

## Supplementary Appendix

<b>Ancillary Studies</b> .....	2
<b>Enrolling Sites</b> .....	3
<b>Cognitive Adjudication in the PREVENTABLE Trial</b> .....	7
<b>Supplementary Table 1. Pivotal trials included in FDA label for atorvastatin</b> .....	8
<b>Supplementary Figure 1. PREVENTABLE biospecimen collection</b> .....	10

## **Ancillary Studies**

The Ancillary Committee oversees proposals for study questions leveraging the PREVENTABLE data collection or population. Currently funded ancillary studies are described below.

### **(1) CAC PREVENTABLE Ancillary Study.**

This ancillary study examines the utility of coronary artery calcium (CAC) scoring and high-sensitivity troponin (hs-Tn) identifying older adults in whom preventive therapy with statins is effective. Baseline CAC scanning and hs-Tn measurement will be done in 10,000 PREVENTABLE participants. At trial end, data will be analyzed to determine the value of an imaging and biomarker enabled approach to precision prevention strategies in older adults and the development of novel risk classification methods.

### **(2) Objectively Measured Sedentary Behavior and Physical Activity Study.**

This ancillary study will differentially examine physical activity and sedentary duration since the two are distinct domains. By recruiting 2,500 PREVENTABLE participants and objectively measuring sedentary, standing and stepping durations and the number of steps/day with a validated accelerometer, the study will examine the effect of sedentary duration and physical activity on the risk of developing MCI and Alzheimer's disease or related dementias (ADRD). In addition, the study will examine if statin therapy will result in higher physical activity levels and lower sedentary duration.

### **(3) Physical Performance Ancillary Study**

By adding the SPPB to the follow-up period, along with additional measures of a 4-m walk, and repeated chair stand test in 2,500 PREVENTABLE participants, this ancillary study will extend the disability data captured by the main trial and determine if statin therapy beneficially affects longitudinal change in physical performance and whether statin-associated muscle symptoms, fatigue, and pain contribute to disability.

## Enrolling Sites

A current list of PREVENTABLE sites can be found at [PreventableTrial.org](http://PreventableTrial.org).

