Alzheimer’s Association®
Leading the Way
to Treatment and Prevention

U.S. POINTER

An impact report prepared for
Sigma Kappa Foundation

August 2021
Dear Lisa and Trustees of Sigma Kappa Foundation,

Thank you for your generous support of the historic U.S. Study to Protect Brain Health through Lifestyle Intervention to Reduce Risk (U.S. POINTER), the world’s largest clinical trial designed to evaluate whether multiple risk-reduction strategies can protect memory and thinking in cognitively unimpaired older adults who are at increased risk of developing memory decline and dementia.

I am pleased to share that just this month, the U.S. POINTER team enrolled and randomized the 1,000th study participant — reaching half the total number of study participants required. Given the minor delay due to the COVID-19 pandemic, recruitment is now projected to continue through October 2022. The trial is scheduled to finish in 2024.

Because the top priority of U.S. POINTER study leadership is the safety and health of the entire U.S. POINTER “family,” including the study participants, researchers and staff, the leaders decided to pause the study in March 2020 due to the outbreak of COVID-19. Based on guidance from the Centers for Disease Control and Prevention and local authorities, they determined that by July 2020 it was safe to restart in-person research activities and did so on July 13, 2020.

During the pause, study leaders and team members worked to protect the scientific integrity of U.S. POINTER by continuing to virtually engage the 240 participants who had been randomized by March 2020 and the individuals who were pending randomization. Participants who had begun the study intervention were engaged weekly and asked to do their best to continue carrying out intervention activities and keep track of them using their POINTER activity logs. The U.S. POINTER team continued to connect by mail and telephone with individuals who had expressed interest in the study.

As we shared previously, the National Institutes of Health (NIH) has awarded four grants expected to total more than $63 million in support of four ancillary studies to maximize the potential of U.S. POINTER — making it a nearly $100 million study. They include the U.S. POINTER Neuroimaging Ancillary Study, the U.S. POINTER NeuroVascular Ancillary Study, the U.S. POINTER-zzz Sleep Study and the POINTER-Microbiome Study. All four studies are now active and recruiting study participants from among U.S. POINTER study participants.
As evidence continues to mount suggesting we may be able to engage in lifestyle/behavioral strategies to protect and/or reduce our risk for cognitive impairment, dementia scientists are more eager than ever to verify whether multiple interventions implemented together can have a significant impact on protecting memory and thinking.

“What’s particularly exciting about U.S. POINTER is that this is the first time that a study has been done in the United States that is looking at a whole recipe of things that one could change,” says epidemiologist and Northern California site co-leader Rachel Whitmer, Ph.D., University of California, Davis. “There have been studies that have looked at perhaps just blood pressure or just diet or just cognitive training. U.S. POINTER is the first time that these things have been really looked at all together.”

Expressing a sentiment shared by all site leaders, neurologist and Houston site co-leader Melissa Yu, M.D., FAAN, Baylor College of Medicine, is thrilled that her city is playing a role in the worldwide effort to end Alzheimer’s and other dementia. “The fact that the Houston site is one little cog in this giant world of people trying to prevent Alzheimer’s disease is really exciting,” says Dr. Yu. “That is really something that I look forward to being part of.”

Thank you, again, for joining with us to make history. With U.S. POINTER, we hope to set the stage for development of our nation’s first accessible, scalable and sustainable program for reducing risk of cognitive decline.

Please contact me if I may provide any additional information about the Alzheimer’s Association or the progress we are achieving together to realize our vision of a world without Alzheimer’s and all other dementia.

Sincerely yours,

Elizabeth Harder, CFRE
Senior Donor Advisor GA, SC, NC
Alzheimer’s Association
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Researchers estimate that more than 40% of all dementia cases worldwide are potentially preventable by addressing modifiable factors. What’s more, new scientific evidence suggests people can take positive steps now to protect their memory and thinking. Participants in FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) showed improvements in memory and other thinking skills after just two years of a lifestyle change that included a healthier diet, more exercise, increased intellectual and social stimulation, and better management of heart and vascular health. More recently the SPRINT MIND study showed that aggressive management of high blood pressure can reduce risk of mild cognitive impairment, a slight but measurable decline in cognitive abilities that increases a person’s risk of developing Alzheimer’s or another dementia.

