Phase 2: 1R61HL151885-01 (9/15/20-8/31/21); R33HL151885 (subsequent years)

	Table of Contents	
Section	Topic	Page

SECTION 1 - BASIC INFORMATION

1.1. Study Title: Women's Health Initiative Strong and Healthy Study
1.2. Is this study exempt from Federal Regulations: No
1.3. Exemption Number: NA
1.4. Clinical Trial Questionnaire
  1.4.1. Does this study involve human participants? Yes
  1.4.2. Are the participants prospectively assigned to an intervention? Yes
  1.4.3. Is the study designed to evaluate the effect of the intervention on the participants? Yes
  1.4.4. Is the effect that will be evaluated a health-related biomedical or behavioral outcome? Yes
1.5. Provide the ClinicalTrials.gov identifier: NCT02425345

SECTION 2 - STUDY POPULATION CHARACTERISTICS

2.1. Conditions or Focus of Study

- Myocardial Infarction
- Stroke
- Cardiovascular Mortality
- Hip Fractures
- Falls
- Mortality
- Venous Thromboembolic Event
- Peripheral Artery Disease
- Physical Function
- Coronary Revascularization
- Mobility and Independence
- Clinical (Non-hip) Fracture

Phase 2 adds to the above:

- Short Physical Performance Battery (SPPB) in subset
- Sleep Disturbance
- Depressive Symptoms

2.2. Eligibility Criteria (at randomization)

Inclusion Criteria

- Currently enrolled in the Women's Health Initiative (WHI) Extension Study
- Known to be alive
- Cardiovascular outcomes will be available (enrolled in the WHI Medical Records Cohort or linked to Medicare Data)

Exclusion Criteria

- Inability to walk
- Dementia
- Residing in a nursing home

2.3. Age Limits (at randomization): Min Age: 66 Years Max Age: 99 years

2.4. Inclusion of Women, Minorities, and Children

Women and Minorities

All participants in the study are women because the *WHISH* trial is embedded in the large, ongoing Women's Health Initiative (WHI) Extension Study. WHI is a study of postmenopausal women designed by the NIH in 1991 to address the critical lack of evidence on postmenopausal women's health when the WHI Program was started in 1993. No men were included in the study, because the specific focus was on addressing interventions (Hormone Therapy, Dietary Modification, Calcium-Vitamin D supplementation) and health outcomes (coronary heart disease (CHD), breast cancer, and hip fractures), of special concern to women. The *WHISH* trial began in 2015 and this application proposes a continuation to extend follow-up to 9 years so that the *WHISH* trial can reach a definitive conclusion. Moreover, older women in the age range of *WHISH* have higher rates of new and recurrent cardiovascular events than men and no previous trials have investigated preventive interventions for cardiovascular disease in women.

The original recruitment to WHI included several strategies for recruiting minorities, e.g., 10 "Minority Clinical Centers" selected by the NIH with the specific goals of recruiting minority women, to ensure that minorities were adequately represented in all WHI component studies. The sampling frame for this study includes substantial minority representation as shown in the Inclusion Enrollment Table. No minority groups are excluded. The *WHISH* trial is 100% women, including 15.7% minorities (9.2% Black or African American, 3.3% Hispanic or Latina, 1.9% Asian or Pacific Islander and 0.3% American Indian or Alaska Native).

NIH-Defined Phase III Clinical Trial, Ensuring Valid Analysis

The *WHISH* randomized trial assigned intervention/comparison arm by random allocation of 50% intervention and 50% comparison stratified by race/ethnicity, age at randomization, data source (WHI Medical Records Cohort with outcomes adjudication or Medicare), and region (West, Midwest, Northeast, and Southeast). This ensures a valid, un-biased analysis.

Reporting on and Analyzing Differences in Race and Ethnicity

The WHI has been maintaining, collecting and presenting data on race and ethnicity as required by the Office of Management and Budget since it was initiated in 1993, including Hispanic, American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, and White.

Prior evidence does not support race/ethnicity differences in the effects of physical activity on cardiovascular disease or associations between physical activity and cardiovascular risk factors. Nonetheless, although we do not have sufficient power to test for treatment effects within the individual groups, we will conduct stratified analyses and test for interaction to explore whether there are differences.

Inclusion of Children

The *WHISH* trial is embedded in the WHI Extension Study which is continuing to follow women who were enrolled in the NIH Women's Health Initiative at ages 50-79 at baseline (1993-1998), and therefore had only adult postmenopausal women participants. The NIH recognized that by focusing on postmenopausal women children would be excluded from the WHI. *WHISH* participants were aged 66-99 at randomization in 2015 (mean age ~80 years).

2.5. Recruitment and Retention Plan

Recruitment

WHISH is a pragmatic trial with a randomized consent design, embedded in the Women's Health Initiative (WHI) Extension Study (2010-2020), for which 49,331 women (9% African American), aged 66-99 years were randomly assigned to a physical activity (PA) intervention or usual activity comparison.

Schema:

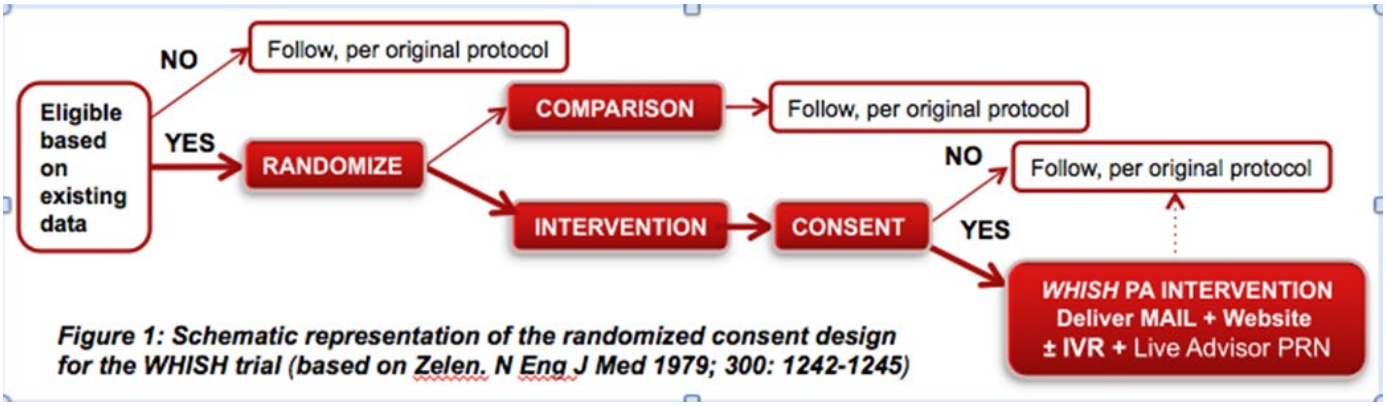
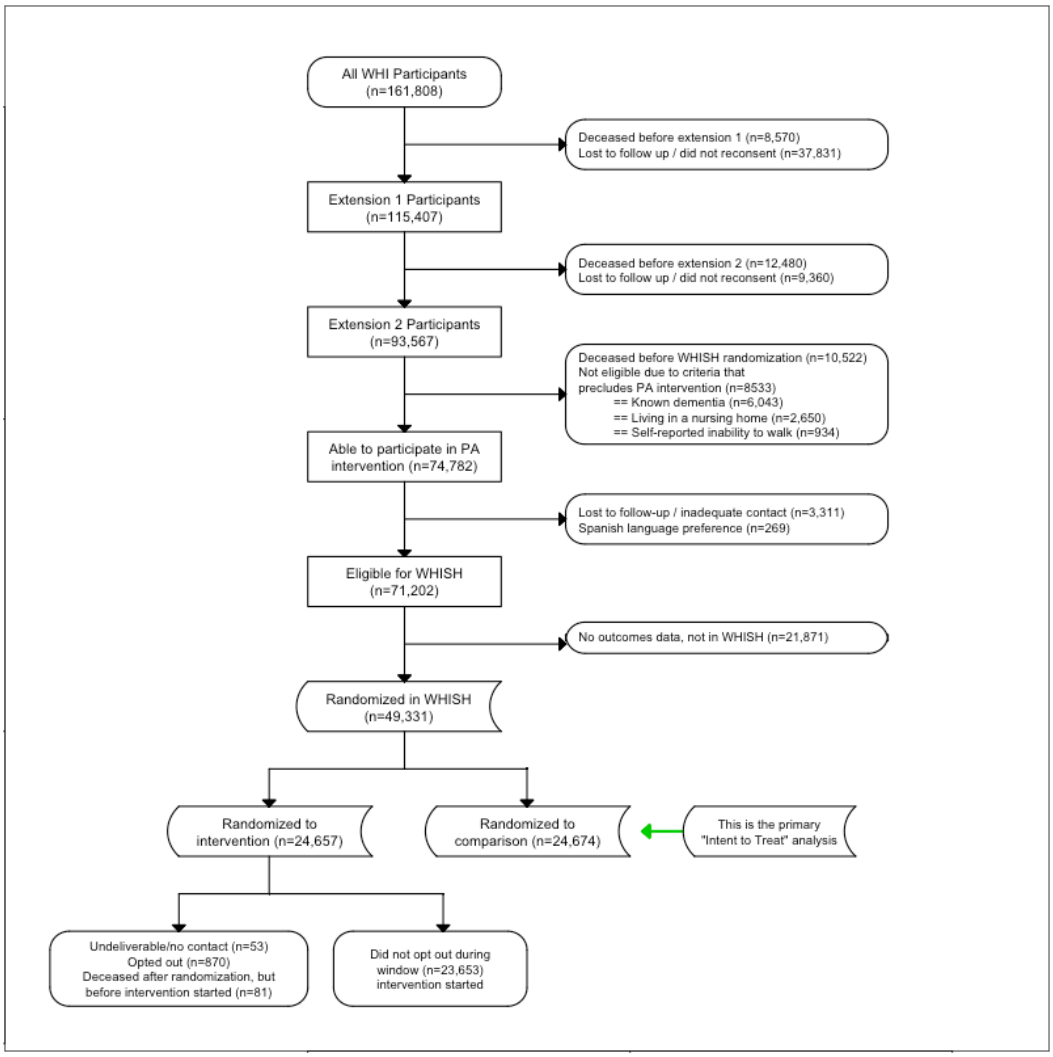


Figure 1: Schematic representation of the randomized consent design for the WHISH trial (based on Zelen. N Eng J Med 1979; 300: 1242-1245)

WHISH utilized a randomized consent design as originally proposed by Zelen (1979). Through this design, women were pre-screened for eligibility based on previously collected WHI data (see section 2.2. Eligibility Criteria). WHI newsletters were sent to all eligible WHI participants in advance of implementing *WHISH* to inform them that a new physical activity study was being started and that they may be invited to participate. After pre-screening, but prior to the first *WHISH* contact, 49,331 WHI participants were randomized.

Women randomized to intervention were sent a welcome packet and asked to call the WHI Clinical Coordinating Center if they did not want further contact from the *WHISH* intervention Center at Stanford. After removing women who "opted out" of this **passive consent process**, did not have a deliverable address or who had died after randomization but before intervention mailings, the intervention began to be delivered to 23,653 women. See Schema above and *WHISH* CONSORT Diagram below.

