hippocampal functioning, greater brain beta-amyloid (Aβ) burden, and increased risk for AD and related disorders. These and other sleep abnormalities are also associated with reduced cardiometabolic health. Although there is some evidence to suggest that diet, exercise, and cardiovascular risk reduction can improve sleep and that improved sleep benefits cognitive function in older adults, these effects have not been confirmed in a large-scale rigorous clinical trial. POINTER-zzz will leverage rich resources provided by the parent trial to examine the effects of intensive lifestyle modification on SDB, sleep fragmentation and duration, and other objective measures of sleep quality. Sleep assessments will be completed at baseline, and at Months 12 and 24 in a subset of approximately 700 parent trial participants (~350 per intervention arm) at all 5 clinical sites using wrist-worn devices for continuous overnight measurement of oxygen desaturation, pulse tonometry, and heart rate using finger pulse oximetry (WatchPAT™), and 6-day/night measurements of total rest-wake activity using actigraphy (ActiGraph Link™).

1.2.1 Primary Aim

Aim 1: Test whether a 2-year intensive lifestyle intervention improves SDB (using oximetry to measure oxyhemoglobin desaturation levels) and sleep fragmentation (using actigraphy to measure K_{RA}) in approximately 700 older adults from the parent trial cohort (60-79 years old), who are all at increased risk for cognitive decline.

1.2.2 Secondary Aims

Aim 2: Assess the degree to which longitudinal and intervention effects on sleep (hypoxemia, fragmentation, duration and other objective measures) predict changes in cognitive trajectory (based on composite scores for global cognitive function, executive function, and episodic memory). The potential impact of improved cognitive function on sleep quality will also be assessed.

Aim 3: Examine whether longitudinal and intervention effects on sleep differ by subgroups defined by baseline characteristics (age, sex, cognitive function, cardiovascular Framingham Risk Score, ODI, sleep fragmentation), genetic risk (*APOE* genotype) and intervention adherence. Intervention effects on sleep will also be examined relative to other parent trial outcomes (e.g., cardiovascular events, physical function, quality of life, health care utilization).

2 BACKGROUND AND SIGNIFICANCE

2.1 Rationale for Studying the Effects of Sleep Disturbances

Sleep disorders in older adults are common, yet frequently undiagnosed and untreated.[10-12] These disturbances are attributable to numerous factors, including underlying medical or psychiatric conditions, medication use, environmental influences, irregular sleep schedules and specific disorders such as insomnia or SDB. SDB leads to nightly, recurring acute hypoxemic episodes and sleep disruption, which can trigger a cascade of pathophysiological responses that can promote adverse health conditions, particularly in older adults who are at higher risk for disease and for chronic sleep disturbance. Over 60% of older adults have at least mild SDB,[5] and chronic exposure to SDB in epidemiological studies of predominantly middle-aged and white individuals has been associated with increased risk for mortality,[13-16] diabetes,[17-19] cardiovascular disease (CVD),[20-22] cancer,[23,24] and cognitive decline.[25,26] The results of a smaller study of older predominantly white women suggest that SDB may forecast significant cognitive impairment a few years later.[26] To date, the impact of SDB on health and cognitive trajectories has not been adequately examined in those who are at increased risk for vascular disease[27-29] and cognitive impairment associated with AD.[30]

Despite the growing number of epidemiological studies linking SDB and risk for CVD, cognitive decline and impairment, and all-cause mortality, only limited work has been done to investigate whether non-pharmacological interventions can improve sleep, and the potential impact of improved sleep on cognitive function in older vulnerable adults. So far, the results from randomized controlled clinical trials to treat sleep apnea have been equivocal. Some studies administering CPAP treatment for sleep apnea report small improvements in cognition[31-33] and gray matter volume,[34] while others report no or limited improvement[35] (reviewed[36]). Although CPAP as an intervention may be highly effective for sleep apnea, only a small proportion of individuals choose to use this treatment option. A few clinical trials have examined the effects of a lifestyle intervention on SDB using objective sleep assessments, but the impact of objectively-measured SDB and other negative sleep exposures on cognitive decline and AD in medically- and cognitively-vulnerable older adults has not been adequately examined. POINTER-zzz will build on the work described above by obtaining in-home objective and validated sleep assessments using oximetry and actigraphy in the context of a large multi-site trial of lifestyle intervention that includes cardiometabolic risk

management, which could have important consequences for the prevention of AD in older *at-risk* individuals.

2.2 Adverse Sleep Exposures and Cognitive Impairment

Chronic sleep disturbances, particularly SDB, can have adverse effects on cognitive function and increase risk of cognitive decline and impairment – including MCI and AD.[37-39] Performance on cognitive tests is lower for community-dwelling older adults with SDB than for those without the disorder,[40] with adverse effects most consistently reported for executive function.[41,42] SDB is associated with reduced gray matter volumes in the hippocampus and other regions supporting memory and executive function.[43-45] To date, only a handful of studies examining the role of SDB on cognition have focused solely on older adults, and of those, most were relatively small and the methods, variable.[46] Despite evidence that the impact of SDB may be modified by genetic and other demographic or medical risk factors, none of these studies had a sufficiently large sample to robustly examine important subgroup differences.

