PROTOCOL

ACTION FOR HEALTH IN DIABETES
Revised Look AHEAD – Extension Study

Look AHEAD 1999-2014

First Issue February 06, 2001

First Revision, May 10, 2001

Second Revision, October 28, 2002

Third Revision, May 16, 2003

Fourth Revision, July 28, 2005

Amendment to Fourth Revision, September 1, 2005

Fifth Revision, November 4, 2005

Sixth Revision, August 20, 2007

Seventh Revision, April 29, 2009

Eighth Revision, October 23, 2009

Ninth Revision, September 5, 2011

Tenth Revision, November 7, 2012

Look AHEAD Continuation began in 2013

Eleventh Revision, June 27, 2013

Twelfth Revision, June 6, 2014

Thirteenth Revision, August 18, 2014

Fourteenth Revision July 27, 2015

Fifteenth Revision November 20, 2015

Look AHEAD Extension beginning in 2016

Sixteenth Revision November 2016

Seventeenth Revision May 4, 2017

Eighteenth Revision November 2017

Nineteenth Revision March 2018

Twentieth Revision May 2018

Twenty First Revision August 2019

Protocol

Addendum to Look AHEAD Protocol

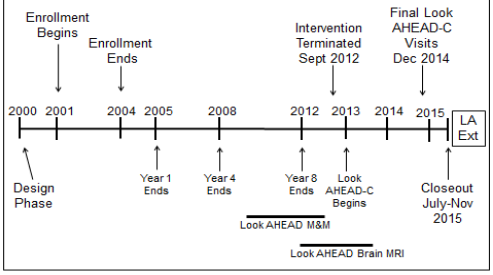
Action for Health in Diabetes (Look AHEAD) Extension Study

1.1 BACKGROUND

The prevalence of type 2 diabetes has increased markedly in the U.S. population and is a major public health concern. According to 2012 estimates from the Centers for Disease Control (CDC, 2014), the overall prevalence of diabetes among U.S. adults 20 years or older was 12.3%. However, this proportion increased dramatically with age, rising from 4.1% among those 20-44 years old to 16.2% among those 45-64 years old and 25.9% among those 65 years or older (CDC, 2014). Most of these older adults with type 2 diabetes are also overweight or obese; during 1994-2010, the proportion of U.S. older adults with diagnosed diabetes who were overweight or obese increased from 73.4% to 85.5% in those 65-74 years old and from 61.1% to 73.5% in those 75 years and older. These individuals are not only at greater risk of reduced lifespans, but also in their last decades of life are likely to have greater health care needs and costs; higher rates of medical complications, comorbidities (including Alzheimer's disease and related diseases), and functional limitations; and lower quality of life compared with older adults who do not have these conditions (Kirkman, 2012). Addressing the issues faced by the growing proportion of overweight or obese older adults with type 2 diabetes is of particular concern since the U.S. population 65 years and older is expected to nearly double from 43.1 million in 2012 to 83.7 million in 2050 (Ortman, 2014), and, according to some projections, by 2050 the number of cases of diagnosed diabetes in this rapidly growing older population will be 26.7 million, an almost 4.5-fold increase from the number of cases in 2005 (Narayan, 2006). Lifestyle interventions focused on weight loss are recommended for overweight and obese individuals with type 2 diabetes; whether these interventions meaningfully improve the lives of older adults over an extended follow-up is unknown, but has great public health importance.

Action for Health in Diabetes (Look AHEAD, 2000-2012) was a 2-arm randomized, controlled multicenter clinical trial to examine whether an intensive lifestyle intervention (ILI) designed to achieve and maintain weight loss of at least 7% by focusing on reduced caloric intake and increased physical activity could reduce cardiovascular morbidity and mortality compared with Diabetes Support and Education (DSE), a standard care control group. Look AHEAD enrolled 5,145 overweight or obese volunteers with type 2 diabetes, with a planned follow-up period of up to 13.5 years. At randomization, the Look AHEAD cohort was comprised of 60% females, 37% minorities, mean age of 59.7 years (range: 45-76 years), and mean BMI of 35.9 kg/m^2; the mean duration of diabetes was 5 years and 14% had a prior history of CVD at baseline. The primary endpoint was the first occurrence of a composite cardiovascular outcome that included death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, and hospitalized angina with a targeted between-group difference of 18% reduction in the composite endpoint in ILI vs. DSE. Three composite cardiovascular outcomes were also examined: 1) death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke; 2) death from any cause, myocardial infarction, stroke, or hospitalization for angina; and 3) death from any cause, myocardial infarction, stroke,