WHISH CONSORT Diagram Data
as of July 20, 2020



During Phase 1 of the *WHISH* trial, the Accelerometry Substudy consented 2,350 participants (1,182 comparison; 1,168 intervention) who had participated in the WHI Objective Physical Activity for Cardiovascular Health (OPACH) study during which they wore a waist accelerometer for 7 days and nights and completed a sleep diary for each of the 7 nights. During phase 1 of *WHISH*, they consented to wear a waist accelerometer 3 times for 7 nights each over the course of 4 years and complete a sleep diary for each of the 7 nights. Participants who completed round 3 (of 3 rounds) of the *WHISH* Accelerometry Substudy (n~1400) will be invited to re-consent to an Accelerometry Substudy in the continuation of the trial, phase 2. To fill to n=2,000 participants, additional *WHISH* participants will be invited to consent for the first time. To reach n=2,000, we will recruit 500 women each quarter during year 7. Assuming a 40% consent and re-consent rate, we plan on mailing to n~5000 participants. There will be an ample number of eligible *WHISH* participants from which to draw for diverse age and race/ethnicity enrollment when recruiting for the next Accelerometry Substudy. The invitational consent packet will include a cover letter from the *WHISH* PIs and an informed consent form. The cover letter will provide a toll-free telephone number that participants may call and leave a message if they have questions about the study or the consent. The message line is monitored daily with calls logged. Staff will return calls to participants within 1-2 days. We have used this system successfully with the initial Accelerometry Substudy consent and several other WHI ancillary studies involving participant informed

consent that is not conducted in-person. The same staff and investigators who were responsible for recruiting and consenting participants for the initial Accelerometry Substudy again will be responsible for recruitment and consenting for the proposed Accelerometry Substudy.

Regarding competition with other clinical trials, over the years many WHI participants have participated in more than one WHI ancillary study. Considering the impact of *WHISH* participation on the main WHI, we use the annual collection rate of the WHI medical history update (outcomes) form as a metric. For WHI overall, the outcomes form response rate between 6/1/2018 and 11/30/2018 of currently active WHI participants not in any ancillary studies was 67.7%. For those in WHI with *WHISH* as the only ancillary study, response rate was 66.2% among *WHISH*-intervention and 70.8% in *WHISH*-comparison. These are in-progress numbers and do not represent final response rates. The WHI participants have been highly committed to the WHI since recruitment began in 1993 with 161,808 postmenopausal women between the ages of 50-79. Up to 26 years later, 66,548 WHI participants remain actively participating (returning outcomes forms) and span an age range of 66-102.

Retention

Retention starts with the WHI. Retention activities in the WHI Extension Study consist of collecting the annual data forms and tracking hard to find and lost participants. Strategies and procedures to ensure a participant's retention and identification with WHI must be used throughout the course of the study, from the consent to the last follow-up contact. Participants receive WHI newsletter annually that includes WHI updates, participant stories, and healthy living tips. In February 2015, all active WHI participants (n=84,658 of 93,500 who had consented to the WHI Extension 2010 forward) received a WHI pendant commemorating WHI's 20th anniversary.

Retention for the *WHISH* intervention is monitored by the Stanford staff to ensure that women who have requested no further intervention are removed from contact lists and receive no further mailings. As of July 20, 2020, 85.3% of alive participants, i.e., not known to be deceased, were receiving the intervention; 12.6% had requested that mailings be stopped; 2.1% had undeliverable addresses. Participant engagement, as assessed by return of annual surveys sent only to Intervention participants, has steadily increased from a low of 48% response rate to the first survey to 72% response rate for the fourth (most recent) survey. Intervention materials are developed with evidence-based behavioral strategies, such as adhering to the social cognitive model of health behavior acquisition and maintenance. The materials have been steadily adapted to reflect participants' interests, based on their input on surveys and feedback from postcards, phone calls, emails, and mail. The materials and now include "targeted" inserts for three groups of women, based on self-reported physical function and physical activity levels reported on WHI forms. *WHISH* intervention staff at Stanford are available by phone, post mail or email to respond to inquiries from individual participants. Refer to the Research Plan for additional details.

Retention for the Accelerometry Substudy is supported by staff at the implementation site at the University of California, San Diego, Exercise and Physical Activity Resource Center (EPARC). This staff call each participant to review the instructions with them before they receive the accelerometer and study materials, as well as during the study. Time is offered to discuss questions. Each participant receives the toll-free telephone number to call if she has questions during the study.

2.6. Recruitment Status: Active, not recruiting

2.7 Study Timeline

Activity	Yr 6	Yr 7	Yr 8	Yr 9
Targeted intervention	X	X	X	X

Behavior change assessments: Form 521	X	X	X	X
Outcomes ascertainment	X	X	X	X
WHISH Accelerometry Substudy		X	X	
WHISH/WHI Long Life Study home exams		X	X	
Study close-out, publication of primary trial reports				X
Plan and conduct biomarker pilot studies			X	X

2.8. Enrollment of First Participant (See Section 6.3.)

2.9. Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
IER 289037	Domestic	

Inclusion Enrollment Report

1. Inclusion Enrollment Report Title: Physical Activity Intervention to Improve Cardiovascular Health in Older Women

2. Using an Existing Database or Resource? No

3. Enrollment Location Type: Domestic

4. Enrollment Country(ies): USA: United States

5. Enrollment Locations: WHI

6. Comments: Cumulative data are for WHISH participants randomized April-July 2015. The planned enrollment table shows the number of WHISH participants who were alive as of the 2019 DSMB report. No further enrollment will occur in the larger cohort of WHISH, although there is planned enrollment for the accelerometry substudy. At the time when race/ethnicity data were obtained for the WHI, 1993-1998, Asian or Pacific Islander was asked under a single question; Hispanic ethnicity was asked as a single category without racial differentiation; unknown was asked whereas more than one race was not asked. Hispanic racial category is reported collectively as unknown.

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	133	0	0	0	133
Asian	845	0	0	0	845
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	3942	0	0	0	3942
White	35471	0	1472	0	36943
More than One Race	0	0	0	0	0
Total	40391	0	1472	0	41863

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	0	0	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	0	0	0	0	0	0	0	0	0	0
White	0	0	0	0	0	0	0	0	0	0
More than One Race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0	0	0

SECTION 3 - PROTECTION AND MONITORING PLANS

3.1. Protection of Human Subjects

3.1.1. Risks to Human Subjects

3.1.1.a. Human Subjects Involvement, Characteristics, Design, and Specific Aims

The *WHISH* Trial is a randomized trial designed to answer a specific question regarding the efficacy of a physical activity (PA) intervention designed to promote levels of PA recommended by the U.S. Department of Human & Human Services for older Americans (https://health.gov/paguidelines/) compared to a usual activity comparison group. Specifically, the trial addresses whether a centralized public health intervention designed to increase and/or maintain aerobic (endurance) activity, primarily walking, combined with muscle strengthening exercises, and exercises to promote balance and flexibility, as well as encouragement to reduce sedentary behavior, primarily sitting, reduces major cardiovascular (CV) events. CV events are defined as myocardial infarction (MI), stroke (in particular, ischemic stroke), and CV death over an approximate 8-year follow-up period.

The specific aims of phase II of the *WHISH* trial are:

Primary Aim: Continue the centralized, adaptive, targeted PA intervention and ascertainment of adjudicated CVD, fracture and non-CVD death endpoints in WHISH women retaining their randomized treatment assignment to provide a minimum of 8 years of follow-up for surviving participants.

Primary hypothesis: The WHISH targeted PA intervention designed to increase aerobic PA combined with muscle strengthening, balance and flexibility exercises, and to reduce sedentary behavior, will reduce major CVD clinical events (composite of MI, stroke, and CV death), compared to the "usual follow-up group.

Secondary Aim: Determine WHISH intervention effects on measures of healthy CV aging including PF measured using the Short Physical Performance Battery (SPPB), sleep disturbances, and depressive symptoms. This Aim will use data collected in the LLS2 funded by the WHI Extension Study 2020-2027.

Hypothesis: The WHISH intervention will result in higher SPPB scores, improved sleep parameters, and lower levels of depressive symptoms compared to the usual activity group.

Exploratory Aim: Create an experimental framework within WHISH and conduct pilot studies to determine whether the WHISH PA intervention influenced levels of novel biomarkers indicative of healthy CV aging and/or occult myocardial injury, such as N-terminal pro-brain natriuretic peptide (NT-proBNP) and high sensitivity cardiac Troponin T (hsTnT). A WHISH Biomarker Advisory Group involving US experts will vet the most promising biomarkers for pilot testing. This aim will facilitate future WHISH/WHI Ancillary Studies and will utilize biospecimens collected in the LLS2 of the next WHI Extension Study, 2020-2027.

Hypothesis: WHISH Intervention women will have more favorable levels of CVD biomarkers.

Safety outcomes include non-cardiovascular death, hip and clinical (non-hip) fractures, falls, and revascularization.

WHISH is a multi-ethnic cohort of 49,331 women aged 66-99 (mean age ~80 years) at *WHISH* randomization April-July 2015 who were enrolled and actively participating in the NHLBI-funded Women's Health Initiative (WHI) Extension Study, excluding those who by self-report were unable to walk, had a recent diagnosis (within past 6 months) of CV disease, dementia, and known to

reside in a nursing home. Among *WHISH* participants, 84% were white, 9% Black or African American, 3% Hispanic, 2% Asian or Pacific Islander, 0.3% Native American or Alaskan Native and 1% undeclared.

A total of 49, 331 participants were randomized to *WHISH* of which 24,674 (50%) were randomized to comparison and 24,657 (50%) to intervention. Of those randomized to intervention, 860 (3.5%) opted out of receiving intervention materials, 53 (0.2%) had undeliverable addresses, and 81 (0.3%) were deceased after randomization but before the intervention started. Thus, 23,653 (96%) intervention participants began receiving intervention materials.

Characteristics of randomized *WHISH* participants are shown in the table below.

Descriptive Statistics of *WHISH* Participants at Randomization – Overall and by Age Tertiles (072020)

	All Participants (n=49331)		<77 (n=16878)		77 - 82 (n=16220)		≥83 (n=16233)	
Category	n	%	n	%	n	%	n	%
Outcome Coverage								
WHI Adjudicated Only	10554	21.4	3849	22.8	3493	21.5	3212	19.8
CMS Only	30346	61.5	10094	59.8	9980	61.5	10272	63.3
WHI + CMS	8431	17.1	2935	17.4	2747	16.9	2749	16.9
Age, mean (SD)	79.7	(6.2)	73.1	(2.2)	79.4	(1.7)	87.0	(3.2)
Ethnicity								
Non-Hispanic White	41606	84.3	13544	80.2	13735	84.7	14327	88.3
Non-Hispanic Black / African American	4514	9.2	1946	11.5	1493	9.2	1075	6.6
Hispanic / Latina	1628	3.3	771	4.6	502	3.1	355	2.2
American Indian / Alaskan Native	151	0.3	73	0.4	45	0.3	33	0.2
Asian / Pacific Islander	923	1.9	375	2.2	277	1.7	271	1.7
Unknown	509	1.0	169	1.0	168	1.0	172	1.1
Current Smoker								
Yes	1216	2.5	603	3.6	385	2.4	228	1.4
No	48103	97.5	16268	96.4	15831	97.6	16004	98.6
Use of BP Meds								
Yes	30136	61.1	8770	52.0	9989	61.6	11377	70.1
No	19195	38.9	8108	48.0	6231	38.4	4856	29.9
Use of Lipids Meds								
Yes	21801	44.2	6841	40.5	7464	46.0	7496	46.2
No	27530	55.8	10037	59.5	8756	54.0	8737	53.8
BMI, mean (SD)	28.0	(5.8)	28.4	(6.3)	28.2	(5.8)	27.4	(5.2)
>30	14921	30.2	11305	67.0	11135	68.6	11943	73.6
≤30	34383	69.7	5561	32.9	5077	31.3	4283	26.4
Physical Functioning Score, mean (SD)	71.6	(25.2)	79.3	(21.8)	72.3	(24.1)	62.7	(26.6)
<65	15152	30.7	3241	19.2	4720	29.1	7191	44.3
65 – 75	8283	16.8	2382	14.1	2894	17.8	3007	18.5
76 – 89	8312	16.8	2921	17.3	2929	18.1	2462	15.2
≥90	17525	35.5	8328	49.3	5657	34.9	3540	21.8
Limited ability to go up one flight of stairs								
No, not limited	35051	71.1	13609	80.6	11762	72.5	9680	59.6
Yes, limited a little	10777	21.8	2650	15.7	3507	21.6	4620	28.5
Yes, limited a lot	3497	7.1	619	3.7	948	5.8	1930	11.9
Limited ability to walk one block								
No, not limited	38899	78.9	14854	88.0	12991	80.1	11054	68.1
Yes, limited a little	7294	14.8	1482	8.8	2330	14.4	3482	21.5
Yes, limited a lot	3130	6.3	542	3.2	897	5.5	1691	10.4
Physical Activity, MET-hr/wk, mean (SD)	11.7	(12.5)	13.5	(13.5)	11.8	(12.4)	9.6	(11.1)
Self-report Treated Diabetes Ever	8446	17.1	2922	17.3	2906	17.9	2618	16.1
WHI Outcomes								
CVD	5041	10.2	1005	6.0	1638	10.1	2398	14.8
MI	1799	3.6	341	2.0	578	3.6	880	5.4
CABG/PTCA	3030	6.1	620	3.7	1001	6.2	1409	8.7
Stroke	1632	3.3	301	1.8	518	3.2	813	5.0