2.3 Changes in Sleep Precede Cognitive Impairment and Forecast the Development of AD

Lower concentration of Aβ in cerebrospinal fluid (CSF) or increased Aβ binding as measured by brain PET imaging, signifying increased deposition and thus increased AD risk, are associated with poorer sleep in non-demented older adults.[47,48] Further, better sleep quality, indicated by lower levels of sleep fragmentation, is protective against *APOE* ε4 effects on AD-related cognitive decline and neuropathological changes.[8] In experimental studies, although unrestricted sleep favorably alters CSF Aβ levels in cognitively normal middle-aged adults, a single night of sleep deprivation can neutralize this effect.[49] This finding likely has important implications for sleep-dependent Aβ processing and thus risk of subsequent AD, particularly in light of recent reports that sleep may be essential for Aβ clearance.[50] Given the potentially potent association between SDB and other sleep exposures with cognitive impairment and neuropathological processes, timely detection of disturbances and identification of effective sleep-restoring interventions could have important consequences for preventive care in older adults at increased risk for cognitive decline and AD.

3 POTENTIAL RISKS AND BENEFITS

3.1 Potential Benefits

Sleep disorders in older adults are extremely common, yet frequently undiagnosed and treated. The prevalence of sleep disorders increases with advancing age, with more than 50% of adults over the age of 65 typically reporting some form of chronic sleep-related disturbance. The high prevalence of undiagnosed sleep disorders (>85% with obstructive sleep apnea[51]) that likely confer potent adverse effects on health and cognitive status, particularly among older adults, underscores the importance of early identification of sleep disturbances. Moreover, the identification of simple, accessible, and objective tools for use in a growing medically- and cognitively-vulnerable older cohort, and the need to test the ability of these tools are critical not only to identify clinically-important sleep disturbance-related outcomes but also response to risk-modifying interventions.

POINTER-zzz provides an unparalleled opportunity to test the effects of lifestyle intervention on sleep abnormalities that have been linked to cognitive decline and AD in a well-characterized and diverse cohort of *at-risk* older adults. The results may identify an effective strategy for improving sleep that could have important consequences for the prevention of AD and other related disorders.

3.2 Potential Risks and Protection against Risks

3.2.1 Potential Risks

There are minimal risks associated with participation in POINTER-zzz. It is possible that the sleep assessment may indicate clinically significant hypoxemia (<90% oxyhemoglobin saturation for more than 10% of sleep), which will be identified by the Brigham and Women's Hospital (BWH) Sleep Reading Center (SRC). Participants may become alarmed when they are notified of this condition.

3.2.2 Protection against Risks

If the sleep assessment indicates clinically significant hypoxemia, the participant will receive a phone call by clinic staff and a letter describing the results. A similar letter may be sent to the primary care provider at the participant's discretion. Safety monitoring will be provided by the U.S. POINTER Data Safety and Monitoring Board (DSMB).

NIH guidelines will be followed to protect participant confidentiality. The data will be collected for research purposes only, and will be managed by the parent trial Data Coordinating Center (DCC) using all established database protections.

4 SAMPLE SIZE AND STATISTICAL PLAN

4.1 Power and Sample Size Determination

The power estimations for Aim 1 are based on the analytical approach – ANCOVA with repeated measures model – to compare average difference in sleep (measured using apnea-hypopnea index [AHI], sleep fragmentation, sleep duration) between SG and STR intervention groups over a period of 2 years, for a two-sided test at significant level of 0.025 (two outcomes with Bonferroni adjustment). The target sample size for this ancillary study is 700 participants, with 350 per arm.

Using oxygen desaturation index (ODI) and AHI data from the Sleep AHEAD study,[52] 1-year differences in baseline standard deviation (SD) units for the intensive lifestyle intervention and diabetes support and education groups were 0.58 and 0.45, respectively. In Baker's WHISPER study, of over 4000 sleep studies completed so far, 91% were deemed valid by the BWH Sleep Data Processing Center (invalid assessments are repeated, which has reduced sleep data loss to less than 3%). We simulated power calculations based on various assumptions of detectable effect size (average difference in SD units between Sleep AHEAD intervention arms), within-subject correlations for the repeated measures on sleep measures, and loss to follow-up rate. Based on these data, if loss to follow-up is 15% and within-subject correlation is 0.3, power to detect a group difference of 0.20 SD is expected to be 87%. Of note, this estimate may be an underestimate given that Sleep AHEAD included only adults with type 2 diabetes (not true of POINTER-zzz).

4.2 Statistical Analysis Plan

The general approach for statistical analysis is described below. A detailed statistical analytic plan will be completed and approved by the parent trial biostatistical team prior to data analysis.

4.2.1 Analyses to Address Primary Aim

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 will compare group differences in SDB (using ODI) and sleep fragmentation (using K_{RA}) at Month 12 and Month 24 using analysis of covariance (ANCOVA) with repeated measures. Site, age and baseline BMI will be included as covariates in the model. Within-subject correlation will be parameterized using a compound symmetry structure. Intervention arm by year interactions will also be examined in follow-up analyses.