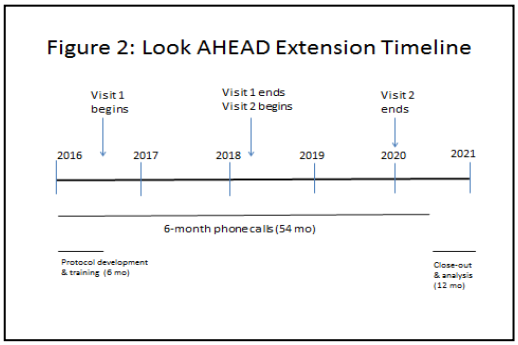
Figure 1: Look AHEAD Timeline



coronary-artery bypass grafting, percutaneous coronary intervention, hospitalization for heart failure, or peripheral vascular disease.

On September 14, 2012, the study's sponsor, National Institutes of Health, including the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), based on the recommendation of the Data and Safety Monitoring Board (DSMB), informed the Look AHEAD study group that analyses of data then available provided sufficient evidence that there was no significant difference between ILI and DSE for either the primary or secondary outcomes or pre-specified subgroup analyses. This evidence was corroborated by a formal futility analysis, which indicated that the probability of observing a significant positive effect of ILI at the end of the planned follow-up (i.e., a hazard ratio of 0.82 for ILI vs. DSE) was estimated to be 1%. NIDDK therefore recommended that "the study proceed, but with a major modification"; and stated that, "Because of the potential importance of completion of ancillary studies and additional data collection that could be valuable for exploratory analyses, the DSMB recommends conversion of the study to a longitudinal cohort study without continuation of the ILI intervention…." Thus, NIDDK instructed the Look AHEAD investigators to terminate the ILI intervention. Data for the primary and secondary endpoints were censored on September 14, 2012, and the study group published its primary results in 2013 (Look AHEAD, 2013).

The Look AHEAD Continuation Study (Look AHEAD-C, 2013-2015) began in August 2013 and consisted of one planned clinic visit for the entire cohort and the continuation of the every 6-month telephone calls to record major clinical events. The primary hypotheses addressed by Look AHEAD-C were that over time participants will have better profiles of healthy aging following 9-11 years of randomization to ILI compared to DSE as indicated by differences on the following parameters: 1) physical function, impairment and disability; 2) cognitive function and impairment; 3) diabetes control and microvascular complications; 4) late life depression; and 5) fractures and cancers. The timeline for Look AHEAD through Look AHEAD-C is shown in Figure1.



The Look AHEAD Extension (Look AHEAD-E) study continues follow-up of the Look AHEAD cohort for an additional 4.5 years, with the goal of determining whether ILI has enduring benefits for the lives of overweight and obese individuals with type 2 diabetes as they age. The timeline for the Look AHEAD Extension is shown in Figure 2.

1.2 OBJECTIVES

The Look AHEAD Extension Study has been designed to achieve the following aims:

Primary aims: test whether ILI relative to DSE has long term legacy effects on:

1. Increased lifespan
2. Reduced health care costs

Secondary aims: test whether ILI relative to DSE has long-term effects on key dimensions of healthy aging:

1. Less frailty
2. Reduced diabetic microvascular complications
3. Improved quality of life

Tertiary aims:

Describe the long-term trajectories of a) weight, b) physical activity, c) fat and lean mass, and d) bone density within and between the intervention groups and examine how these are related to outcomes defined by the primary and secondary aims

Assess the legacy of behavioral intervention on the prevalence of cognitive impairment and rates of cognitive decline

Identify factors related to cognitive resilience

1.3 STUDY POPULATION

All of the Clinical Centers that participated in Look AHEAD will continue to participate in the Look AHEAD Extension, and all surviving participants will be eligible for the Look AHEAD Extension We anticipate including 3800 with current ages 58-89 years.