WHI HT Trial Arm								
Active	5736	11.6	1841	10.9	1881	11.6	2014	12.4
Placebo	5645	11.4	1743	10.3	1863	11.5	2039	12.6
Not Randomized	37950	76.9	13294	78.8	12476	76.9	12180	75.0
WHI DM Trial Arm								
Intervention	6402	13.0	2221	13.2	2252	13.9	1929	11.9
Comparison	9932	20.1	3507	20.8	3508	21.6	2917	18.0
Not Randomized	32997	66.9	11150	66.1	10460	64.5	11387	70.1
HI CaD Trial Arm								
Active	7369	14.9	2572	15.2	2514	15.5	2283	14.1
Placebo	7079	14.4	2439	14.5	2436	15.0	2204	13.6
Not Randomized	34883	70.7	11867	70.3	11270	69.5	11746	72.4
WHI Study Component								
Clinical Trial	24186	49.0	8096	48.0	8297	51.2	7793	48.0
Observational Study	25145	51.0	8782	52.0	7923	48.8	8440	52.0

At Fred Hutch, Dr. Charles Kooperberg is the contact PI and will provide leadership guidance and statistical guidance. He will oversee presentation of materials for the DSMB and progress reports. As contact PI, Dr. Kooperberg will provide fiscal oversight, and be responsible for reporting to the NHLBI. He is the contact PI of the *WHISH* Data Coordinating Center (WHI-CCC) during this current phase of the *WHISH* trial; his activities for that project were identical to the current project. At Stanford University, Dr. Marcia Stefanick has been and will continue to be responsible for the development and delivery of the physical activity intervention, including all mailed materials, email and automated telephone systems that deliver monthly motivational messages to participants, the www.whish.org website and its physical activity tracking tool, and unscheduled communications between Intervention participants and staff. Dr. Stefanick is the contact PI of the *WHISH* Clinical Coordinating Center (referred as the *WHISH* Intervention site) during this current phase of the *WHISH* trial. She collaborates with Dr. Abby King to integrate behavioral principles and implement the PA intervention in an adaptive manner. At the University of California, San Diego, Dr. Andrea LaCroix will continue to provide leadership in all aspects of the *WHISH* trial including oversight of the accelerometry and physical activity monitoring activities at the UCSD Exercise and Physical Activity Resource Center (EPARC). At the University of Buffalo, Dr. Michael LaMonte will provide expertise on exercise physiology and accelerometer-measured physical activity and sedentary time, advice on intervention messages, and work with the multi-PI team on data analysis and interpretation, development of additional ancillary studies using these (and other) results as preliminary supporting evidence, and, help evaluate the proposed biomarkers in response to trial randomization. Except for Dr. Kooperberg, all other PIs will be blinded to the data and data analytic activities. Decisions regarding the project management to meet the scientific objectives will be made jointly by the PIs with the exception of Dr. Kooperberg, who will not be a part of making decisions regarding the intervention component of the study. Drs. Stefanick, LaCroix, and LaMonte will all take active roles in unblinded primary data analyses under the project specific aims during the entirety of the blinded intervention phase. All PIs will take an active role in ongoing evaluation of data quality and manuscript writing; and will provide support in all aspects of study administration and scientific dissemination.

3.1.1.b. Study Procedures, Materials, and Potential Risks

Institutional Review Board (IRB) Review. All Phase 2 procedures, data gathering tools, consent form (e.g., accelerometry) and other study materials will be provided to the Fred Hutch IRB for review and approval once developed and before implementation.

Study Procedures. Under the Zelen design, *WHISH* comparison participants participate solely through their usual WHI mailed annual medical history update. In the first year, the *WHISH* participants randomized to intervention received an invitational welcome packet describing the PA program and materials, and the opportunity to ask questions or request that they not receive materials by calling a toll-free telephone number. Only 3.5% “opted out” of receiving materials, though by the Zelen

experimental design, they continue to participate through their usual WHI mailed annual medical history update. They will be analyzed as Intervention participants in intention-to-treat analyses. The invitational packet included an initial *WHISH*ful Actions newsletter (designed by the Stanford Intervention team) which included key information regarding the Department of Health and Human Services (DHHS) PA guidelines for older adults and the Workout to Go pamphlet from the National Institute on Aging (NIA) *Go4Life*® program, featuring strength, balance, and flexibility exercises. Intervention participants who did not opt out received three additional mailings spaced a month apart that included the full *Go4Life*® *Exercise & Physical Activity: Your Everyday Guide*, a pedometer, a calendar for tracking their steps and activity, if they so desired, an introduction to and sample from the interactive voice response system (IVR) "health coach" phone call system, "Adriana", and tips for how to use the materials. After the three initial mailings, intervention participants have been receiving quarterly (seasonal) *WHISH*ful Actions newsletters which feature tips on physical activity, balance, flexibility, fall prevention, and muscle strengthening. Participants were provided with resistance bands, accompanied by examples of exercises, information on the www.whish.org website which features exercise videos, participant stories, advice from a geriatric physical therapist, and links to selected websites, such as *Go4Life*®, https://go4life.nia.nih.gov, and Health.gov 'Move Your Way' for adults https://health.gov/moveyourway/#adults. Comparison women have access to the key intervention messages, including the NIA *Go4Life*® materials and Health.gov sites (see details below, Materials).

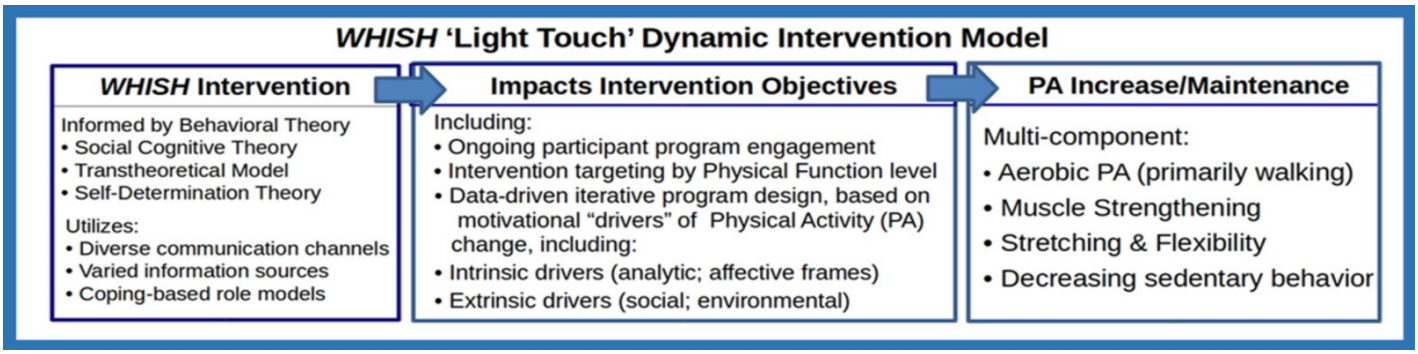
To monitor changes in PA in the Intervention and comparison groups "objectively", a substudy in 2350 *WHISH* participants (1,182 comparison; 1,168 intervention) was conducted during phase 1 during which consenting participants wore a waist accelerometer for 7 days and nights at 6, 18 and 42 months after randomization and completed a sleep log for each of the 7 nights. During phase 2, an accelerometry substudy will again be conducted to monitor changes "objectively." Please see section 2.5. Recruitment and Retention for the recruitment plan.

The *WHISH* trial will leverage the planned Long Life Study 2 (LLS2) in the Women's Health Initiative Extension Study (2020-2027) by utilizing data and biospecimens from an LLS2. Specifically, through *WHISH* specific aim 2, we will determine the intervention effects on measures of healthy CV aging including physical function (PF) measured using the Short Physical Performance Battery (SPPB), sleep disturbances and insomnia symptoms, and depressive symptoms. Under the *WHISH* Exploratory Aim, we will create an experimental framework within *WHISH* and conduct pilot studies to determine whether the *WHISH* PA intervention influenced levels of novel biomarkers indicative of healthy CV aging and/or occult myocardial injury, such as N-terminal pro-brain natriuretic peptide (NT-proBNP) and high sensitivity Troponin T (hsTnT). A *WHISH* Biomarker Advisory Group involving US experts will vet the most promising biomarkers for pilot- testing. This aim will facilitate future *WHISH*/WHI Ancillary Studies. The specific aim 2 and exploratory aim are contingent on WHI Extension Study contract funding of the LLS2.

Materials. Women randomized to the PA intervention group were contacted by mail by the *WHISH* DCC (WHI- CCC) to obtain (passive) informed consent. This initial mailing included three items: (1) a cover letter from the WHI-CCC Principal Investigator with information about the *WHISH* trial and the 800-number to "opt out" of receiving materials for the *WHISH* PA Intervention; (2) *WHISHful Actions: National Recommendations for Physical Activity in Older Adults* (i.e., basic information on the national DHHS PA recommendations with health and safety tips); (3) the *Go4Life® pamphlet "Workout to Go: A Sample Exercise Routine from the National Institute of Aging at NIH".* Women who did not "opt out" received an initial set of materials mailed from the Stanford University *WHISH* PA intervention site a month apart, including the *Go4Life*® book, *"Exercise & Physical Activity: Your Everyday Guide from the National Institute on Aging,"* a pedometer and calendar for tracking activity, and information on a website physical activity tracking tool. After this initial set of three mailings, mailed materials have included quarterly (seasonal) newsletters (*WHISH*ful Actions), a resistance band complemented by exercises, information about an automated interactive voice response system ('Adriana') which also provided a tracking tool, annual physical activity logging calendars, another pedometer, and a *WHISH* visor for sun protection. The

quarterly *WHISH*ful Actions newsletters included additional written information using American College of Sports Medicine "Exercise as Medicine" messages, the new 2018 DHHS Physical Activity recommendations for older adults, findings from the WHI OPACH study regarding benefits of light intensity physical activity and harms of sitting, and safety tips and advice from a geriatric physical therapist regarding gait and balance. Materials are developed to promote activity with friends, neighbors and family, (e.g., grandchildren), and facilitate social support. A survey was sent every year to obtain input from participants which is used to adapt materials to reflect their personal activity preferences and inserts are developed for three "target" groups based on self-reported physical function and physical activity levels from WHI forms. The website (with a secure login for participants who had been randomized to the intervention) was overhauled to be more user friendly for older women. Materials are described in more detail in the Research Plan and in the subsequent paragraphs until the potential risks section.