4.2.2 Analyses to Address Secondary Aims

For **Aim 2**, we will examine whether intervention-related changes in sleep predict change in cognitive function using general linear models. For these analyses, we will examine associations between 2-year intervention effects on sleep and global and domain-specific cognitive composite outcomes obtained in the parent trial. We will also examine whether longitudinal change (without regard to intervention assignment) in sleep predicts change in cognitive composite outcomes. We will also explore the potential impact of improved cognition on sleep using a similar general linear models approach.

For **Aim 3**, we will examine whether intervention effects on sleep vary by subgroups defined by baseline characteristics (age, sex, cognitive function, cardiovascular Framingham Risk Score, ODI, sleep fragmentation), genetic risk (*APOE* genotype), and intervention adherence using a similar model as that described to address Aim 1. Omnibus type 1 error will not be controlled in these exploratory analyses. Results will be reported as estimates and 95% confidence intervals. In addition, intervention effects on sleep will be examined relative to other parent trial outcomes (e.g., cardiovascular events, physical function, quality of life, health care utilization) using general linear models or survival analysis.

5 STUDY POPULATION

Sleep data will be collected in a subset of approximately 700 parent trial participants.

5.1 Inclusion and Exclusion Criteria

5.1.1 Exclusion Criteria

Hearing impairment that significantly interferes with completing a telephone interview.

5.1.2 Inclusion Criteria

- Parent trial inclusion criteria apply.
- Participants must identify a local friend or family member who could help track down the sleep assessment devices (WatchPAT, ActiGraph Life) if needed after the sleep assessments so that they can be successfully returned to the clinic. If the parent trial Study Partner lives in same city as the participant, then the Study Partner may fill this role.

5.2 Recruitment and Screening

U.S. POINTER participants will be approached to assess their interest in POINTER-zzz participation at the parent trial baseline visit. Interested participants will receive an informational brochure to take home and a follow-up phone call to answer questions. Participants with continued interest will be consented at the second parent trial baseline visit, and the first sleep assessment will be scheduled.

5.3 Inclusion of Women and Minorities

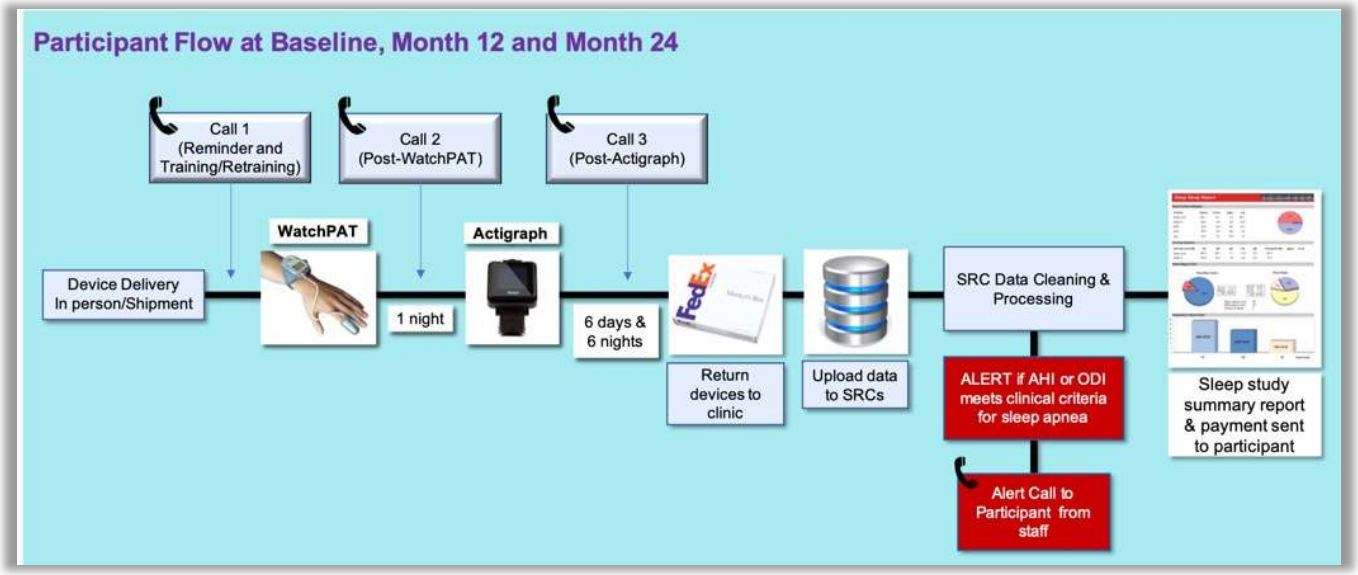
No candidate will be excluded for reasons of sex, race, or ethnic group. Consistent with enrollment goals for the parent study, the POINTER-zzz study will target enrollment of 50% women, and a minimum of 23% from racial/ethnic minority groups, which reflects the demographics of the U.S. population as reported by the Census Bureau in 2016.