1.3.1 Study Sites

Sixteen Clinical Centers will participate in the Look AHEAD Extension. Each Clinical Center corresponds to a single location, with three exceptions: 1) Boston (MGH) and Boston (Joslin) comprise a single Clinical Center operating at two sites, 2) Memphis (UT) and Memphis (East) comprise a single Clinical Center operating at two sites, and 3) Phoenix and Shiprock comprise a single Clinical Center operating at two sites. The clinical sites involved in Look AHEAD are listed below geographic location and institutions.

Baltimore	Johns Hopkins University School of Medicine
Baton Rouge	Pennington Biomedical Research Center
Birmingham	The University of Alabama at Birmingham
Boston (MGH)	Massachusetts General Hospital
Boston (Joslin)	Joslin Diabetes Center

Denver	University of Colorado
Houston	Baylor College of Medicine
Memphis (UT)	The University of Tennessee-Memphis,
Memphis (East)	The University of Tennessee-Memphis East Clinic
Minneapolis	University of Minnesota
NYC	Columbia University Medical Center
Philadelphia	University of Pennsylvania
Pittsburgh	University of Pittsburgh
Providence	The Miriam Hospital
San Antonio	The University of Texas Health Science Center at San Antonio
Seattle	Seattle Institute for Biomedical and Clinical Research
Phoenix	Southwest American Indian Center/Phoenix
Shiprock	Southwest American Indian Center/Shiprock
USC	University of Southern California

1.3.2 Eligibility Criteria

The main eligibility criteria that defined the original cohort for Look AHEAD were:

- Age 45 to 76 years
- Self-reported type 2 diabetes, as verified by the use of glucose-lowering medication, a physician's report, or glucose levels
- BMI ≥ 25 kg/m^2 (≥ 27 kg/m^2 if currently taking insulin)
- Completion of a maximal graded exercise test without symptoms or signs of cardiac ischemia

1.3.3 Eligible Population

All surviving members of the original Look AHEAD cohort are eligible to participate in the Look AHEAD Extension. Projected enrollment is based on the outstanding retention achieved during the Look AHEAD trial and Look AHEAD-C, which has been similar for the two study arms. Based on the very high rates of retention for both Look AHEAD and Look AHEAD-C, we anticipate that 3800 participants (96% of those currently active) will enroll in the Look AHEAD Extension.

1.3.4 Informed Consent

Written informed consent will be obtained for all Look AHEAD Extension participants in accordance with all local IRB requirements. Model consent forms appear in Appendix 1. Look

AHEAD Extension clinical staff will receive central training in the administration of informed consent. As with Look AHEAD-C, special attention will be given to obtaining informed consent from aging participants who may have experienced declines in their ability to comprehend key information contained in the informed consent document. The Look AHEAD Extension will continue to use the procedures put in place for Look AHEAD-C, which were drawn from models provided by other clinical trials in older individuals. These procedures are as follows:

Prior to each participant's initial clinic exam, when formal informed consent is obtained, a staff member who is familiar with the participant and is certified to obtain informed consent will contact the participant and briefly review the study procedures with them. If, based on prior interactions with the participant or his/her responses during the call, the staff member has any concern about the participant's ability to provide informed consent, the participant will be asked to have another person who could serve as a surrogate accompany them to the visit to assist in the consent process. The staff member will confirm that the person who will accompany the participant meets local, state, and IRB regulations for serving as someone who can give surrogate consent, if needed. These regulations vary across study sites and may include first-degree relatives (spouse, adult children, and siblings), legally appointed guardian, health care proxy, or participant-chosen surrogate.