The *WHISH* pragmatically designed, PA intervention is an innovative "light touch", remotely delivered behavioral intervention, consistent with the multicomponent DHHS PA recommendations for older adults.[28, 29] *WHISH* applies state-of-the-science behavioral theory,[30-32] embedded in an iterative framework based on participant input from annual surveys and other sources, to motivate women to increase or maintain PA levels and reduce sedentary behavior. "Light-touch" refers to interventions delivered primarily by non-health professional staff and resources.[33]



Initial mailings to Intervention participants included the NIA *Go4Life® Exercise & Physical Activity:* Your *Everyday Guide* book, easy-to-use PA tracking calendars, pedometers, resistance bands, and a toolkit of specific exercises. Seasonal (quarterly) "*WHISH*ful Actions" newsletters (e.g. Figure 4) emphasize walking and aerobic activities, muscle strengthening, balance and flexibility exercises, and reducing sedentary behavior, which women are encouraged to track. The multi-modal/multi-channel, remotely-delivered intervention also includes an algorithm-driven interactive voice response (IVR) system of tailored advice, support, and personal goal setting for the 98% of participants who are receiving the IVR outbound motivational messages, and email-based messages for the 33% of participants who provided email addresses, and a website (www.whish.org) with a self-monitoring (tracking) tool aimed at the 76% of *WHISH* participants who reported using the Internet and provides links to *Go4Life®*,[34] Health.gov, and other sites. Participants can also reach staff with questions and feedback through inbound email, phone, and mail channels throughout the intervention.

Intervention materials are continuously adapted and improved in response to participant engagement that occurs through mailed surveys, postcards, e-mail, and telephone contacts. Participants report their activity preferences, information on what motivates them to move more and be less sedentary, and their perceived barriers to PA. PA resources and intervention materials are adapted to reflect this input. An array of motivational drivers of PA change are addressed[35] including informational drivers, e.g., news and research stories featured in *WHISH* newsletters and on the *WHISH* website, affective drivers (thoughts and feelings), social drivers (friends and family, caregiver activities) and environmental cues and contexts (e.g., coping with weather, strategically posting PA reminders, etc.). Participants

themselves serve as “coping” role models through sharing their personal stories (and photos) about overcoming barriers to PA, e.g., recovery from injuries, illnesses, and personal losses, in regular “Life Happens” newsletter features, which are particularly well-liked by participants. The *WHISH* website offers even more participant stories, as well as videos of participants demonstrating exercises from the newsletters and links to a range of PA websites, such as Health.gov ‘Move Your Way’ for adults https://health.gov/moveyourway/#adults/), and materials reviewed and approved by a geriatric physical therapist who recommends specific exercises, advises on the instructions and provides safety tips.

Targeted Intervention Materials. To increase the salience and accessibility of messages to older women with diverse PF levels, targeted materials have been developed, based on participant feedback that materials were too challenging for some and not challenging enough for others. Starting with the Fall 2018 newsletter, which emphasized the health benefits laid out in the 2018 Physical Activity Guidelines (PAG) for Americans (Older Adults)[36], we created three sets of instructional materials to promote high intensity interval training activities (HITT) appropriate for women at different physical functioning levels, defined by a combination of physical function and PA scores based on each woman’s most recent WHI- reported measures (PF=RAND-36[37] [higher score reflects greater PF]; PA=MET-hrs/week) (percentages in low, generic, and high function/PA categories= 36%, 32%, and 32%, respectively; see Table 5). These categories have been used to more specifically adapt and target *WHISH* materials to the needs and preferences of each group, starting with a “micro-experiment” (see below).

Table 5. Characteristics by Targeted Intervention Group.

Group	Low	Generic	High
N	7064	6122	6004
Age (ave (sd))	81.0 (6.0)	79.0 (5.8)	76.9 (5.2)
Current Age			
<77	24%	32%	44%
77-82	38%	32%	30%
>82	17%	31%	52%
PF (ave (sd))	40.7 (20.5)	70.4 (20.0)	91.7 (6.4)
Race/ethnicity			
White	37%	32%	31%
African-Amer	43%	30%	27%
Hispanics	31%	34%	35%
Asian/PI	29%	35%	36%

Launching of “micro-experiments” to optimize intervention adaptations for key subgroups. To inform more intensive targeting of the multi-component intervention to key subgroups based on PF and PA levels— the major factors predicting future PA—a micro-experiment was launched to assess the low, “generic”, and high “targeted” inserts. Women in a lower function category were randomly assigned to receive either mailed instructional materials targeted to low function or more generic materials, i.e., a mix of different function and PA levels, while women in a higher function category were randomly assigned to receive either the generic materials or materials targeted to high function. Current age, body mass index, and walking aids differed between these two randomized groups (see Table 6), whereas both groups are composed of ~82% white, 10-11% black, 3- 4% Hispanic, 2-2.5% Asian/PI, 0.2-0.4% Native American or Alaskan women. Participant engagement (% of surveys and postcards returned) and responses to specific questions about the usefulness of intervention materials are currently being analyzed and will inform further targeting activities.

Table 6. Micro-Experiment: Targeted Intervention Groups.

	Random Low		Random Low Generic		Random High Generic		Random High	
N	2561		2518		2491		2522	
Current age	N	%	N	%	N	%	N	%
<77	582	22.7	637	25.3	948	38.1	999	39.6
77-82	938	36.6	850	33.8	937	37.6	926	36.7
>=82	1041	40.7	1031	40.9	606	24.3	597	23.7
BMI								
<25.0	708	27.7	687	27.3	946	38.0	955	37.9
25.0-29.9	878	34.3	808	32.1	928	27.3	913	36.2
>=30.0	973	38.0	1023	40.6	616	24.7	652	25.9
Aids								
No aid	1709	71.5	1676	71.2	2218	96.0	2247	95.1
Cane	438	18.3	449	19.1	64	2.8	91	3.8
Walker	238	10.0	224	9.5	26	1.1	25	1.1

Continuing Participant Engagement. The above suite of intervention and communication activities has resulted in a strong and sustained level of participant engagement *in this pragmatic trial, which women may not have sought out and were not actively recruited.* As of April 20, 2019, 86% of the initial 23,940 women (and >93% of racial/ethnic minority women) who were randomized to the Intervention and did not opt out and are not known to be deceased, *remain in the intervention.* Response rates to annual surveys have steadily increased each year; Survey #1, 49%; Survey #2, 53%; Survey #3, 63%; Survey #4, 72%.

Survey #4 response rates ranged from 63-65% in the oldest women and in women reporting low PF scores, to 77% in younger women and those with high PF, and >63% in every race/ethnic group, with

the greatest increase from early survey response rates demonstrated among African American *WHISH* participants. As only 45% of black women had returned Survey #2, we conducted a formative evaluation of barriers and enablers in a small set of African American "non-responders" to learn why these individuals hadn't returned the surveys and to inquire about their physical activity. A couple of these personal stories were featured in the "Life Happens" section of the *WHISH* newsletter which may have resonated with other participants. Similar efforts are made to create materials, present stories, and include photos that reflect the heterogeneity of the *WHISH* study population and to develop materials that participants who respond to surveys report liking and wanting. Our mini-experiment of targeted materials will provide invaluable information on the success of this approach.

Planned Intervention Activities Moving Forward. Building on the successes from the initial intervention period, which include solid ongoing participant engagement and WHI data-derived changes observed in all PA behavior domains relative to the Comparison group our planned intervention aims are to:

- continue to focus on aerobic activities, particularly walking, occurring throughout the day, while emphasizing the importance of the continuum of PA intensities (light, moderate, vigorous) for older women, and promoting the concept of relative intensity, as experienced by the "Talk Test" (Light: can sing and talk while moving; Moderate: cannot sing, but can still talk; Vigorous: can only speak a couple of words at a time). In addition, a particular emphasis for the entire intervention will be on helping women optimize their ability and motivation to ***maintain their PA levels*** in the face of the typically observed ongoing decline associated with aging;
- increase the emphasis on the additional ***multi-component PA domains and a well-rounded routine*** that often receive less attention in PA interventions, but have been shown to be particularly important for older adults, i.e., muscle strengthening, stretching and flexibility, balance, and gait (presented as *"wiser walking"*);
- expand information related to reducing sedentary behaviors throughout the day, including breaking up inactive sitting or lying down, and replacing with light and moderate forms of PA;
- strive to increase survey response rates and participant engagement, including accessing the *WHISH* PA website which has been developed specifically for the *WHISH* study population of older American women.
- systematically explore the addition of "light-touch" mobile app interventions for the more than half of the *WHISH* Intervention women who reported having smartphones;
- conduct further micro-experiments to continue to advance intervention targeting and adaptations to specific subgroups who are particularly vulnerable to PA decline or diminished program engagement (e.g., low physical function participants).

Methods that we will employ to promote the intervention objectives include:

- continued targeted data collection to drive adaptive program design, including delivery of intervention components that particularly focus on four major domains of motivational drivers for PA, i.e., analytic (targeted and personalized facts and information concerning PA and its benefits), affective (thoughts and feelings), social (*WHISH* participant role models and success stories), and environmental drivers (increasing cues, prompts, and contexts that motivate PA);
- instructing participants in easy and safe field-based self-testing (e.g., portions of Rikli and Jone's field-based physical function tests for older adults,[38] along with *Go4Life*®'s[34] self-assessment) that can provide individualized feedback and promote PA and physical function increases;
- increasing real-time data collection via the IVR-based outdialer system (which reaches 98% of participants), whereby participants can answer simple questions by phone, to continue to shape and enhance intervention relevance and potency;
- partnering with Stanford's interdisciplinary bio-engineering Mobilize Center (http://mobilize.stanford.edu/) to test out the delivery of interactive smartphone apps aimed at increasing PA and decreasing sitting throughout the day.[39, 40]

Potential Risks. The *WHISH* PA Intervention is based on the DHHS Physical Activity Guidelines for older adults (originally 2008, now 2018) https://health.gov/paguidelines and has featured materials developed for the *Go4Life*® campaign of the National Institute on Aging (NIA) at the NIH (http://go4life.nia.nih.gov),

which was designed to help older adults fit exercise and PA into their daily lives. Materials include an easy-to-read guide *Exercise & Physical Activity: Your Everyday Guide from the National Institute on Aging*ˆ(available in Spanish) and the *Go4Life*® website which includes a **"Stay Safe"** section that states, "almost anyone, at any age, can safely do some kind of exercise" and "most people do not need to check with their health care provider first before doing physical activity". A geriatric physical therapist advises on and reviews print materials and videos posted on the www.whish.org website. Risks associated with the intervention are those typically associated with common physical activities like walking, including muscle soreness, fatigue, possible falls and other PA-related injuries. However, it is also true that sedentary behavior is associated with poor health outcomes including falls and fractures. No psychological, social, cultural, financial, and legal risks; risks to privacy and/or confidentiality; or other risks are anticipated.

Alternate treatments. All *WHISH* participants may be physically active on their own, including group and health clubs. The *Go4Life*® materials are available at no charge from the NIA *Go4Life*® website (go4life.nia.nih.gov) and all participants can access Health.gov 'Move Your Way' for adults https://health.gov/moveyourway/#adults/ and other public websites linked to the www.whish.org site.

3.1.2. Adequacy of Protection Against Risks

3.1.2.a. Informed Consent and Assent

Participants were randomized into intervention and comparison at equal rates (50-50) under the Zelen design. Under the Zelen design, a separately conducted consent process was not conducted. *WHISH* comparison participants participate solely through their usual WHI mailed annual medical history update. The *WHISH* participants randomized to intervention received an invitational welcome packet describing the physical activity (PA) Program, introductory PA materials, and the opportunity to ask questions or opt-out of receiving materials by calling a toll-free telephone number. The invitational mailing was approved by the Fred Hutch Institutional Review Board (IRB) to serve as a passive consent. *WHISH* intervention participants who did not opt-out began receiving additional intervention materials monthly for the first three months followed by quarterly (seasonal) mailings, monthly motivational messages delivered by telephone, and for women who provided email addresses, by email. Women may request no further mailings, calls, etc., which 12.8% of participants assigned to the Intervention have done to date. See 1.b. Study Procedures, Materials, and Potential Risks for details about the intervention materials. Participants who were selected for the Accelerometry Substudy received an invitational mailing that included a formal consent process by mail and phone. The invitational mailing included a cover letter from the *WHISH* DCC PIs, study description, toll-free number to call for questions about the study, and a copy of the consent form. Participants who returned a signed consent form were enrolled into the substudy.