6 SLEEP ASSESSMENTS

6.1 Sleep Assessment Procedures

A schematic of the sleep assessment procedures is provided in **Figure 1**. At each of the baseline, Month 12, and Month 24 clinic visits, participants will receive training (or re-training) to correctly use each of the two sleep assessment devices. Participants will be sent home with a WatchPAT (to obtain 1 night of oximetry data) and an Actigraph Link (to provide 6 days and nights of actigraphy data), printed instruction cards that review how to use each of these devices and a printed multi-night sleep diary. If training cannot be provided in person at the clinic, then the sleep assessment devices will be shipped to consenting participants and the instructions will be reviewed over the phone with a study coordinator. One night of oximetry provides reliable estimates of SDB given little night-to-night variability in the AHI/ODI.[53] The longer collection period for actigraphy is needed given normal higher night-to-night variability in these data. A study coordinator will call participants before and after each device is used to answer questions, to ensure that the devices are worn and sleep diaries are completed, and to facilitate return shipping of the devices and diaries to the clinic. The participant may also return the devices and diaries to the clinic in person. Once the devices are received by the clinical site, the data are electronically uploaded to the appropriate Sleep Reading Center (oximetry to Brigham and Women's Hospital; actigraphy to California Pacific Medical Center) using device-specific software and a secure FTP server. Dates of the sleep assessment, and the participant's weight, height and sex are also provided to the Sleep Reading Centers. After the data are cleaned and processed by the SRCs, the clinical site will send payment and a letter to participants describing their results.

Figure 1.



6.2 Outcome Measures

6.2.1 Pulse Oximetry

Figure 2. WatchPAT

Recent technological advances in sleep apnea screening have greatly reduced the cost and participant burden of collecting measures of nocturnal hypoxemia such as the oxygen desaturation index (ODI) and the apnea-hypopnea index (AHI). The WatchPAT is a small, low-burden wrist-worn device (**Figure 2**) that includes a wrist-band, finger sensor and chest sensor. Data capture is automatically initiated when a finger is inserted into the finger

sensor. The device is used to provide continuous high-resolution sampling of pulse oxyhemoglobin saturation (SpO2) and accelerometry throughout 1 night of sleep. The WatchPAT chest sensor is secured with surgical tape to the upper sternum to provide continuous measurement of chest movement that may indicate airway obstruction. The BWH SRC will clean and process these data using established protocols, and will prepare a dataset for analysis. Sleep apnea alert values will be identified and communicated to the clinical sites, to participants, and to the Coordinating Center using standard protocols of our prior studies. The sleep apnea alert thresholds include:

- Oxygen saturation <85% for >10% of total sleep time
- AHI >50

6.2.2 Quality Assurance

The BWH SRC has supported data collection activities involving over 50,000 research sleep assessments from diverse individuals participating in major cohort studies and clinical trials. The BWH SRC was established in 1994 to support the first large-scale multicenter sleep cohort study, the Sleep Heart Health Study, and has collaborated with Wake Forest on other large sleep studies in older adults (e.g., WHISPER). For these studies, inter- and intra-scorer reliability for key sleep variables exceeds 0.94.

For POINTER-zzz, a single, registered polysomnologist will review all oximetry records to identify artifacts and annotate the sleep period based on changes in heart rate and actigraphy data. Quarterly, 5% of the records will be reanalyzed to assess scoring reliability and to identify need for re-training. The minimal criteria for study acceptability will include at least 4 hours of recorded data during the sleep period. The raw oximetry data can be analyzed to select ODI at the 3% criterion (i.e., 3% drop in SpO2 for >10s) as well as the 4% criterion. ODI, the number of SpO2 dips per hour of sleep, will serve as the primary hypoxemia index – as the literature supports the use of this key exposure as a salient predictor of CVD and cognitive decline. Our primary predictor will be 4% ODI, as this has the strongest relationship to clinical outcomes, is more specific for significant SDB, and accurately quantifies intermittent hypoxemia. Secondary predictors will include 3% ODI, % time with SpO2 <90%, 3% and 4% AHI, and mean baseline and nocturnal SpO2.

6.2.3 Actigraphy

Actigraphy is used to estimate sleep-wake periods over consecutive 24-hour periods, providing measures of sleep fragmentation, duration and other activity-based metrics. Although less accurate than EEG monitoring, enhanced reliability is achieved by multiple nights of recording per individual. Wrist-worn actigraphy will be collected using the ActiGraph Link (ActiGraph, Inc., **Figure 3**). The participant will be instructed to place the watch-like device on the non-dominant wrist and wear it continuously for 6 days and 6 nights. The ActiGraph has a validated tri-axial accelerometer and integrated gyroscope and magnetometer to capture absolute position and rotation information. The data can be readily downloaded for additional analyses and application of other algorithms (e.g., circadian rest-activity rhythms, sleep fragmentation).[54,55]

Figure 3. ActiGraph Link

6.2.4 Sleep Diary

Participants will complete a diary following each night of the sleep assessment that will include questions to document sleep/wake times; difficulty falling asleep; pain while sleeping; use of sleep-aid medications, and use of alcohol, caffeine or tobacco in the 4 hours preceding sleep.