With your partnership, the Alzheimer’s Association is leading a historic clinical trial to further test this emerging evidence. The U.S. Study to Protect Brain Health through Lifestyle Intervention to Reduce Risk (U.S. POINTER) is building on the last decade of scientific advances and expanding on lessons learned in FINGER to evaluate the effectiveness of lifestyle interventions in 2,000 Americans from a wide range of racial, ethnic, socioeconomic and geographic backgrounds who are at increased risk of developing memory decline and dementia. It is the first such clinical trial to be conducted in a large group of older adults across the United States.

**U.S. POINTER could set the stage for the development of our nation's first accessible, scalable and sustainable program for reducing risk of cognitive decline.**

Study participants are being assigned randomly to one of two groups, either a self-guided lifestyle intervention group or a structured lifestyle intervention group. The two-year program for each group provides nutritional guidance, coaching for heart and vascular health, and opportunities for increased physical exercise and cognitive and social stimulation. Participants in both groups attend regular meetings with other participants to receive information about healthy lifestyle practices and strategies to adopt healthier habits.

The success of the interventions to protect or improve cognitive function are being evaluated every six months for all participants. Vascular and metabolic health, physical function, mood, quality and quantity of sleep, and quality of life also are being assessed.
U.S. POINTER Leadership, Sites and Enrollment

U.S. POINTER is being led by some of the world’s leading experts on dementia risk reduction, including:

- Laura Baker, Ph.D., Wake Forest School of Medicine
- Mark Espeland, Ph.D., Wake Forest School of Medicine
- Miia Kivipelto, M.D., Ph.D., Karolinska Institutet, Sweden. FINGER PI
- Rachel Whitmer, Ph.D., UC Davis School of Medicine
- Maria Carrillo, Ph.D., Chief Science Officer, Alzheimer’s Association
- Heather Snyder, Ph.D. Vice President, Medical & Scientific Relations, Alzheimer’s Association
- U.S. POINTER Scientific Advisory Board
- Alzheimer’s Association Chapter Leadership

U.S. POINTER comprises five sites:

Western North Carolina
- Research institution: Wake Forest School of Medicine
- Site investigators: Jeff Williamson, M.D., and Maryjo Cleveland, M.D.
- Clinical partner: Wake Forest Baptist Health
- Association chapter: Western Carolina

Northern California
- Research institution: UC Davis School of Medicine
- Site investigators: Rachel Whitmer, Ph.D., and Sarah Farias, Ph.D.
- Clinical partner: UC Davis Health
- Association chapter: Northern California and Northern Nevada

Chicagoland
- Research institutions: Advocate Health Care and Rush University Medical Center
- Site investigators: Christy Tangney, Ph.D., and Darren Gitelman, M.D.
- Clinical partners: Advocate Health Care and Rush University Medical Center
- Association chapter: Illinois

Houston
- Research institution: Baylor College of Medicine
- Site investigators: Valory Pavlik, Ph.D., and Melissa Yu, M.D.
- Clinical partner: Kelsey-Seybold Clinic
- Association chapter: Houston and Southeast Texas

New England
- Research institution: Butler Hospital
- Site investigators: Stephen Salloway, M.D., and Rena R. Wing, Ph.D.
- Clinical partners: The Miriam Hospital
- Association chapter: Massachusetts / New Hampshire
As of August 16, 2021, U.S. POINTER has enrolled and randomized 1,000 study participants — half the total number of study participants required. Because of the minor delay due to the COVID-19 pandemic, recruitment is now projected to continue through October 2022. The trial is scheduled to finish in 2024.

Each site will enroll 400 or more adults ages 60-79 years. Eligible volunteers will have medical conditions thought to increase later-life risk for cognitive decline such as mild hypertension and slightly elevated blood sugar levels. They must have “room for improvement” in their physical and nutritional health and a first-degree relative (mother, father, brother or sister) who had or has a noticeable memory problem.