At the scheduled clinic exam, certified staff will review the written consent form with the participant and the surrogate (if present) and answer any questions that the participant or surrogate may have. Following this thorough review, the staff member will tell the participant that s/he is going to ask a few questions to make sure that the participant understands what the study is about and appreciates what s/he is being asked to do and why. The staff member will than complete the "Evaluation to Give Consent" form designed to ascertain whether the participant's comprehension of what is entailed in the study is sufficient for the participant to give informed consent on his/her own behalf. The form includes five items: 1) Why are we doing this study?; 2) Tell me two things that we will ask you to do as part of this study; 3) If you joined the study today, could you stop the study at any time?; 3) Tell me one benefit to being in the study; and 5) Tell me one risk of being in the study. The participant's verbatim answers will be recorded on the form. If the participant's answers do not demonstrate sufficient understanding to give informed consent on their own behalf and a qualified surrogate is present, the surrogate will be asked to give consent on behalf of the participant and the participant will be asked to give assent (i.e., affirmative agreement) to participate. If a qualified surrogate is not present, then the staff member will help the participant identify such a person and ask the participant's permission to contact that person and arrange for another time when the surrogate can accompany the participant to help with the informed consent process.

Participants who have the capacity to consent at the initial Look AHEAD Extension visit will be given the opportunity to decide in advance whether they do or do not want a qualified surrogate to make decisions for them to continue their participation in the study should they lose capacity to consent in the future. The participant's decision will be discussed with the staff member and documented on the procedures consent note in the participant's research chart. Participants who choose to designate such a surrogate will be encouraged to discuss their future research participation with the designated surrogate. For those participants who choose not to have a surrogate make study participation decisions for them in the future and who lose the capacity to consent, their study participation will cease at the time they lose capacity to consent. In the

event a legal representative is identified they will be consulted regarding the individual's participation in the study.

In addition to the above procedures related to the capacity to consent, participants will be asked to consent to having their Protected Health information shared with and electronically transferred to the coordinating center at Wake Forest School of Medicine. Participants are not required to consent to this sharing of information; their decision not to share this information will not affect their participation in the Look AHEAD Extension. However, if provided, this shared information will be used at the coordinating center in the event of natural or other major disaster affecting a clinical site (for example, if a clinic were destroyed by a hurricane or tornado, the coordinating center would be able to provide contact information for the participant to the clinics). Also, the information would be used to allow searches of national databases such as the National Death Index (NDI) or Centers for Medicare and Medicaid Services (CMS) for the purpose of determining date and cause of death, and diagnosis codes and dates for health care utilization. These would require that the coordinating center have access to names, addresses, birth dates, social security number, and/or Medicare number. In addition, in the event that future funding is not available for the clinics to contact their participants, this information would be used to allow direct contact by the coordinating center with the participant, by telephone or mail, for the following purposes: to invite the participant to take part in an ancillary study; to conduct the study outcomes interview; to conduct other types of interviews, e.g., to inquire about current health status, body weight, and to update contact information on informants/proxies.

1.3.5 Retention

Look AHEAD has had outstanding participant retention throughout its history. Continued high participant retention among our aging cohort will be a particular focus of Look AHEAD Extension and will be achieved by:

Continuity of clinic staff who have gained a high level of rapport and loyalty with participants

Maintaining frequent contact with participants through the 6-month telephone calls, birthday cards, newsletters prepared by the Retention Committee , and social retention events

Conducting home-based and nursing home visits as needed

Monitoring of retention by the Look AHEAD Extension Retention Committee and the Clinic Operations and Quality Control Committee, who work with local clinic sites to review and help develop plans for maintaining and re-engaging participants

1.3.6 Description of the Clinical Sites

Since the beginning of Look AHEAD, all clinical sites have operated under a common protocol. This approach will be followed in Look AHEAD Extension, that is, data from each site will be obtained, managed, and protected according to a standard study protocol that has been developed and vetted by the Steering Committee. Clinic sites will use a standard informed consent template, modified as needed by local IRB requirements. All clinic staff will be trained and certified using the Manual of Procedures (MOP) and will follow a standard set of data collection procedures. Clinic staffs will participate in both central training and study continuing

education offered by the coordinating center at Wake Forest University. Clinical Center investigators and staff participate in ongoing working groups and established Look AHEAD Committees to ensure that identical procedures are followed at each site for the purpose of recruitment, retention, and ensuring the highest quality of study data.