3.1.2.b. Protection Against Risks

Women who receive the PA program intervention materials were encouraged to talk with their health care provider (HCP) before engaging in the PA intervention if they weren't already engaging in activity. At any time during the trial, these participants are encouraged to consult with their HCP about any new symptoms they are concerned about that they haven't previously discussed with their HCP. A licensed geriatric physical therapist reviews all materials and advises on exercises. The *WHISH*ful Actions newsletters provide tips regarding balance and fall prevention, including materials tailored for women who use walkers or canes, those who have trouble rising from sitting, and those who may not be able to stand (such as "sit and be fit" activities). These tips also are presented on the *WHISH* website (including video tutorials) and with monthly automated tips calls implemented through the outbound "Adriana" telephone system.

The privacy of participants and confidentiality of research data are protected through several mechanisms. The WHI Clinical Coordinating Center (*WHISH*-DCC) was required to submit to the NHLBI an extensive and detailed System Security Plan addressing how we ensure data integrity, security, and confidentiality. The WHI-CCC runs a standalone Windows-based network with its own Windows domain controllers, firewall, VPN, routers, and switches. All WHI database and analysis files are located on a file server located in the WHI-CCC Data Center, which sits behind an enterprise class Sonicwall firewall with Intrusion Protection enabled. The server runs Windows 2008 R2 Advance Server and Oracle, both configured with the latest security patches. Only WHI-CCC IT personnel required to maintain the server and data personnel are authorized to access the data. CCC employees who access confidential participant data have password-protected computers that are in locked offices. All WHI-CCC staff are required to sign a confidentiality agreement as well as attend HIPAA and IT security training. This helps ensure that staff are educated regarding their responsibility for the security and confidentiality of the WHI and CMS data.

3.1.2.c. Vulnerable Subjects

Not relevant to *WHISH* as no fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals or other vulnerable populations are included.

3.1.3. Potential Benefits of the Proposed Research to Research Participants and Others

The direct benefits of participating in a regular exercise program may be increased aerobic fitness, muscle strength, flexibility, and balance, possible reduction in falls and/or fractures, in addition to a possible reduction in the risk of developing cardiovascular disease. Evidence suggests that women who increase their PA levels develop fewer disabilities and are more likely to remain mobile and have better physical and cognitive function. Women will also learn more about monitoring and improving their fitness level in general. Although these potential benefits are stated in the DHHS Physical Activity Guidelines for older adults, many have never been proven in large, randomized clinical trials, which is the main purpose of the *WHISH* trial.

For the Accelerometry Substudy, wearing an accelerometer for 7 days entails only minor risks, such as irritation caused by the elastic belt around the waist, or inadvertent pinching by the belt clasp. In addition, wearing the belt and device during the day and night may cause minor discomfort or annoyance. If women experience discomfort or difficulty wearing the accelerometer, they are advised to call study staff and report these problems. A better fitting belt may be supplied, or the woman may be advised to discontinue the monitoring.

3.1.4. Importance of the Knowledge to be Gained

The information obtained in this study could influence national guidelines on physical activity for older women, and influence how health care providers advise older adults about PA. The study findings could contribute to efforts to promote PA in older adults, leading to improvements in health status of older adults. The study is especially well positioned to determine how much and what kind of physical activity is needed to reduce the risk of cardiovascular outcomes in older women, including how much moderate/vigorous activity is needed, if any, as well as potential benefits of light intensity activity and reduced sedentary behavior to cardiovascular outcomes. Information, additionally and importantly, will be obtained about the safety of PA in this population and about possible improvements, or at least lesser age-related decline, of physical function and mobility.

Overall, we consider the risks associated with slowly increasing PA levels to achieve national recommendations regarding PA for older adults to be reasonably low for the PA intervention participants, as is the burden associated with providing information on changes in behavior. The potential benefits to

participants are increased fitness and the positive consequences therein. The findings may influence national guidelines on physical activity for older adults, which is of tremendous value. Thus, on balance, the overall risks are minimal relative to the expected benefits.

3.2. Is this a multi-site study that will use the same protocol to conduct exempt human subjects research at more than one domestic site? No

3.3. Data and Safety Monitoring Plan

The *WHISH* trial has a Data Safety Monitoring Board (DSMB), appointed by the National Heart, Lung, and Blood Institute (Eugene R. Passamani, MD, chair) that is meeting annually. The DSMB approved a monitoring plan. This plan was adapted to the original proposal and assumed a trial end in 2020.

The monitoring plan below has two changes compared to the approved monitoring plan. (i) There is a change in meeting times and numbers, as they would be adjusted to accommodate an 8-year follow-up. (ii) There will be an interim monitoring taking place in the spring of 2022. These changes naturally would have to be approved by the DSMB. The additional outcomes that we are proposing in this extension (SPPB, Sleep Disturbance, and Depressive Symptoms) are not used for monitoring under the currently approved plan. The DSMB would see data on these outcomes, but they are not discussed in this monitoring plan.

3.3.1. Protocol Defined Outcomes

The primary outcome of the *WHISH* trial is

- CVD: defined as (first event since enrollment in *WHISH* of) MI, stroke, cardiovascular (CV) death

Safety outcomes are:

- Non-CV death
- Hip fracture
- Revascularization
- Falls
- Clinical (non-hip) fracture

Secondary outcomes are:

- Venous thrombosis (VTE)
- Peripheral artery disease (PAD)
- Physical function, as determined by the Rand-36 score

Phase 2 adds to the above:

- Short Physical Performance Battery (SPPB) in a subset
- Sleep disturbance
- Depression

3.3.2. Monitoring Guidelines

Trial monitoring for WHISH has two main purposes, assuring the safety of participants and that this effort will result in an adequate test of the hypotheses.

During the first phase of WHISH, the WHISH trial had no formal monitoring boundaries for stopping early for CVD efficacy: the intervention is already publicly available, thus the benefit of getting a definitive answer was deemed to outweigh the benefit of making a less clear result public. This position was first

offered by the DSMB and agreed upon by the investigators in the pre-trial discussion and justified by the following: 1) the need for a broader assessment of the benefits and risks of increasing physical activity in the elderly, 2) the benefits for CVD being strongly anticipated from prior studies mostly in younger populations, and 3) the availability of the intervention materials means that the study is not denying anyone access. Similarly, the trial was not be monitored for futility with respect to the cardiovascular outcomes, recognizing the importance of establishing changes in physical activity by itself.

In discussions with the NHLBI it was agreed upon that during the second phase of WHISH there will be one formal monitoring (interim analysis) of the primary CVD/stroke/Cardiovascular Death endpoint, both for benefit and futility. This interim analysis will take place in the spring of 2022. Details are provided in the next section, 3.3.3. Interim Analysis for the WHISH Trial to be taking place in 2022.

Safety is our highest concern. This physical activity intervention, which is built upon materials provided by the National Institute on Aging, is thought to be safe for older Americans. It has not been tested, however, in a population of this size and so there is real value in documenting the impact of this intervention on multiple health conditions.

Among the safety outcomes, non-CV death and hip fracture are much more severe than the others (revascularization falls and clinical (non-hip) fracture) so safety monitoring guidelines will be defined only for the more severe outcomes, although data on all outcomes will be provided regularly. The primary outcome (CVD) should also be monitored as a (severe) safety outcome. CVD, non-CV death, and hip fracture will be monitored for safety at the (annual) DSMB meetings after Medicare data is available. The DSMB decided for the first phase of WHISH that each of the three outcomes would be monitored for safety at each of four monitoring meetings using a Z-value of 2.51. Based on simulations, the cumulative probability that the Z-statistic for one of these outcomes will exceed 2.51 at the first four meetings, if in truth there is no effect, is approximately 5%, assuming that the three monitored safety outcomes are independent. After WHISH is extended there will be three additional monitoring meetings, bringing the total to seven. Based on simulations, the cumulative probability that the Z-statistic for one of these outcomes will exceed 2.51 at the any of the eight meetings, if in truth there is no effect, is approximately 6.3%, assuming that the three monitored safety outcomes are independent.

Increased levels of activity in the intervention group may uncover symptoms of angina or claudication, and lead to revascularization procedures (coronary and peripheral artery, respectively). These procedures could actually reduce the rate of subsequent, more serious complications, such as myocardial infarction, and hence would not carry the same adverse safety signal as the other events to be monitored in WHISH. There are other plausible explanations for possible differences in revascularization rate. Similarly, there are multiple explanations of why rates of falls may differ between both arms of the trial. Therefore, while CVD and hip fracture are monitored outcomes, rates of revascularization and falls are reported but not formally monitored since the clinical implications for differences in these rates may or may not be apparent at the time they are observed.

Medicare data obtained from CMS is available in annual “batches”. Formal monitoring of the WHISH trial will take place in the late spring or early fall, at the time of the first DSMB meetings after receipt of Medicare/CMS data. These analyses would include adjudicated data for women in the WHI Medical Records Cohort (MRC) through the approximate date at which the Medicare data becomes available (see Section 3.3.8). The amount of follow-up available to women that are part of the MRC will be approximately the same as that for those women whose data is available through Medicare/CMS.

A final analysis including all available Medicare/CMS data, as well as adjudication of all self-reports not covered by Medicare/CMS through the end of the study will be presented within six months after that.

At DSMB meetings where there is no formal monitoring, updated outcomes data will be presented for informational purposes.

Additional analyses of safety outcomes will be provided to the DSMB at each meeting, as described in Section 3.3.3.

Interim analyses will employ use of a constant boundary for the three safety endpoints, as described above.

3.3.3. Interim Analysis for the WHISH Trial to be taking place in 2022

Background: An interim analysis for the WHISH trial will be carried out in the spring of 2022 (before July 1, 2022). The analysis will focus on the primary WHISH outcome of CVD/stroke/cardiovascular death. The analysis will allow for possible early stoppage for either benefit or futility. We propose conservative bounds/approaches, as we believe that there is much to be learned from the continuation of the WHISH trial for outcomes other than the primary outcome (e.g. for the secondary outcome of physical function) and subgroups of particular interest.

It is expected that at the spring of 2022 approximately 65% of the primary outcomes for the WHISH trial will have been observed.

Stopping for benefit: the null hypothesis for the WHISH trial is that there is no cardiovascular benefit, with an alternative hypothesis of cardiovascular benefit. This hypothesis is to be tested at a two-sided alpha level of 0.05; thus the test for benefit is one-sided at 0.025. The test-statistic for the primary outcome is already computed for each DSMB meeting using a stratified Cox proportional hazard model. We propose to apply an O'Brien-Fleming (OBF) boundary to this test-statistic. With one interim analysis at information of about 0.65 of the projected total, the OBF boundary is Z=2.547; the critical value at the end of the trial would correspondingly be adjusted from Z=1.965 to Z=1.990, to correct for the earlier look. The interim analysis uses alpha=0.00543 of the total alpha of 0.025 assigned to benefit.

Stopping for futility: we propose to calculate conditional power for the primary WHISH outcome using the same procedure as we used in the calculations provided to NHLBI leadership in January of 2020. These calculations, in turn, were modifications of the unconditional power calculations that were presented in our application for R61-HL151855 (the application for the continuation of WHISH). Details are given below. We propose that consideration be given for stopping for futility at that point if the conditional power for the primary outcome is below 20%. However, we note that, depending on the results for the secondary outcome, there may be reason to continue the trial even if the conditional power of the primary outcome is below this value.

These proposed statistical boundaries represent a change from the current plan adopted by the WHISH DSMB and thus will require their ratification. Further, these statistical boundaries do not address the complexity associated with these decisions when multiple clinical outcomes may be affected on different timescales. Thus, the DSMB will need to weigh the totality of the available evidence as well as what could yet be gained relative to any ethical demands when considering early termination.