### NON-VA INSTITUTION SITES

Albert Einstein College of Medicine: Andrew Telzak (PI), Yessica Estrella Vanterpool (SC)  
 Allina Health: Sandra Oberembt (PI), Irena Davies (SC)  
 Atrium Health: Lindsay Shade (PI), Kelsey Strout (SC)  
 Baylor, Scott and White: Heather Kitzman (PI), Meera Patel (SC)  
 Case Western Reserve University: Goutham Rao (PI), Kelsey Ufholz (SC)  
 Doctors Hospital at Renaissance: Sohail Rao (PI), Esmeralda Cardoso (SC)  
 Duke Kannapolis: Ranee Chatterjee (PI), Jenifer Allen (SC)  
 Duke University Medical Center: Ranee Chatterjee (PI), Trina Phan (PI)  
 Emory University: Ambar Kulshreshtha (PI), William Brown (SC)  
 Essentia Health: Catherine Benziger (PI), Ryan Thiel (SC)  
 Intermountain Healthcare: Kirk Knowlton (PI), Shanelle Cripps (SC)  
 Johns Hopkins University: Daniel Ford (PI), Megan Gauvey-Kern (SC)  
 Marshfield Clinic: Jeff VanWormer (PI), Diane Kohnhorst (SC)  
 Mayo Clinic: Alanna Chamberlain (PI), Angela Meilander (SC)  
 Mayo - NW Wisconsin: Steven Rosas (PI), Joshua Druckrey (SC)  
 Mayo - SW Wisconsin: Thomas Loepfe (PI), Jodi Kaseno (SC)  
 Medical College of Wisconsin: Jeffrey Whittle (PI), Madeline Berendt (SC)  
 Meharry Medical College: Richmond Akatue (PI), Steven Houtschilt (SC)  
 Northwestern: Jeff Linder (PI), Tiffany Brown (SC)  
 Ochsner Health: Lydia Bazzano (PI), Shannon Williams (SC)  
 Ohio State University: Seuli Brill (PI), Matthew Jindra (SC)  
 Rush: Raj Shah (PI), Erin Yurko (SC)  
 University of Alabama: Mehta Tapan (PI), Leigh Kirkwood (SC)  
 University of Arkansas for Medical Sciences: Gohar Azhar (PI), Amanda Pangle (SC)  
 University of Chicago: Tamar Polonsky (PI), Matthew Carlson (SC)  
 University of Florida – Gainesville: Marco Pahor (PI), Jane Lu (SC)  
 University of Florida – Jacksonville: Marco Pahor (PI), Brandi Wells (SC)  
 University of Illinois at Chicago: Howard Gordon (PI), Naomi Ashley (SC)  
 University of Iowa Healthcare: Michael Ernst (PI), Tammy Lowe (SC)  
 University of Kansas Medical Center: Kristin Grdinovac (PI), Erica Lower (SC)  
 University Medical Center New Orleans: Jennifer Hart (PI)  
 University of Miami: Olveen Carrasquillo (PI), Veronica Linares (SC)  
 University of Mississippi Medical Center: Michael Hall (PI), Lane Boyer (SC)  
 University of Missouri: Kristin Hahn-Cover (PI), Vickie Grieshaber (SC)  
 University of Nebraska Medical Center: Alfred Fisher (PI), Sarah Kirke (SC)  
 University of North Carolina: Christine Kistler (PI), Jeannie Ake (SC)  
 University of Pittsburgh: Daniel Forman (PI), Emily Klawson (SC)  
 University of Texas Health Science Center at Houston: Jessica Lee (PI), Kim Johnson (SC)  
 University of Texas Health Science Center at San Antonio: Nicolas Musi (PI), Kevin Brown (SC)  
 University of Texas Southwestern Medical Center: Craig Rubin (PI), Gentina Thompson (SC)  
 University of Utah: Clint Allred (PI), Haddy Bah (SC)  
 Vanderbilt University Medical Center: Amanda Mixon (PI), Jennifer Wharton (SC)  
 Wake Forest – Cardiology: Michael Shapiro (PI), Michele Wall (SC)  
 Wake Forest – Geriatrics: Ezequiel Zamora (PI), Jesus Betancourt (SC)  
 Washington University St. Louis: Ellen Binder (PI), Amy Young (SC)

Weill Cornell Medical College: Parag Goyal (PI), Fernando Park (SC)  
 Yale University: Thomas Gill (PI), Aimee Almonte (SC)