Furthermore, data are managed and protected through a study-wide web-based data system developed and managed by the coordinating center. Study data are entered into the data system within established time windows using a password-protected, dedicated computer terminal at the site. The system allows only authorized users to access clinic and participant information for the purpose of entering and editing study data. Hard copies of data and subject-sensitive information are maintained in secure locations at the clinic. Confidentiality Data security is described below in Section 1. 9.

1.3.7 Study Interventions and Adherence

At enrollment into Look AHEAD, participants were randomized within center on a 1:1 basis to the ILI or DSE conditions. The ILI included diet modification and physical activity and was designed to achieve and maintain weight loss of at least 7% (Wadden, 2006). ILI participants were assigned a caloric goal of 1200 – 1800 kcals/day based on their initial weight, with < 30% of total calories from fat and a minimum of 15% of total calories from protein. The physical activity goal was ≥175 minutes of unsupervised moderately intense physical activity per week and focused on activities similar in intensity to brisk walking. ILI participants were seen weekly for the first 6 months and three times per month for the next 6 months, with a combination of group and individual sessions. During years 2-4, participants were seen individually at least once per month and had a minimum of one additional contact by phone, mail, or email per month. During Year 5+, participants were encouraged to continue individual monthly sessions and annual campaigns were used to promote adherence. A tool kit of strategies was available for ILI participants having difficulty achieving the weight loss goals.

DSE participants were invited to three group sessions focused on diet, physical activity, or social support each year for the first 4 years and one session annually thereafter.

All interventions were terminated in September, 2012, as instructed by NIDDK based on the recommendation of the DSMB. For intention-to-treat analyses of the potential legacy effects of ILI on Look AHEAD Extension outcomes, participants will be categorized according to their original randomization assignments.

1.4 OUTCOMES

1.4.1 Primary Outcomes

The co-primary outcomes for Look AHEAD Extension are lifespan, and health care costs

Lifespan will be measured by all-cause mortality from the time of randomization and is determined at a six-month interval through telephone contact with the participant, or through family members or obituaries. In addition, a National Death Index search will be conducted at several time points during the Look AHEAD Extension. Cause-specific mortality (a supporting analysis) will be determined through adjudication of death certificates, recent hospitalization

records (discharge summaries only), and previous outcomes interviews. These records will be sent to the coordinating center for processing, and a central adjudication committee (study investigators/physicians) will meet by conference call to adjudicate deaths for the purpose of determining cause-specific deaths, using procedures currently in place for Look AHEAD.

Health care costs will be assessed post-intervention from the perspective of the payer. Costs will be calculated from hospitalization records (medical coded discharge summaries), outpatient visits (office, hospital clinic, other), outpatient tests and procedures, rehabilitation/long-term care, home care, and medications identified at the six-month telephone contacts and biennial clinic visits. Supporting analyses will include measures of health care utilization: hospitalizations and days hospitalized, medication use, nursing home residences. The Look AHEAD Extension will also report separately costs for each of the major components of total costs.

1.4.2 Secondary Outcomes

The secondary outcomes are: 1) frailty, 2) diabetic microvascular complications, and 3) quality of life.

Frailty will be assessed using the Fried criteria (Fried, 2001), which is based on the presence of five frailty characteristics: (1) walking speed standardized based on median height and sex, (2) grip strength standardized based on body mass index (BMI) and sex, (3) energy expenditure standardized based on sex, (4) exhaustion based on self-report, and (5) weight loss of 10 lbs. or more in the last year without intention. Walking speed will be assessed using the timed short walk included in the Short Physical Performance Battery (SPPB). Grip strength will be measured twice in each hand to the nearest 2 kg using an isometric Hydraulic Hand Dynamometer (Jamar, Bolingbrook, IL), and the value from the stronger hand will be used. Participants will be excluded if they report hand pain or recent hand or wrist surgery. Energy expenditure will be based on kcal/week of energy derived from the Paffenbarger Physical Activity questionnaire (Paffenbarger 1978), a short instrument designed to measure participation in leisure time physical activity. Exhaustion will be assessed using the PHQ-9 question: “During the past two weeks, how often have you been bothered by feeling tired or having little energy – not at all, several days, more than half of the days, nearly every day?” Weight loss will be assessed by self-report (we acknowledge that this is a difficult item to interpret for the Look AHEAD cohort, and will also examine the impact on a construct without this item). Based on these assessments, frailty will be classified into three stages: non-frail (no frailty characteristics present), pre-frail (1 or 2 frailty characteristics present), and frail (3 or more frailty characteristics present).