6.3 Temporary Discontinuation

Temporary discontinuation of study assessments is treated differently than study withdrawal (see Section 7). In the event of temporary discontinuation due to circumstances such as travel or unavailability, a study

coordinator will work with the participant to schedule the sleep assessment in a timely manner. Temporary discontinuation of parent trial activities and discontinuation from POINTER-zzz activities are independent. Specifically, sleep assessments may continue in the event of temporary intervention discontinuation. Decisions regarding continuation and discontinuation in the parent and ancillary studies are made on a case-by-case basis by the Coordinating Center, in collaboration with the ancillary study and Site PIs. If the participant discontinues the POINTER intervention but agrees to continue with parent trial assessments, the participant will be permitted to remain in POINTER-zzz.

Reason(s) for temporary POINTER-zzz discontinuation will be captured in the appropriate case report form (CRF) and coded as follows:

- Hospitalization
- Participant or family emergency
- Travel outside the country

7 STUDY WITHDRAWAL

Participants may withdraw their consent to participate in POINTER-zzz at any time. When a participant withdraws from the ancillary study, a Study Withdrawal Form will be completed. If a POINTER-zzz participant withdraws consent for the parent trial, this participant will also be withdrawn from the ancillary sleep study. Participants who withdraw from the parent trial but agree to an early termination outcomes assessment visit will also be offered an early termination sleep assessment.

Reasons(s) for study withdrawal will be coded as follows:

- Participant is unwilling or unable to participate
- U.S. POINTER or POINTER-zzz are terminated
- Lost to follow-up: participant could not be recalled to the clinic for follow-up assessments
- Death

8 PERSONNEL REQUIREMENTS

8.1 Coordinating Center Personnel

- POINTER-zzz Coordinating Center Project Manager: The CC Project Manager is responsible for ensuring that the sleep assessments are carried out at each site as per protocol, for management of accounting, subcontracts and equipment acquisitions, and for oversight and tracking of IRB-related activities.The CC Project Manager will also oversee sleep data monitoring at clinical sites and will provide support as needed to POINTER-zzz site Study Coordinators.

8.2 Site POINTER-zzz Study Personnel

- U.S. POINTER Site Principal Investigator: The Site PI is responsible for overseeing all POINTER-zzz ancillary activities at the site. The Site PI will work with the POINTER-zzz site Study Coordinator to ensure that sleep assessments are carried out according to protocol.
- U.S. POINTER Site Project Manager: The Site Project Manager oversees all day-to-day participant activities for the parent trial and ancillary studies. The Site Project Manager will supervise the POINTER-zzz Study Coordinator to help ensure that sleep assessments are appropriately integrated within parent trial activities.

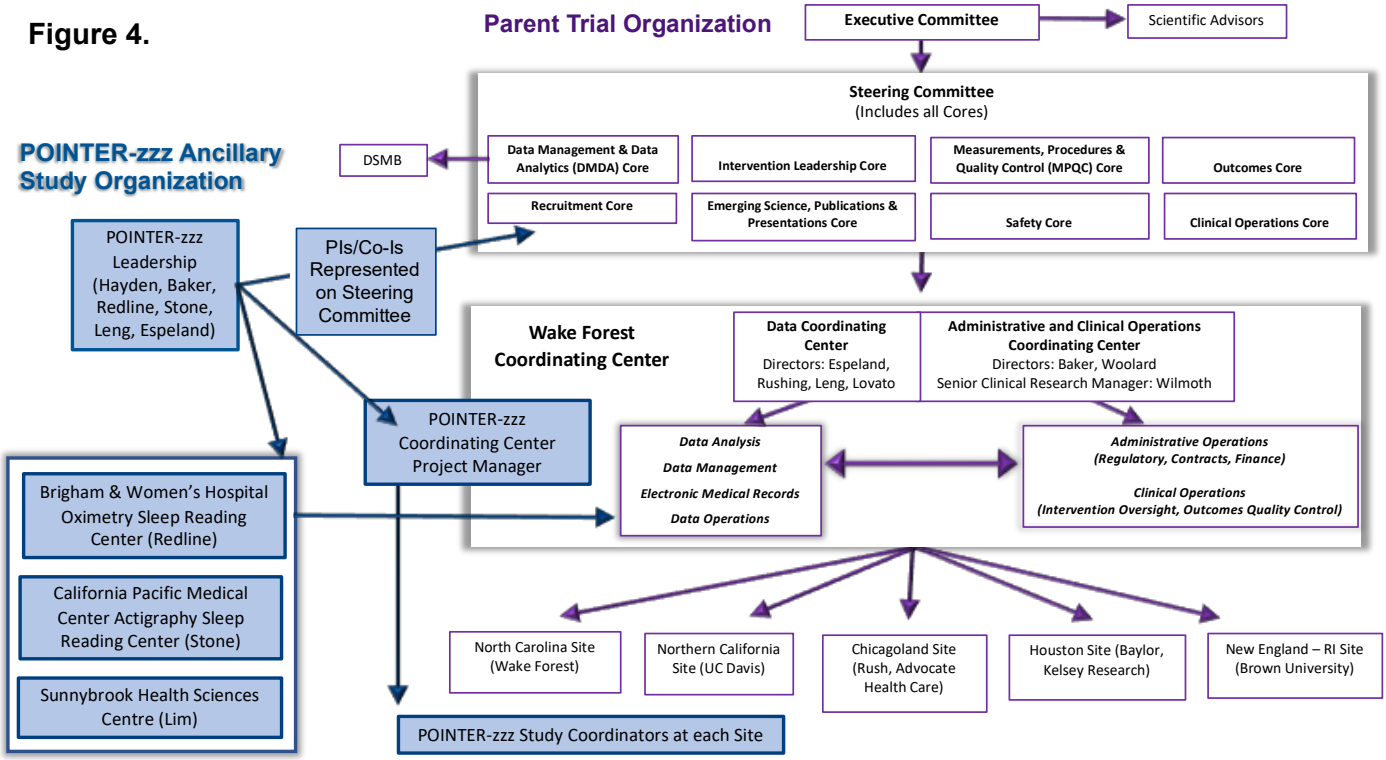
- POINTER-zzz Site Study Coordinator: The Study Coordinator is supervised by the parent trial Project Manager and the Site PI. The Study Coordinator is responsible for carrying out day-to-day POINTER-zzz study activities including consenting, scheduling, participant training and communication, device management, sleep assessments, data management and tracking. The Study Coordinator serves as the main liaison between the site and the Coordinating Center.