### VA HOSPITAL SITES

Asheville Charles George VA Medical Center: Brian Peek (PI), Jessica Michael (SC)  
 Atlanta VA Medical Center: Camille Vaughan (PI), Mechelle Lockhart (SC)  
 Bay Pines VA Health Care System: Dennis Hall (PI), Cortny Withee (SC)  
 Birmingham VA Health Care System: Alayne Markland (PI), Donald Davis (SC)  
 Captain James A. Lovell Federal Health Care Center: Raul Gazmuri (PI), Teresa Todela (SC)  
 Central Arkansas Veterans Healthcare System: Dennis Sullivan (PI), Linda Sawyer (SC)  
 Cincinnati VA Medical Center: Jack Rubinstein (PI), Julie Bunke (SC)  
 Clement J. Zablocki VA Medical Center: Jeffrey Whittle (PI), Julie Lorscheter (SC)  
 Dayton VA Medical Center: Ankur Gupta (PI), Tiffany Castle (SC)  
 Durham VA Medical Center: Kenneth Schmader (PI), Julianne Reynolds (SC)  
 Edward Hines VA Medical Center: Holly Kramer (PI), Corliss Taylor (SC)  
 G.V. (Sonny) Montgomery VA Medical Center: Kent Kirchner (PI), Anita Kaye Spencer (SC)  
 Hunter Holmes McGuire VA Medical Center: Michael Godschalk (PI), Charmaine Taylor (SC)  
 James J. Peters VA Medical Center: Steven Atlas (PI), Raynier Baez Guerrero (SC)  
 Jesse Brown VA Medical Center: Manyank Kansal (PI), Jose Tenorio Jr. (SC)  
 Kansas City VA Medical Center: Vikas Singh (PI), Shamsa Kiran (SC)  
 Maine (Togus) VA Health Care System: Marie Albert (PI), Vanessa Knipping (SC)  
 Memphis VA Medical Center: Richard Childress (PI), Brandon Beaverson (SC)  
 Miami VA Healthcare System: Leonardo Tamariz (PI), Jennifer Denizard (SC)  
 North Florida/South Georgia Veterans Health System: Sriram Peruvemba (PI), Julianna Venetucci (SC)  
 Nebraska-Western Iowa VA Health Care System: Vijay Shivaswamy (PI), Ramesh Ramalingam (SC)  
 Providence VA Medical Center: Gaurav Choudhary (PI), Adrianna Ricci (SC)  
 Ralph H. Johnson VA Health Care System: Jyotika Fernandes (PI), Taylor Willis (SC)  
 Richard L. Roudebush VA Medical Center: James Walsh (PI), Lauren Espique (SC)  
 Robley Rex VA Medical Center: Sathya Krishnasamy (PI), Jordan Ricks (SC)  
 Salt Lake City VA Health Care System: Paul Eleazer (PI), Stephen Thongsa (SC)  
 San Diego VA Health Care System: William Penny (PI), Melissa St. John (SC)  
 South Texas Veterans Health Care System: Sara Espinoza (PI), Amir Tavabi (SC)  
 Southern Arizona VA Health Care System: Mark Liu (PI), Iliana Romero (SC)  
 St. Louis VA Medical Center: Jiafu Ou (PI), Socorro Marie White (SC)  
 VA Caribbean Healthcare System: William Rodriguez-Cintrón (PI), Sara Fuentes-Medina (SC)  
 VA Central California Health Care System: Sudeshna Kundu (PI), Kieu Chau (SC)  
 VA Ann Arbor Healthcare System: Pearl Lee (PI), Carly Runge (SC)  
 VA Boston Healthcare System: Ariela Orkaby (PI), Enzo Yaksic (SC)  
 VA Connecticut Healthcare System: Brian Malm (PI), Kasey Spreyer (SC)  
 VA Eastern Kansas Health Care System: Alexander Hallock (PI), Karen Reuben-Hallock (SC)  
 VA Greater Los Angeles Health Care System: Cathy Lee (PI), Angela Zeng (SC)  
 VA Long Beach Healthcare System: Kenny Vu (PI), Christina Hy (SC)  
 VA North Texas Health Care System: Kyaw Soe (PI), Jodie-Ann Clarke (SC)  
 VA Tennessee Valley Healthcare System: Christianne Roumie (PI), Jennifer Wharton (SC)  
 William Jennings Bryan Dorn VA Medical Center: Andres Munoz (PI), Ariana Tinker (SC)  
 William S. Middleton Memorial Veterans Hospital: Cynthia Carlsson (PI), Hannah Zylstra (SC)

## **Trial Organization and Study Committees**

The Steering Committee, along with its subcommittees and in partnership with the National Institute on Aging (NIA) and National Heart, Lung, and Blood Institute (NHLBI), oversees the study.

### **Executive Committee**

Adrian Hernandez (Co-Chair Steering Committee), Jeff Williamson (Co-Chair Steering Committee), Karen Alexander (Clinical Coordinating Center PI), Walter Ambrosius (Data Coordinating Center PI), Jacob Joseph (VA Coordinating Center PI), Sergei Romashkan (NIA), Larry Fine (NHLBI), Nick Pajewski, Mary Ann Sellers, Letitia Perdue, Sheronda Peoples, Nancy Woolard.

### **Steering Committee**

Adrian Hernandez (Co-Chair), Jeff Williamson (Co-Chair), Karen Alexander, Walter Ambrosius, Jacob Joseph, Nick Pajewski, Mark Weiner, Rhonda Cooper-DeHoff, Mark Effron, Dan Forman, Jacob Joseph, Christine Kistler, Raj Shah, Mark Supiano, Neely Williams, Schuyler Jones, Rowena Dolor, Brad Hammill, Kate Callahan, Kristin Newby, Mine Cicek, Adam Henrie, Catherine Benziger, Sara Espinoza, Jeff Whittle, Jack Rubinstein, Heather Snyder, Maria Carrillo.