<u>Details of the proposed procedure to compute the conditional power</u>

1. We estimate the currently observed event rates for the primary outcome of CVD and the censoring outcome (non-CVD death) pooled over both arms, smoothed over 5-year windows (e.g. the rate at age 86 is the average of the rates between ages 84 and 88). The rates (which will be updated in 2022) that were used in January 2020 are shown in Figure 1 of the appendix to the Proposed Interim Analysis Plan for the WHISH trial document, reproduced here. We note that the rates are almost identical to those shown in the proposal, as computed in 2019.
2. For participants who have not yet observed the primary WHISH event, and who have not been censored, we assume an end of follow-up of December 31, 2024.
3. For the assumed intervention effect, we will assume an effect of 8.5%, which is what we assumed in our proposal.

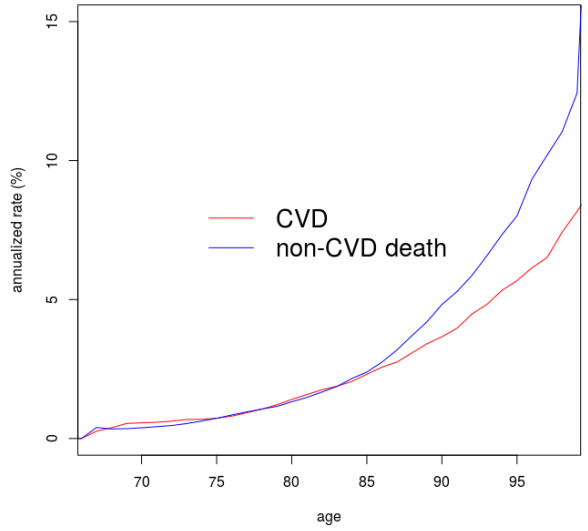


Figure 1. Observed incidence rates for CVD and non-CVD death in WHISH.

4. The power is then computed by simulation.
    a. If a participant had a CVD event (*T*) or a censoring event (*C*, non-CVD death) occur by the time of the database closure of the interim analysis, these are the event (or censoring) time for that participant.
    b. For participants alive and without events at the time of the database closure of the interim analysis, we generate possible event times *T* and censoring times *C* according to the rates computed at (1) starting at their last follow-up time. We create a difference in the event time rates assuming a difference of 8.5% in event rates of CVD for the remaining study period. If the participant had no event and was not censored before December 31, 2024, the participant is censored on December 31, 2014.
    c. We set, as in a standard survival analysis, $X=\min(T,C)$ and $\delta=(\text{Ind}(T<C))$. We fit a proportional hazard model, correcting for age stratum (as is done in the primary analysis), and compute the P value for intervention effect.
    d. For each of the 100,000 simulations we count how often P<0.025, corresponding to the alpha=0.025 assigned to benefit.

3.3.4 Reporting of Primary, Safety and Secondary Outcomes

At each interim analysis we will show for each of the primary, safety, and secondary outcomes intervention effect sizes (unadjusted 90%, unadjusted for multiple comparisons), confidence intervals, and Z-statistics. For all of these outcomes, except for falls and physical function, these estimates will be based on Cox-proportional hazards models. The rate of falls will be compared using Poisson regression. For physical function the mean level of physical function between the groups will be compared using linear regression with a possible log transformation to improve normality.

In addition to the individual outcomes, we will also provide analyses for the first event of any of CVD, hip fracture, or non-CV death ("global index"), noting that this global index is not a formal part of the monitoring plan, but can be used by the DSMB to balance effects if different outcomes have effects in different directions. The randomization of the *WHISH* trial is stratified by outcomes data source (MRC or

Medicare), age on April 1, 2015 (in tertiles), race/ethnicity, and region (West, Midwest, Northeast, and Southeast). The analyses will also all be stratified by the same categories.

The formal analyses will be based on confirmed outcomes (adjudicated or using Medicare/CMS data); however, we will also provide analyses where adjudicated outcomes are complemented with self-reported, but not-yet-confirmed, outcomes. We note here that in WHI, MI and stroke events are confirmed on review for about 60% of self-reports. For hip fracture about 80% of self-reports are confirmed.

All analyses will be carried out using an intent-to-treat analysis, including all women randomized: participants who "opt out" will be included in all analyses in their assigned arm for monitoring and primary reporting purposes. In particular, deaths that occurred between randomization and the start of intervention are included in the analyses. Similarly, participants who stop the intervention, or participants who become ineligible will remain in these analyses. For safety considerations, intent-to-treat analyses may be supplemented with analyses restricted to the women in the intervention who consented to receive the intervention, or to women who made noteworthy changes in exercise levels.

Additional analyses will be provided for these pre-specified subgroups:

- Participants with adjudicated outcomes versus those with only Medicare data.
- Stratification by age in tertiles.
- Analyses excluding participants who "opt out".

For approximately 10,000 participants we will obtain both Medicare and adjudicated outcomes. For these participants the adjudicated outcomes will be used for monitoring. Analysis comparing the Medicare and adjudicated outcomes for these participants will be presented to provide insight in how comparable both sources of data are.

3.3.5. Reporting of Physical Activity Levels

Self-reported physical activity levels are ascertained on an annual basis from all participants in both arms of the trial through Form 521. Reports will include (self-reported) time spent walking, METS spent while walking, frequency of activities and total time spent on activities as assessed by the Community Healthy Activities Model Program for Seniors (CHAMPS) instrument (1).

An Accelerometry Substudy is carried out in 2000 participants in both arms of the study (1,000 in each arm) at approximately 6, 18, and 36 months after randomization, an additional round of accelerometry will be carried out in 2021 or 2022. This study will provide a more unbiased estimate of the activity levels than the self-reported activities. We will provide results from this study to the DSMB, including computed average activity level, and time spent sedentary, and in light and moderate/vigorous activity.

3.3.6. Reporting of Intervention Activities

We will report on the following intervention activities:

- Percentage of women in the intervention arm opting out.
- Percentage of women completing the Accelerometry Substudy, by arm.
- Activity levels of the intervention women.
- Engagement with the intervention: e.g., percentage of women returning surveys.

3.3.7. Reporting of Additional Outcomes

We will report on the following outcomes in manners similar to the primary, safety, and secondary outcomes:

- Cancer (including specific sites)
- Context of fall (inside/outside, during exercise, etc.).

3.3.8. Timeline for Outcomes Data Collection and Availability

For logistical reasons, *WHISH* participants were initially randomized in batches: the first 9,865 subjects (half intervention, half comparison) were randomized in April 2015, the next 30,801 were randomized in May 2015, and the remaining subjects were randomized in July 2015. These numbers included a small number of WHI participants who were deceased at the time of randomization, but for whom that was not known. The Consort Diagram (in Section 2.5) presents that information. The enrollment time for any *WHISH* participant was the first day invitation letters are mailed for subjects in the batch the subject was in, irrespective of whether the subject was randomized to intervention (and received such a letter) or was a comparison.

The average amount of time participants were enrolled in *WHISH* was about 7 months by December 31, 2015.

Self-reports are collected annually on WHI Form 33. Because of the annual cycle, there is an average 6-month delay in the outcomes collection of self-reports, plus an additional several weeks because of delays of returning the forms. Thus, self-reported outcomes will have an average 7-month delay.

The outcomes documentation and adjudication process takes on the average 2-3 months. Thus, outcomes for participants with full adjudication will have an average 9-10 month delay.

Medicare data is obtained from CMS on an annual basis. We expect to receive partial CMS data for the previous year in February of the next year, and (virtually) complete data by the following July. It will take at least two months to incorporate CMS data in the reports for the DSMB. Therefore, if the DSMB meetings are in March of any given year, the data for the subjects for whom we have CMS data will be approximately 15 months out of date. At the end of the study we will adjudicate all self-reports that were not yet covered by CMS data, thus reducing the delay for these participants to the same 9 months as for the participants with adjudicated outcomes.

Death reports are obtained from proxies as they occur, or when Form 33 data gets collected. It is important to note that reports of death may be obtained differentially in the two arms of the trial because of more frequent contact with intervention participants. To reduce the bias that this may introduce, proxy reports of death will only be included in the analysis at the time a participant was due for her Form 33. Periodic NDI searches occur in late spring – resulting in additional death reports typically after the proxy reports, but well ahead of the Medicare data. Rules regarding the classification of death, in particular when deaths are not yet adjudicated, are discussed in Section 3.3.8.

The proposed extension of *WHISH* will be funded as a 4-year project through 2024. It is envisioned that the trial will have a no-cost extension, allowing for a final analysis based on the database on January 1, 2025.

3.3.9. Outcome Definitions

Self-reports

- All clinical outcomes and falls are self-reported annually on WHI Form 33.
- Deaths are reported by proxies. Proxy reported deaths are only "counted" after the due-date of Form 33, to prevent differential ascertainment between both trial arms.

Validated outcomes for participants in the Medical Records Cohort (roughly 40% of the WHISH cohort, defined as former WHI Hormone Trial participants plus all African American and Hispanic participants):

- All adjudicators involved in WHI are blinded to *WHISH* treatment assignment.
- Stroke is adjudicated by neurologists using standard WHI procedures, including the Toast classification.
- Cancer is currently adjudicated by SEER coders using standard WHI procedures. Cancer is also adjudicated for participants not in the Medical Records Cohort. At the time of writing of this monitoring plan, it has not been determined whether cancer outcomes will continue to be adjudicated for WHI. If cancer will not be adjudicated, we will develop CMS algorithms, and use self-reports, if needed.
- All other clinical outcomes, except for clinical (non-hip) fractures, are adjudicated by physician adjudicators using standard WHI procedures.
- Clinical (non-hip) fractures are not adjudicated. In WHI it was found that fact of fracture (though not the site of the fracture) was self-reported at a high accuracy of about 80-85%. Finger and toe fractures are not counted for *WHISH*.
- Cause of death is adjudicated by physician adjudicators using standard WHI procedures. Not-yet- adjudicated death is classified with non-CV death until adjudication is complete. (The coding of death provided by NDI has been mapped to the classification used for WHI by physician adjudicators.)

Medicare/CMS outcomes:

We use the following algorithms to identify clinical outcomes using Medicare/CMS data:

- MI: Diagnosis codes of 410.x0 or 410.x1 in any position. (2)
- Stroke: Diagnosis codes 430, 431, 433.x1, 434.x1, and 436 in any position. Codes 430 and 431 correspond to hemorrhagic stroke, codes 433.x1, 434.x1, and 436 correspond to ischemic stroke. (3)
- Hip fracture: Diagnosis codes 820.00, 820.01, 820.02, 820.03, 820.09, 820.10, 820.11, 820.12, 820.13,

  820.19, 820.20, 820.21, 820.30, 820.31, 820.8, 820.9 in any position.
- Coronary artery bypass graft surgery: procedure codes 36.1x, 36.2.
- Percutaneous coronary intervention: procedure codes 00.66, 36.0, 36.00, 36.01, 36.02, 36.05, 36.06, and 36.07.
- Venous thrombosis (VTE): Pulmonary embolism (PE): diagnosis codes 415.11, 415.19 in any position, and Deep venous thrombosis (DVT): diagnosis codes 453.40, 453.41, 453.42, 453.8 in any position.
- Peripheral artery disease (PAD): Diagnosis codes (440.20 – 440.24, 440.9, 443.9, 444.22, 444.81, 447.1, 443.81, or 250.70 any position) AND either (1) a procedure code for surgery (39.50, 39.90, 00.55, 17.56, 99.10, 38.08, 38.14, 38.16, 38.18, 39.25, 39.29, 84.11, 84.12, 84.15, or 84.17 any position) or (2) a procedure code for imaging (88.01, 88.42, 88.47, 88.48, 88.76, 88.77 any position) without a procedure code for surgery. The diagnosis and procedure codes must occur during the same hospitalization.