9 POINTER-zzz INTEGRATION WITH THE PARENT TRIAL

9.1 Study Organization

Ancillary study organization relative to that for the parent trial is depicted in **Figure 4**. Ancillary study leadership includes the PIs (Hayden, Baker), sleep expert co-investigators (Redline, Stone), Co-Investigators (Molina-Henry, Leng, Espeland). In addition, Dr. Lim of the University of Toronto Sunnybrook Health Sciences Centre will provide additional actigraphic data processing expertise. Baker and Espeland are PIs of the parent trial and its Coordinating Center. Sleep experts Stone and Redline currently collaborate with Baker on another large national sleep and cognition study in older adults. Hayden and Espeland co-PI a large prospective observational study focused on lifestyle and metabolic disease in older adults. This overlap in investigator teams between POINTER-zzz and other ongoing studies provides a solid foundation for POINTER-zzz leadership.

Figure 4.



POINTER-zzz Integration with Parent Trial Leadership

Ancillary study investigators are members of the parent trial Steering Committee that meets monthly to discuss leadership issues related to trial conduct. The Steering Committee includes several Core Workgroups that focus on specific aspects of the trial, and POINTER-zzz investigators are members on one or more of these Cores that relate to aspects of POINTER-zzz conduct. All major scientific decisions for the parent trial and its ancillary studies will be determined by majority vote of the Steering Committee.

POINTER-zzz Integration with the Parent Trial Coordinating Center

The Coordinating Center holds the primary responsibility for ensuring proper regulatory oversight, setting up and managing subcontracts with sites, overseeing implementation of all study procedures including intervention, outcomes assessments, training and certification of staff, and data monitoring, tracking and analysis. A POINTER-zzz Coordinating Center Project Manager will work closely with other CC staff to ensure seamless integration of POINTER-zzz procedures with those of the parent trial at the clinical sites. The CC Project Manager will also serve as the liaison with Sleep Reading Centers to resolve issues as they arise and to oversee timely communication with participants when their WatchPAT data indicates possible sleep apnea.

9.2 Schedule of Sleep Assessments

Sleep assessments will be completed at baseline and just prior to or following the Month 12 and Month 24 clinic visits.

9.3 Masking

Participants enrolled in POINTER-zzz, regardless of intervention group assignment, will complete sleep assessments.

9.4 Study Coordination

POINTER-zzz will be coordinated by the U.S. POINTER Coordinating Center to facilitate efficient use of study resources, data security and data sharing.

9.5 U.S. POINTER Coordinating Center

The parent trial CC is comprised of two branches, the Administrative and Clinical Operations Coordinating Center (ACOCC) and the Data Coordinating Center (DCC).

9.5.1 Administrative and Clinical Operations Coordinating Center

The ACOCC will oversee operations related to participant-facing POINTER-zzz activities. Examples of relevant operations are provided below.

1. Finances, including development and management of subcontracts with sites.
2. Regulatory, including development of IRB applications and tracking of approvals.
3. Training and certification of study coordinators to properly carry out the POINTER-zzz protocol.
4. Safety monitoring, including the reporting of sleep apnea alerts to participants, and of protocol deviations and adverse events to the IRB.
5. Site auditing.

9.5.2 Data Coordinating Center

The DCC will carry out data-related operations for POINTER-zzz as outlined below.