### **PCORnet Study Leadership**

Russ Waitman (Greater Plains Collaborative), Russell Rothman (STAR), Betsy Shenkman (OneFlorida), Tom Carton and Beth Nauman (ReachNet), Kathleen McTigue (PaTH), Mark Weiner (Insight), Raj Shah (CaPRICorn)

### **PREVENTERS (Participant Advisors)**

Minnie Jefferson, John Wing, Shirley Bloodworth, Alva Owens, Linda Bordelon, Murray Heimberg, Jesse Massey, Miriam Gonzalez, Bob Brashears (retired), Konrad Kaczowski.

### **VA Pharmacy and Data Integration Committee**

Adam Henrie, Mark King, Kimberly Hoisington, Jeanette Lovato, Julissa Almonte, Jack White, Nick Pajewski, Walter Ambrosius, Brad Hammill, Katie Burnet, Rhonda Cooper-Dehoff, Michael Gaziano, Laura Lovato, Sheronda Peoples, Mary Ann Sellers, Krishna Poddar, Zachary Taylor, Mark King, David Hunt

### **Recruitment and Retention Committee**

Rowena Dolor (Chair), Schuyler Jones, Jennifer Hervey, Michelle Kelsey, Renee Leverty, Bryan Batch, Al Richmond, Manda Hufstedler, Alain Chang, Mary Ann Sellers, Sheronda Peoples, Joanne Hetzel, Melissa Laffey

### **Geriatric Outcomes Working Group**

Ariela Orkaby (Chair), Jeff Williamson, Mark Supiano, Marco Pahor, Chrissy Kistler, Raj Shah, Dan Forman, Nancy Woolard, Kate Callahan, Denise Houston, Sara Espinoza, Dalane Kitzman, Steve Rapp, Bonnie Sachs, Nick Pajewski, Scott Lang, Randy Nulph, Emily Rives, Susan Zieman

### **Ancillary Studies Committee**

Raj Shah (Co-Chair), Kristin Newby (co-chair), Anne Newman (ex-officio chair), Ariela Orkaby, Jacob Joseph, Mark Effron, Rhonda Cooper DeHoff, Michael Bancks, Neely Williams, Susan Zieman, Kate Callahan, Karina Kapitanovsky, David Reboussin

**Biorepository Committee**

Kristin Newby (Co-chair), Mina Cicek (Co-Chair), Katie Halverson, Sarah Gaussoin, Claire Dohner, Letitia Perdue, Katrina Kapitanovsky, Katie Burnet, Julissa Almonte, Sheronda Peeples, Pamela Monds, Rhonda Cooper-Dehoff

**Measurements, Procedures, and Quality Control**

Mark Supiano (Co-Chair), Michael Bancks (Co-Chair), Clint Alred, Jennifer Bowman, Sheronda Peeples, Julie Bunke, Julissa Almonte, Nancie Deckard, Jennifer Hervey, Laura Lovato, Tammy Lowe, Christianne Roumie, Michael Shapiro, Ryan Thiel, Kyra VanDoren, Mark Weiner, Heidi Whiteside

**DSMB**

David Reuben (Chair), Peter Peduzzi, Scott Solomon, Hermes Florez, John Breitner, Phil Greenland, Tom Trivison

## Cognitive Adjudication in the PREVENTABLE Trial

An adjudication panel of experts in the diagnosis of MCI or dementia masked to study group assignment will make the final determination of probable dementia, MCI or no impairment. Data used in the adjudication will include cognitive test data (TICS-M, Extended Cognitive Assessment Battery), functional assessments (FAQ) (or, in specific cases, the Dementia Questionnaire), PHQ-8, demographic information, cognition-relevant medication, and medical history. Two experts will independently review each case. Disagreements will be resolved at periodic meetings. Annual cognitive assessments will stop after a participant is classified as probable dementia.