Death:

- Fact of death can be proxy-reported, determined from the CMS/Medicare data, or identified from the NDI data.
- WHI Form 124. This form codes the underlying cause of deaths. Codes 11-19 are considered CVD death; all other codes are coded as non-CVD death.
- Cause of death for participants in the Self-Report Cohort (SRC) (as well as those in the MRC for whom insufficient documents can be collected) are determined using NDI data according to rules determined by the WHI Outcomes Adjudication Committee.
- For deaths not yet adjudicated, the fact of death and the date on the proxy report, are used in the monitoring tables. This differs from clinical outcomes, which are only used after the adjudication is complete, as death adjudication often takes substantially longer than adjudication for clinical outcomes, and NDI data will typically be available later than CMS/Medicare data. Date of death on proxy-reports is, however, not always accurate.
- The underlying cause of death for not-yet-adjudicated deaths are taken to be unknown, and are combined with the non-CVD death. The one exception is that not-yet-adjudicated death for participants who have an MI or stroke within the last six months before their death that is confirmed either by an adjudicator or by Medicare/CMS data are taken to be CVD death. When adjudication is complete, these deaths are reclassified, if needed.

For additional information see:

Stewart AL, Mills KM, King AC, Haskell WL, Gillis D, Ritter PL. CHAMPS physical activity questionnaire for older adults: outcomes for intervention. Med Sci Sports Exerc 2001;33(7):1126-41.

Hlatky M, Ray RM, Burwen DR, Margolis K, Johnson KC, Kucharska-Newton A, Manson JE, Robinson JG, Safford MM, Allison M, Assimes T, Bavry A, Berger J, Cooper-DeHoff RM, Heckbert S, Li W, Liu S, Martin L, Perez M, Tindle H, Winkelmayer WC, Stefanick M. Use of Medicare data to Identify coronary heart disease outcomes in the Women's Health Initiative. Circ Cardiovasc Qual Outcomes 2014;7(1):157-62.

Lakshminarayan K, Larson JC, Virnig B, Fuller C, Allen NB, Limacher M, Winkelmayer WC, Safford MM, Burwen DR. Comparison of Medicare claims versus physician adjudication for identifying stroke outcomes in the Women's Health Initiative. Stroke 2014;45(3);815-21.

3.4. Data and Safety Monitoring Board

WHISH is monitored under the Women's Health Initiative Data and Safety Monitoring Board

3.5. Overall Structure of the Study Team

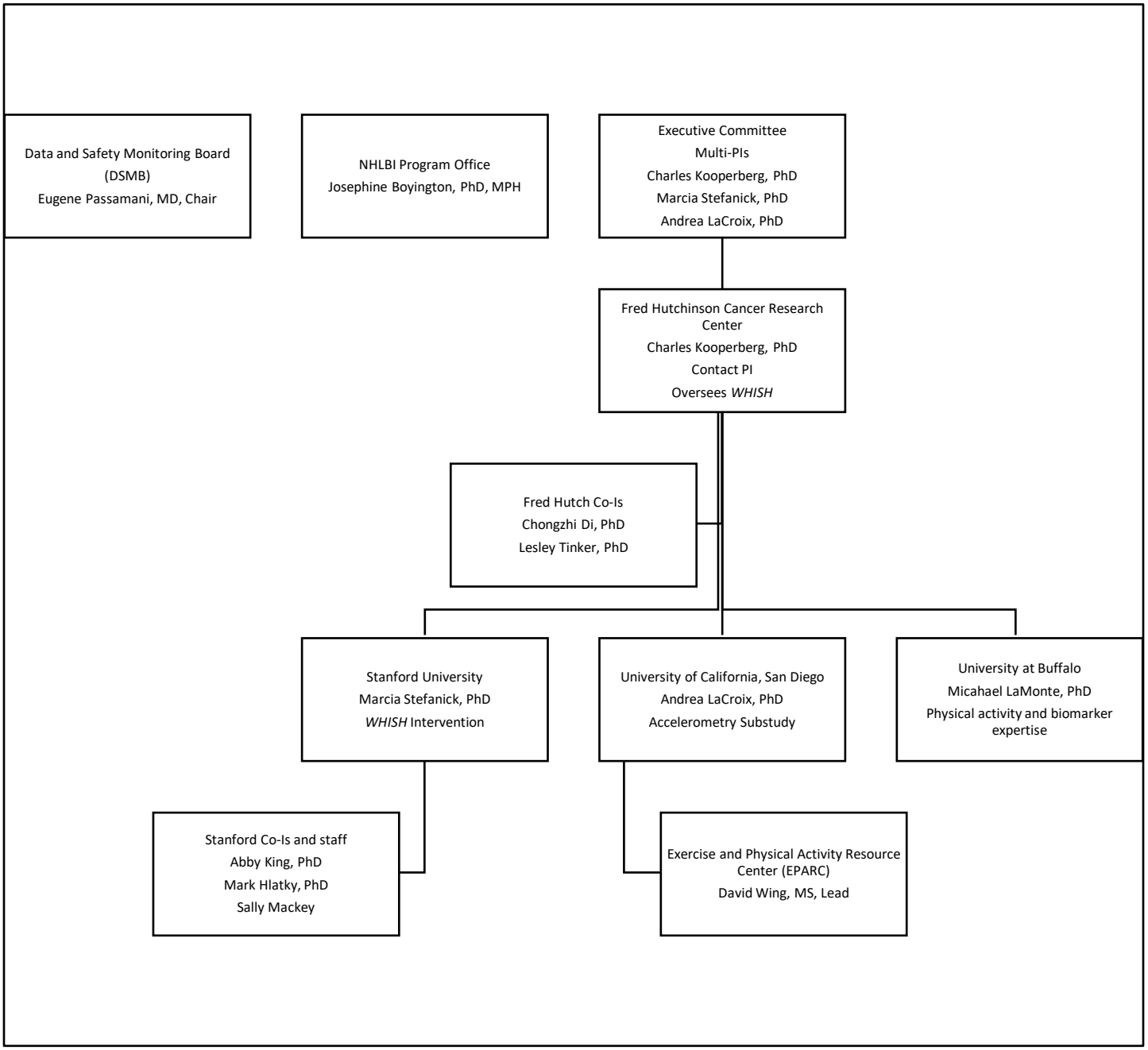
The Multiple Principal Investigators (Drs. Kooperberg, Stefanick, and LaCroix) comprise the Executive Committee which oversees the activities at Fred Hutchinson Cancer Research Center (including study monitoring and data management) and all participating subcontract sites: Stanford University (the *WHISH* physical activity intervention site), the University of California, San Diego (the Accelerometry Substudy), and the University at Buffalo (Aim 3 activities). The Executive Committee will meet bi-monthly via Zoom videoconference and in-person 3 times annually (in May at the WHI Investigator meeting; in July at Stanford; and each fall for the DSMB meeting) to review all aspects of the Research Plan. This includes the following activities:

1. Review of scientific progress including timeliness of outcomes ascertainment, completenessof data collection, and monitoring of data quality;
2. Evaluation intervention materials and intervention effects on self-reported and accelerometer measures of behavior change;

3. Preparation of annual DSMB reports, and presentations for the annual meetings;
4. Reporting to the WHI Executive Committee, Ancillary Study Committee, and at the WHI Annual Investigator meetings on study progress;
5. Implementing the data sharing plan for *WHISH* intervention and data elements at the end of the trial;
6. Preparing manuscripts for publication, and abstracts and symposia for scientific meetings.

The organizational structure of the study team is depicted in the figure below.

Study Team



SECTION 4 – PROTOCOL SYNOPSIS

4.1. Study Design

4.1.a. Detailed Description: See Protocol Part 1, Section 4.

4.1.b. Primary Purpose: Prevention

4.1.c. Interventions (from ClinicalTrials.gov as of June 2019):

Type	Name	Description
Behavioral (e.g., Psychotherapy, Lifestyle Counseling)	Physical Activity	The PA intervention will consist of a multimodal activity program of aerobics, balance, strength, flexibility. The intervention will involve encouraging participants to increase all forms of PA throughout the day and to decrease sedentary time, such as sitting. This may include activities such as leisure sports, gardening, use of stairs instead of escalators, leisurely walks with friends, and less use of remote control devices. The intervention is conducted primarily by mail with website support and resources available.

4.1.d. Study Phase:

Is this an NIH-defined Phase III Clinical Trial? Yes

4.1.e. Intervention Model: Parallel

4.1.f. Masking: Yes (Outcomes Assessor)

4.1.g. Allocation: Randomized

4.2. Outcome Measures: See Sections 3.3.1. and 4.3.

4.3. Statistical Design and Power

As agreed upon with the *WHISH* DSMB, the outcomes in *WHISH* are:

1. CVD (composite of myocardial infarction, stroke, cardiovascular death)
2. Non-cardiovascular death
3. Hip fracture
4. Clinical (non-hip) fractures
5. Falls
6. Venous thromboembolic event
7. Peripheral artery disease
8. Physical function (Rand-36)
9. Coronary revascularization

Phase 2 adds to the above:

10. Short Physical Performance Battery (SPPB) (in a subset)
11. Sleep disturbance - WHI Insomnia Rating Scale
12. Depressive systems scale (CES-D)

As described elsewhere, 49,331 WHI participants have been randomized to either intervention or comparison in *WHISH.* All outcomes are ascertained on all (surviving) participants, except for the SPPB (outcome #10), which will only be ascertained on participants that are part of the WHI Long Life Study 2. Clinical outcomes are based on self-report and adjudication and on reports by the Center for Medicare

and Medicaid Services (CMS) of Medicare outcomes and information from the National Death Index (NDI), as described in Section D of the Research Plan. The other outcomes are based on self-report, or measured at an in-home visit (SPPB, #10).

For the time-to-event outcomes (1-4, 6, 7, and 9 above), effect estimates will be based on Cox-proportional hazards models. The rate of falls (5) will be compared using Poisson regression. For the remaining outcomes (8 and 10-12) the mean level of physical function between the groups will be compared using linear regression with a possible log transformation to improve normality.

The analyses will be stratified by outcomes data source (adjudicated or Medicare (CMS) data), age on April 1, 2015 (in tertiles), region of residence (West, Midwest, Northeast, and Southeast), and race/ethnicity. Using standard risk-set in survival analysis, participants who change from fee-for-service to managed care will have their self-reports adjudicated after their switch and will "move strata" at the time of the switch. Similarly, participants who have two types of data, but do not return their self-report Form 33, will have their outcomes after their last returned Form 33 assessed using CMS data.

All analyses will be carried out using an intent-to-treat analysis, including all women randomized: participants who "opt out" will be included in all analyses in their assigned arm for monitoring and primary reporting purposes. For example, the few deaths that occurred between randomization and the start of intervention are included in the analyses. Similarly, participants who stop the intervention, or participants who become ineligible will remain in these analyses. For safety considerations, intent-to-treat analyses may be supplemented with analyses restricted to the women in the intervention who consented to receive the intervention, or to women who made noteworthy changes in exercise levels.

Additional analyses will be provided for these pre-specified subgroups:

- Participants with adjudicated outcomes versus those with only Medicare data.
- Stratification by age in tertiles.

For several thousand participants we obtain both Medicare and adjudicated outcomes. For these participants the adjudicated outcomes are used for monitoring. Analysis comparing the Medicare and adjudicated outcomes for these participants are presented to provide insight in how comparable both sources of data are.

We note that not all outcomes are used for interim monitoring (see the DSMB plan, Section 3.3, for details); however, all outcomes are provided to the DSMB at each monitoring meeting.

Power

This section provides more details on how we obtained the power estimates described in the Research Plan.

Primary Outcome:

1. We combined all outcomes data from both arms of the *WHISH* trial as of the time of the last DSMB meeting (Fall 2018).
2. Using this data, for each one-year interval, we computed that, within the *WHISH* cohort, the probability that a participant, who was age X at the beginning of the year, during that year will get either the primary CVD outcome of MI, stroke, or cardiovascular death, or the censoring outcome of non-cardiovascular death (acknowledging computing risks). These rates are averaged over three-year

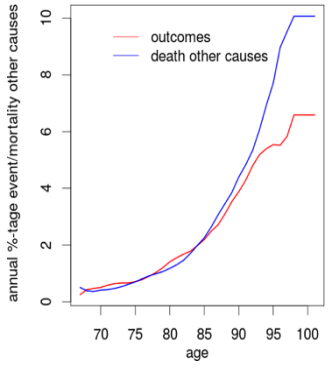


Figure 7. Observed event and censoring rates in the combined *WHISH* arms.

overlapping intervals for smoothing (e.g., to estimate the rate for 78-year-olds, we averaged the observed rate of 77-year-olds, 78-year-olds, and 79- year-olds), and we kept the rate constant for the over-98-year-olds. This yielded the rates shown in Figure 7 of the Research Plan, which is reproduced here.