1. Forms development for data collection and tracking.
2. Tracking of sleep assessment devices and completed assessments.
3. Monitoring site performance (e.g., recruitment, sleep assessment completion rates, sleep data validity rates).
4. Store and analyze sleep data provided by the SRCs.
5. Generate reports as requested for the parent trial Steering Committee and DSMB, and for the NIA.
6. Develop a web-based data system for data capture, secure storage, reporting and disaster recovery.

7. Ensuring confidentiality of participants' Protected Health Information throughout the lifespan of data collection, storage and sharing.
8. Coordinate sharing of data with other parent trial ancillary studies for operational, safety, and scientific purposes, and with national databases for future scientific investigation.

9.6 POINTER-zzz Clinical Sites

Personnel at each site that will assist with POINTER-zzz protocol implementation include parent trial personnel (Site PI, Project Manager) and the POINTER-zzz Study Coordinator. Site responsibilities to support POINTER-zzz are listed below.

1. Recruit and confirm eligibility of participants.
2. Obtain informed consent from interested parent trial participants.
3. Train participants to use the sleep assessment devices and to accurately complete the Sleep Diaries.
4. Clean and maintain sleep assessment devices.
5. Ensure the return of sleep assessment devices and questionnaires from participants.
6. Collect and upload oximetry, actigraphy, sleep questionnaire and self-report data according to protocol.
7. Mail sleep assessment results and payments to participants.
8. Mail sleep assessment results to participants' providers when appropriate to do so.
9. Ensure the safety of participants and report SRC-generated alerts to participants as needed.

9.7 Sleep Reading Centers

Sleep data will be uploaded to Sleep Reading Centers (SRCs) for cleaning, processing, and preliminary analysis using a secure server and dedicated device-specific software. Oximetry data will be uploaded to BWH (Dr. Redline) and actigraphy data will be uploaded to California Pacific Medical Center (Dr. Stone) and the University of Toronto (Dr. Lim). Analysis-ready datasets will be created by the SRCs and shared with the POINTER CC for analysis.

10 SAFETY MANAGEMENT

10.1 Potential Risks

POINTER-zzz will pose minimal risk. Participants may experience minor skin irritation due to friction that could occur when wearing a device or when medical tape that holds wires in place are removed.

10.2 Sleep Apnea Alerts and Reporting

Sleep apnea alerts will be issued for participants if the sleep assessment indicates clinically significant hypoxemia (<90% oxyhemoglobin saturation for more than 10% of sleep), identified from the WatchPAT data by the BWH SRC. In the event an alert is generated, the BWH SRC will contact the POINTER-zzz Project Manager who will log this event in the database and contact the site Study Coordinator. The site Study Coordinator will call the participant and will also send a summary of the sleep results that the participant can share with his/her health care provider. If the participant has granted the site permission to send the sleep report directly to the provider, the site Study Coordinator will do this as well.

10.3 Adverse Events and Serious Adverse Events: Definitions and Reporting

In POINTER-zzz, adverse events (AE) are defined as clinically relevant unfavorable or unintended health events that occur during the sleep assessment whether they resulted in hospitalization or met other criteria for reporting as SAEs. Expected risks described in the consent form, such as mild skin irritation at the site

of the chest sensor, finger probe or writstband, or discomfort sleeping while wearing a device will be recorded and reported to the DSMB but not logged as AEs. A sleep apnea alert (indicating more severe apnea) will only be reported as an AE if it leads to the discontinuation or termination of the intervention. All AEs will be classified using MedDRA coding.

Serious Adverse Events (SAEs) are defined 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 include: 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.

Adverse events and serious adverse events will be recorded on the electronic AE Report Form per study instructions. AEs reported after informed consent must be recorded on an AE Report Form and entered in the central database accessed through the study website. All completed AE Report forms will be reviewed for completeness by the parent trial Safety Officer to ensure that documentation of each event is adequate to permit accurate inferences regarding causation (e.g., temporal associations, onset, course, response to patient or physician intervention, alternative etiologies) and severity.

SAEs must be entered in the central database within 72 hours of learning of the event, and reported to the sIRB within 7 days of learning of the event. SAEs may also be reported to the local IRB as per local institution requirements. SAEs will be reported as required to the NIA and DSMB. If a participant develops an SAE, the participant's primary care provider and the site PI and/or study clinician will collaborate to ascertain the safety of continuing the intervention.

10.4 Data and Safety Monitoring Board

Data and safety monitoring will be provided by the DSMB for the parent trial. The DSMB will review all AEs and SAEs and will provide a report to the Steering Committee and to the sIRB.

11 DATA MANAGEMENT

The POINTER DCC is responsible for overseeing research clinic data collection and standardization, data management, data transfer and QC analyses of non-sleep assessment data.

11.1 Data Collection and Management Responsibilities

The ACOCC is responsible for overseeing sleep data collection across all clinical sites. Clinical sites are responsible for collecting pulse oximetry and actigraphy data and uploading these data to the appropriate SRCs. The BWH SRC is responsible for pulse oximetry data processing and QC analyses. California Pacific Medical Center is responsible for actigraphy data processing and QC. The University of Toronto will also receive actigraphy data for processing and QC, in preparation for analyses to examine sleep fragmentation. Analysis-ready datasets will be provided by the SRCs to the Coordinating Center.