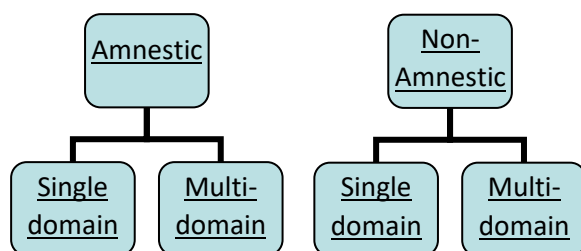
*Criteria used for identifying probable dementia and MCI, as described in National Institute on Aging-Alzheimer's Association (NIA-AA criteria):*

*Criteria used for classifying probable dementia:*

- Cognitive symptoms that interfere with the ability to independently perform activities of daily living at the usual level
- Cognitive symptoms represent a decline from a previous level of functioning
- Symptoms are not explained by delirium or psychiatric disorder
- Cognitive impairments are detected through information from the patient and/or informant and through objective cognitive assessment
- Cognitive impairments occur in at least two domains of the following:
  2. Learning and memory
  3. Reasoning and executive functions
  4. Visuospatial abilities
  5. Language
  6. Behavior or comporment

*Criteria used for identifying MCI are:*

- Concern regarding a change in cognition, in comparison with the person's previous level
- Objective evidence of impairment in one or more cognitive domain that is greater than expected based on the patient's age and education level
- Relative preservation of independence of functional abilities
- No evidence of dementia



Note: The site investigator and the participant's clinician may be notified of a probable dementia adjudication via a secure transfer. Such an adjudication is NOT the equivalent of a clinical diagnosis, so the participant's primary care team will need to discuss with the participant and decide whether further work-up is indicated. Steps regarding notifying the clinical site team of a probable dementia adjudication result are in the MOP.

**Supplementary Table 1. Pivotal trials included in FDA label for atorvastatin<sup>1-6</sup>**

<b>Trial</b>	<b>Study Characteristics</b>	<b>Study Drug</b>	<b>Follow-up (Yrs)</b>
<b>Early Studies</b>	N=3065 Age ≥75: 300	Atorvastatin 10–80 mg	---
<b>(ASCOT-LLA)</b> Anglo-Scandinavian Cardiac Outcomes Trial	N=10,305 patients with hypertension Age: 40–80 years	Atorvastatin 10 mg vs. placebo	3.3
<b>(CARDS)</b> Collaborative Atorvastatin Diabetes Study	N=2838 patients with diabetes Age: 40–75 years	Atorvastatin 10 mg vs. placebo	3.9
<b>(TNT)</b> Treating to New Targets Study	N=10,001 patients Age: 29–78 years	Atorvastatin 10 mg vs. 80 mg	4.9
<b>(IDEAL)</b> Incremental Decrease in Endpoints through Aggressive Lipid Lowering Study	N= 8888 patients with CHD Age: 26–80 years	Atorvastatin 80 mg vs. Simvastatin 20-40 mg	4.8
<b>(SPARCL)</b> Stroke Prevention by Aggressive Reduction in Cholesterol Levels	N=4731 patients Age: 21–92 years	Atorvastatin 80 mg vs. placebo	4.9
<b>TOTAL</b>	N= 39,828 patients <b>Age ≥75: 2800 (7%)</b>		~3.8

1. Atorvastatin Package Insert. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2009/020702s056lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020702s056lbl.pdf). Accessed October 13, 2022.
2. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;361:1149–1158.
3. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;364:685–696.



4. Waters DD, Guyton JR, Herrington DM, et al. Treating to New Targets (TNT) Study: does lowering low-density lipoprotein cholesterol levels below currently recommended guidelines yield incremental clinical benefit? *Am J Cardiol* 2004;93:154–158.
5. Pedersen TR, Faergeman O, Kastelein JJP, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial *JAMA* 2005;294:2437–2345.
6. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) investigators. High Dose Atorvastatin after Stroke or Transient Ischemic Attack. *N Engl J Med* 2006;355:549–559.

Supplementary Figure 1. PREVENTABLE biospecimen collection