3. Using these observed rates, and the actual ages of the randomized women, we generated 100,000 data sets with various effect sizes and various lengths of follow-up, noting that for an effect size of x%, we assume that the comparison arm has rate (100+x/2)%, and the intervention arm has (100-x/2)%, as the rates in Figure 7 combine both arms.

4. We then used Cox models, as described above, to test (at level 0.05) whether the simulated results yielded a significant effect. The number of significant results yield the power curves of Figure 8 of the Research Plan, also reproduced here.

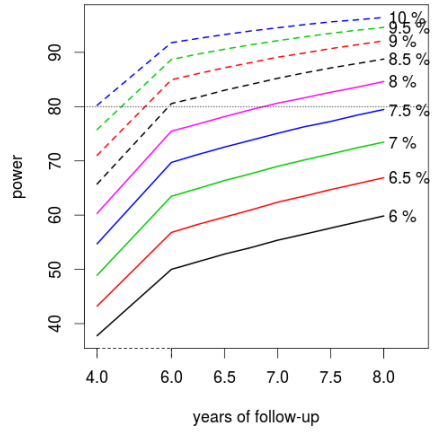


Figure 8. Estimated power for the *WHISH* primary endpoint as a function of the observed effect size of physical activity.

Our conclusion was that with an effect size of about 8.5% we have 85- 90% power to observe significant results after 8 years of follow-up. The effect size of 8.5% is consistent with the effect that we observed in walking (see Section C.d of the Research Plan). The effect size of walking has been consistently increasing over the length of the trial.

Additional Outcomes. The additional outcomes for which we provide power calculations are the Rand-36 Physical Function outcome, the Short Physical Performance Battery (SPPB), the WHI Insomnia Rating Scale (WHIIRS), and the Depressive Systems Scale (CES-D). These outcomes would only be tested after the primary outcome has been evaluated. As described in the Research Plan, we divide the type 1 error into 0.05/2 for the Rand-36 scale, and 0.05/6 for the remaining three outcomes, so that the combined type 1 error for the additional outcomes is controlled by 0.05. Other than the SPPB, these outcomes are evaluated among all the surviving participants at the end of the study (estimated to be ~36,000); the SPPB is measured in 5,000 participants who are part of the LLS2. For the Rand-36 and SPPB we have good estimates for the standard deviation, for the other two outcomes, we provide the power in terms of SDs. The power was shown in Table 8 of the Research Plan, reproduced here.

Table 8. Detectable differences for the additional outcomes measures of the *WHISH* trial with 8% and 90% power. The type I error for the Rand-36 outcome is .05/2, the type 1 error for the other three outcomes is .05/6.

	SD	Differences detectable with	
		80% power	90% power
Rand-36	26	0.85	0.97
WHIIRS, CES-D	Differences in SDs of measure	0.039	0.042
SPPB	2.4	0.26	0.29

Biomarker Pilot (Aim 3). The biomarker Aim 3 is intended to be a pilot study for future projects. As described in the Research Plan, the actual biomarkers and study design are not yet determined. As such, we do not provide power estimates – in line with the goal of this aim, to provide power estimates for future studies.

Conditional Power Analyses. Please see 3.3.3. Interim Analysis for the WHISH Trial to be taking place in 2022.

SECTION 5 - OTHER CLINICAL TRIAL-RELATED INFORMATION

5.1 Project Management Plan

Because *WHISH* began in 2015 and is underway, recruitment is complete. In addition, the intervention program is underway and retention rates for return of behavior change and outcomes forms is exceptionally high. Therefore, our trial benchmarks will focus on continuing this record of rigorous trial implementation through this trial continuation period.

The project management team includes the three multiple PIs, Dr. Charles Kooperberg, Dr. Marcia Stefanick and Dr. Andrea LaCroix. Refer to Section 3.5 for the project oversight responsibilities. The team will be responsible for administrative functions of the project in addition to the scientific functions. Drs. Kooperberg, Stefanick and LaCroix each bring extensive knowledge and necessary expertise in the creation, management and analysis, as well as the commitment to make major decisions on the project via consensus. Dr. Kooperberg will be designated the contact PI at FHCRC. He will be responsible for communications with the CCC investigator team at Stanford, including regular (approximately monthly) project conferences that will also include Dr. LaCroix and Dr. Stefanick. Except for Dr. Kooperberg, all other PIs will be blinded to the data and data analytic activities. Decisions regarding the project management to meet the scientific objectives will be made jointly by the PIs with the exception of Dr. Kooperberg, who will not be a part of making decisions regarding the intervention component of the study. Drs. Stefanick, LaCroix, and LaMonte will all take active roles in unblinded primary data analyses under the project specific aims during the entirety of the blinded intervention phase. All PIs will take an active role in ongoing evaluation of data quality and manuscript writing; and will provide support in all aspects of study administration and scientific dissemination. Staff and investigators will meet regularly, and as needed, to address questions, review progress, and manage the work at-hand. Drs. Kooperberg and LaCroix will share responsibility for communicating with the WHI. A project management timeline with and milestones pre- milestone benchmarks will be developed and monitored at each conference call. The pre-milestone benchmarks will be used to determine if contingency plans need to be put into place. The team is confident of meeting progress goals and budget based on their individual and combined history of meeting these goals.

The team has worked together successfully for the past four years with *WHISH* and has demonstrated early attentiveness to and resolution of all study aspects, including budget, monitoring and attending to corrective responses, meeting all reporting timelines. The multi-PI team meet annually with the WHI DSMB, which oversees *WHISH,* to monitor safety and give advice about the trial continuing.

Decisions will be made by consensus. In the event of not reaching consensus, Dr. Charles Kooperberg will decide.

Dissemination of *WHISH* trial data and results is described under the Dissemination Plan (Section 4.7) and will be executed in accordance with the WHI data sharing plan established with the NHLBI Program Office.

The *WHISH* study protocol and standard WHI operating procedures for data collection are followed. The protocol is reviewed periodically and revisions made as needed.

5.2 Single Site Justification Plan

The *WHISH* trial is conducted primarily by mail with no participant clinic visits. The nature of the trial lends itself to be enrolled through a single site. All *WHISH* participants were enrolled and randomized out of the Women's Health Initiative (WHI) Clinical Coordinating Center (CCC) at the Fred Hutchinson Cancer Research Center in Seattle, WA, although the participants themselves span across the United States and are associated with one of four WHI regional centers. *WHISH* is a novel and pragmatic clinical trial for its use of a randomized Zelen consent design. Women were pre-screened for eligibility based on previously collected WHI data (ambulatory, enrolled in the WHI Medical Record Cohort, or in

fee-for-service Medicare with CMS data). A total of 49,331 WHI participants were randomized with 24,674 to usual-activity comparison and 24,659 to physical activity (PA) intervention. The *WHISH* comparison participants receive their usual WHI contact through mailings but, as part of the *WHISH* pragmatic design, do not receive materials from *WHISH*. Women randomized to intervention receive materials, have access to an intervention website, and have the opportunity for telephone contact through Stanford University. Enrollment in the *WHISH* trial was completed as planned in 2015.

An Accelerometry Substudy within *WHISH* objectively monitors changes in PA in the intervention and comparison groups through accelerometry wear. The substudy invited, consented, and ultimately enrolled 2,350 *WHISH* participants (1,182 [50%] comparison, 1,168 [50%] intervention) within the allotted timeline. Deployment of the substudy among enrolled participants occurred through a single site. The accelerometers were delivered by mail with written instructions. Experienced staff contacted participants just before accelerometers were mailed as well as during the 7-week wear period as support for providing instructions. This substudy is directed by the *WHISH* team at the WHI-CCC and conducted by the University of California, San Diego (UCSD) Exercise and Physical Activity Resource Center (EPARC). During the proposed trial period, approximately 2,000 *WHISH* participants will be recruited to wear an accelerometer during one 7- day/night time period. Recruitment primarily will occur among participants who have successfully completed the initial *WHISH* accelerometer wearings and supplemented as needed by newly recruited *WHISH* participants. We plan to conduct the Accelerometry Substudy during the first year of the *WHISH* trial. Based on our past experience, we expect to successfully complete recruitment in the allotted timeframe.

NHLBI has classified *WHISH* to be a single-site study due to the centralized pragmatic nature of the trial structure, including enrollment, intervention and follow-up. There are no clinical sites managing participant intervention or follow-up.

5.3. Dissemination Plan

A thoughtful and broad-based plan to disseminate *WHISH* trial findings is critical to ensuring that the scientific research and public health community, policy makers, research study participants, and the general public are informed of the results, particularly as they pertain to health benefits and risks of increasing physical activity and decreasing sedentary behavior in older women in the U.S. We will use a diverse portfolio of strategies, including: (a) media coverage through press releases and interviews targeted to local and national newspapers, television and radio outlets; (b) production of the research summary document and fact sheet targeted to the general public, which clearly and concisely summarizes the key conclusions of the trial; (c) production of professionally designed flyers, posters, brochures, and research briefs targeted to broad audiences; (d) study newsletters targeted to study participants who were randomized to the intervention arm; (e) distribution of dissemination materials to community agencies, professional societies, and health-related websites and list-serves; (f) hosting and attending seminars, conferences, community forums and health fairs; and (g) mailing of personal thank-you letters to research study participants. The *WHISH* Dissemination Plan also includes: 1) Full support and compliance with the data sharing policies of NHLBI; 2) Rapid publication of initial trial results after year 8, during the NCE; 3) Simultaneous posting of results to ClinicalTrials.gov (NCT02425345); and 4) Use of a data sharing plan that follows policies established for other WHI core studies. Analytic datasets will be made available to the WHI investigator community after the data have been prepared and documented for distribution and the main trial outcome paper has been published, typically within 12 months of trial closure. Any investigator (in the US or internationally) can request use of the data by submitting a paper proposal to the WHI Publications & Presentations (P&P) committee. The data will also be submitted to the NHLBI Project Office on a pre-specified schedule and made available to the public through limited release datasets. In addition, if the *WHISH* Intervention is found to be beneficial, we will develop a plan and seek additional resources to package and disseminate this unique and timely resource to the American public on a broad scale.

SECTION 6 - CLINICAL TRIAL MILESTONE PLAN

6.1. Study Primary Completion Date: 12/31/24 Anticipated

6.2. Study Final Completion Date: 12/31/24 Anticipated

6.3. Enrollment and randomization Enrollment of the First Participant:

(Study Start Date) 4/2/15 Actual

6.3.1. Milestones for Protocol Phase 2

- Year 01 - Milestone 1: Submission of a revised protocol to NHLBI for transmission to DSMB for review/approval in 2020
- Year 01 - Milestone 2: Submission of a plan to NHLBI by early September 2020 for the conduct of the interim analysis on the primary CVD measure, to occur no later than July 1, 2022.
- Year 01- Milestone 3: Submission of IRB approval
- Year 01 - Milestone 4: Submission of an interim progress report by the 9th month to transition to the R33.
- Year 01- Milestone 5: Send quarterly reports of the number of cases (observed and expected) month 3, via e-connect
- Year 01 -Milestone 6: Send quarterly reports of the number of cases (observed and expected) in month 6, via e-connect
- Year 01 - Milestone 7: Send quarterly reports of the number of cases (observed and expected) in month 9, via e-connect

6.4. Completion of primary endpoint data analyses

6.5. Reporting of results in ClinicalTrials.gov

6.6. Is this an applicable clinical trial under FDAAA? No

7. REFERENCES (Phase 2; numbering continued from Phase 1)

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