Individuals meeting these requirements are being identified through a three-step process that involves a search of electronic medical records (EMRs), mailed recruitment materials and a telephone interview. Sites are also searching for potential participants through grassroots efforts, including leveraging the extensive network of the Association. Each site features:

- Lead investigators who have experience conducting large-scale, nonpharmacological trials and assessing cognition in older adults;
- Extensive clinical networks and access to EMRs;
- A community partner with high-quality older-adult fitness programming;
- Clinic capacity and commitment to the study;
- Access to PET tracers and/or PET brain imaging;
- A history of engaging diverse populations; and
- A commitment to ensuring racial/ethnic diversity in the study staff.

“People are very excited to participate because of the preventative aspect,” says Houston site co-leader Melissa Yu, M.D., FAAN, Baylor College of Medicine. “The participants have family members who have been affected by the disease, often a parent or an aunt or a grandparent. It’s an exciting thing to be able to give them something to do to hopefully stave off the onset of the disease and change their trajectory.”

Diversity is essential to the success of U.S. POINTER. The recruitment process is designed to increase participation by communities that have been historically underrepresented in research and to engage both rural and urban populations. To achieve racial and ethnic diversity representative of the U.S. population, at least 23% of the participants will be from non-White groups (2016 U.S. Census demographics), with an equal number of women and men. Of the 1,000 study participants, 24.6% are Black, Hispanic, Native American, Asian or multiple races.

In late July 2021, researchers at the Alzheimer’s Association International Conference® (AAIC®) — the world’s largest and most influential international meeting dedicated to advancing dementia science — shared new, evidence-based insights into why people do and do not choose to participate in clinical trials:
• Individuals are most willing to volunteer if invited to participate (85%), if they want to contribute to research (83%) or have a family member with the disease (74%).

• Black, Hispanic and American Indian respondents are significantly more likely to volunteer if asked by a person of the same race.

• According to a review of Alzheimer’s and dementia clinical trials funded by the National Institute on Aging (NIA), part of the NIH, commonly used exclusion criteria disproportionately affect Black Americans and Hispanics and may play a role in their reduced enrollment in research.

Oanh Meyer, Ph.D., M.A.S., associate adjunct professor at the Alzheimer’s Disease Center at UC Davis Health, is leading grassroots recruitment at the Northern California site. “The onus is on us, as a research team, to go into places where we can engage diverse individuals in our research,” says Dr. Meyer. “Whether it’s faith-based institutions or other community-based organizations, we need to meet people where they are.”

Dr. Meyer meets biweekly with grassroots recruiters at the other four sites. “We share ideas with one another — what’s working at your site, how are you engaging this specific population,” she says. “It has been really helpful.”

**NIA-Funded Ancillary Studies**

We have leveraged our investment and leadership to help investigators obtain four awards expected to total $63.35 million for ancillary studies. The four NIA awards bring the total amount invested in U.S. POINTER to nearly $100 million. The studies include:

• **U.S. POINTER Neuroimaging Ancillary Study**, the first large-scale investigation of how lifestyle interventions affect biological markers (biomarkers) of Alzheimer’s and other dementia in the brain. As of August 13, 2021, 388 participants have been enrolled and randomized.

• **U.S. POINTER NeuroVascular Study (POINTER-NV)**, an investigation of how changes in blood flow and blood vessel health, resulting from a lifestyle intervention, impact cognitive health. As of August 13, 2021, 35 participants have been enrolled and randomized.

• **U.S. POINTER-zzz Sleep Study**, an ancillary study using in-home sleep assessments to investigate whether lifestyle interventions improve chronic sleep problems and how this may benefit cognitive function. As of August 13, 2021, 469 participants have been enrolled and randomized.

• **The POINTER-Microbiome Study**, an investigation of how a healthy lifestyle improves gut bacteria and how these changes might help protect brain function. As of August 13, 2021, 34 participants have been enrolled and randomized.
COVID-19 Pandemic Impact

The COVID-19 pandemic has had a significant impact on medical research. Though most have now restarted, clinical trials worldwide paused the testing of investigational interventions from early spring through early summer 2020. Observational trials paused their work or reconfigured how they are conducted. These changes were not unique to dementia studies.