11.2 Clinical Data Management

11.2.1 POINTER-zzz Study Website

All clinical sites use a secure website for data entry. Access to the data portal by staff is password-protected, and access to certain types of information on the website is restricted depending on the staff member's role in the study. Site-specific and study-wide dynamic reports will be available.

11.2.2 Data Collection and Entry

Sleep questionnaire and self-report data will be securely uploaded from participating sites to the DCC using secure electronic case report forms (eCRF) provided by the DCC. Each clinical site 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. Sleep assessment data collection is the responsibility of the POINTER-zzz Study Coordinator under the supervision of the Site Project Manager and the Site PI. The Site PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

11.2.3 Pulse Oximetry and Actigraphy Data

Actigraphy and pulse oximentry data will be uploaded to SRCs by the POINTER-zzz site Study Coordinator using two different portals, one for pulse oximetry data (maintained by BWH) and one for actigraphy data (maintained by California Pacific Medical Center). Summary data will be provided by each of the SRCs to the DCC on a regular basis.

11.2.4 Randomization

POINTER-zzz will rely on the parent trial randomization schedule to provide approximately equal numbers of POINTER-zzz participants in each of the two intervention groups at each of clinical site.

11.2.5 Participant Tracking

The participant tracking system for the parent trial will be expanded to accommodate POINTER-zzz. This system permits dynamic tracking of recruitment, enrollment, participant contact, staff training and certification, completed assessments, data and safety monitoring, and regulatory activities. The system includes a notification system that alerts clinic staff about upcoming appointments and various deadlines.

11.2.6 Security and Data Protection

Procedures are in place to provide disaster recovery of the database if needed using prior nightly back-ups.

11.2.6.1 Database Security

All data collected will be identified only by participant identification (PID) number and stored in a central U.S. POINTER database, with access only via a secure and encrypted website. Website access and priviledges are managed by the parent trial DCC. 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 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 local servers at the clinical site are encrypted and password-protected.

Protected Health Information such as participant name, address and other identifiers collected and data-entered are securely stored separately from de-identified data. Access to PHI is limited to a few members of the clinical site, the Coordinating Center and the SRCs.

Documents pertaining to the study are to be retained for a minimum of 2 years after discontinuation of the parent trial. These documents should be retained for a longer period if required by local regulations. It is

the responsibility of study leadership to inform the Site PI when these documents no longer need to be retained.

11.2.6.2 Research Clinic Data Security

Hardcopy and/or local server electronic records are stored at the clinical sites. Access to these data is controlled by locked storage or password-protected access to electronic records by authorized study personnel only.

12 ETHICS AND REGULATORY CONSIDERATIONS

12.1 Good Clinical Practice

The POINTER-zzz study, consistent with the parent trial, 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 U.S. 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.

12.2 Institutional Review Board

The Wake Forest IRB serves as the single IRB (sIRB) of record and is responsible for the review, approval and regulatory oversight of U.S. POINTER and its ancillary studies.

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 U.S. 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 study (ICH 4.5.4). The Site PI shall notify the Coordinating Center and sIRB of deviations from the protocol or severe adverse events (SAEs) occurring at the site, in accordance with local procedures. SAEs will be reported to the DSMB and to NIA. Per NIA policy, SAEs that are unanticipated will be reported to the NIA and DSMB within 48 hours of site PI notification.

12.3 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 study, 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.

Consent forms will be developed by the U.S. POINTER Coordinating Center in collaboration with POINTER-zzz 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 local 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.

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 research participants 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 local IRB, is responsible for ensuring that all applicable HIPAA regulations and State laws are met.

12.4 Study Monitoring

Data collection forms and source documents will be reviewed at regular intervals by the Coordinating Center throughout the study to verify adherence to the protocol, completeness and accuracy of the data, and adherence to local regulations regarding 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.

12.5 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 U.S. 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 U.S. POINTER website. POINTER-zzz will abide by this policy.

13 AUDIT

In accordance with ICH GCP, representatives of Wake Forest University Health Sciences, the Alzheimer's Association, and/or the National Institute on Aging 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 integrity of trial conduct and compliance with the protocol may also occur.

14 PUBLICATION POLICY

The U.S. POINTER Emerging Science, Publications and Presentations Core will coordinate dissemination of data from this study. The Core, whose membership will be approved by the U.S. 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 U.S. 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 U.S. POINTER website.

15 SHARING OF THE POINTER-zzz STUDY DATA

Data from POINTER-zzz 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.

16 STUDY GUIDANCE

The Steering Committee is the governing body that provides the leadership for U.S. 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 PIs, Ancillary Study PIs and Leads, Core workgroup chairs, Coordinating Center PIs and Leads, representatives from the sponsors of the parent trial (Alzheimer's Association) and funding agencies of the ancillary study (NIA), and representatives from the Executive Leadership. Executive level trial oversight by the Steering Committee is outlined in the Steering Committee Charter. POINTER-zzz will rely on executive level leadership input from the parent trial Steering Committee.

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