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During the pause, study leaders and team members worked to protect the scientific integrity of U.S. POINTER by continuing to virtually engage the 240 participants who had been randomized by March 2020 and the individuals who were pending randomization. Participants who had begun the study intervention were engaged weekly and asked to do their best to continue carrying out intervention activities and keep track of them using their POINTER activity logs. The U.S. POINTER team continued to connect by mail and telephone with individuals who had expressed interest in the study.

All study team meetings and convenings of participants have been occurring virtually. The study team has worked to ensure access to necessary technology for all participants. They also have worked through best practices to ensure the virtual convenings are engaging for the participants. Closely tracking and monitoring the intervention aspects is essential. The research team has been ensuring that all sites are managing intervention delivery virtually, conducting proper hygiene protocols at sites for in-person clinic visits, collecting and evaluating data and more.

Study leadership has been expecting to resume in-person activities at all sites in September 2021, but the resurgence of COVID-19 could further delay in-person activities.

World-Wide FINGERS

U.S. POINTER is a member of World-Wide FINGERS (www.alz.org/wwfingers/), a growing interdisciplinary network currently comprising 25 multidomain dementia prevention initiatives by researchers and other stakeholders in 30 countries.

WW-FINGERS is co-led by the Association and the FINGER research team. Members share experiences, harmonize data and plan joint international initiatives for reducing risk of cognitive impairment or dementia. Coordinating these efforts will create opportunity for rapid knowledge dissemination and implementation, potentially accelerating the development of an evidence-based model to reduce risk of cognitive decline.
The U.S. POINTER statistics team, in partnership with the FINGER statistics team, have been leading WW-FINGERS efforts to develop and disseminate guidance on intervention delivery and data considerations during the COVID-19 pandemic. This guidance is helping members and others to overcome challenges to their studies caused by the pandemic. The WW-FINGERS network has convened members to discuss strategies regarding missing data, adjusted interventions, tracking adherence and more.

In March 2021, WW-FINGERS researchers published a peer-reviewed article, “Impact of the COVID-19 pandemic on statistical design and analysis plans for multidomain intervention clinical trials: Experience from World-Wide FINGERS,” in *Alzheimer’s & Dementia: Translational Research & Clinical Interventions*. The researchers reported that, “The [WW-FINGERS] network convened a forum for researchers to discuss statistical design and analysis issues they faced during the pandemic. We report on experiences of three trials that, at various stages of conduct, altered designs and analysis plans to navigate these issues.”

They found that, “The pandemic led researchers to change recruitment plans, interrupt timelines for assessments and intervention delivery, and move to remote intervention and assessment protocols. The necessity of these changes add emphasis to the importance, in study design and analysis, of intention to treat approaches, flexibility, within-site stratification, interim power projections, and sensitivity analyses.”

They also provided recommendations for future trials to consider as they develop and launch behavioral intervention trials.

**Leading the Way**

*The Alzheimer’s Association has committed $35 million to power U.S. POINTER — the most we ever have committed to one scientific study.* We are very glad to share that many philanthropic partners have stepped up to help fulfill our commitment, making and pledging gifts totaling nearly $15 million to date in support of this unprecedented study.

Together, with our philanthropic partners and the U.S. POINTER family, we are making history. With chapters nationwide; numerous partnerships with health care systems and community organizations; our international research network; and a growing base of philanthropic support — we have both the will and the way to ensure the success of U.S. POINTER.

Lifestyle changes have helped drive down death rates from cancer, heart disease and other major diseases, and they could to the same for Alzheimer’s and other dementia.

*Thank you for your generous gift to ensure the success of U.S. POINTER and help realize our vision of a world without Alzheimer’s and all other dementia.*
The Alzheimer’s Association is a worldwide voluntary health organization dedicated to Alzheimer’s care, support and research.

Our mission is to lead the way to end Alzheimer’s and all other dementia — by accelerating global research, driving risk reduction and early detection, and maximizing quality care and support.

Our vision is a world without Alzheimer’s and all other dementia®.