Supporting analyses for the secondary outcome of frailty will assess the outcomes of persistent major mobility disability (PMMD) and SPPB. PMMD is considered present when an individual fails to complete two successive 400-m walks (Newman, 2006; Pahor, 2014). The 400-m walk is a proxy for the ability to move without assistance from place to place within a community context, which is a key contributor to maintenance of independence in the community as one ages. Performance on the 400-m walk, a marker of major mobility disability, has been associated with morbidity, disability, hospitalization, and mortality (Pahor, 2014; Newman, 2003; Newman, 2006; Vestergaard, 2009) and was assessed in Look AHEAD-C. Those who failed the 400-m walk for the first time at their last scheduled clinic visit (and who are not adjudicated as

persistent failures), will be invited to return 6 months later for a repeat assessment to establish persistence.

The SPPB was developed to measure lower-extremity physical function as reflected in balance, gait speed, strength and endurance. It is comprised of the ability to stand with feet together in the side-by-side, semi-tandem, and tandem positions; time to walk 4-meters; and time to rise from a chair and return to the seated position 5 times (Guralnik, 1994). The SPPB was modestly expanded to minimize ceiling effects (which may occur when the original version is used for younger, more-well functioning cohorts). In this expansion, the holding time of the standing balance is increased to 30 seconds and a single leg stand is added (Simonsick, 2001). Additional supporting analyses are based on self-reported falls; Falls Efficacy Scale International (Yardley, 2005); and Pepper Assessment Tool for Disability (Rejeski, 1995), which includes 19 items, covering 3 domains: basic activities of daily living (ADL), mobility, and instrumental ADLs.

End-stage renal disease (ESRD) is the principal microvascular outcome and will be defined as renal replacement therapy (RRT) or death from nephropathy, and will be obtained by self-report through the six month telephone contact and biennial clinic exams, and by adjudication of death certificates.

Supporting analyses will focus on nephropathy derived from serum creatinine (i.e., doubling of serum creatinine since randomization or serum creatinine exceeding ≥2.5 mg/dl, both representing high risk of need for RRT or death from renal failure. Supporting analysis will also include a neuropathy outcome assessed by the Michigan Neuropathy Screening Instrument (MNSI), comprised of a self-report history questionnaire; a foot inspection for evidence of excessively dry skin, callous formation, fissures, and frank ulceration or deformities; vibration sensation; ; and monofilament testing for touch sensitivity (Feldman, 1994). We will also continue to obtain self-reported information on the diagnosis of diabetic retinopathy, amputations, laser treatment, and cataract extraction.

Quality of life will be measured by the Medical Outcomes Study Short Form 36 (SF-36), which assesses health across eight domains: physical functioning; role limitations because of physical health problems; bodily pain; social functioning; general mental health (psychological distress and psychological well-being); role limitations because of emotional problems; vitality (energy/fatigue); and general health perceptions (Ware, 1992).

Supporting analyses will include the individual domains of the SF-36, the SF-6D, late life depression assessed by the Patient Health Questionnaire (PHQ-9) (Kroenke, 2001); healthy non-disabled life-years estimated using the SF-36 and mortality data; and the EuroQual Feeling Thermometer (The EuroQual Group, 1990), the Loneliness Questionnaire (Hughes 2004; Russell 1996), the Resilience Questionnaire (Smith, 2008), and the Pittsburgh Fatigability Scale for Older Adults (Glynn, 2015).

1.4.3 Tertiary Outcomes

Tertiary outcomes include weight, physical activity, fat and lean mass, bone density, and cognitive function.

Their long-term trajectories will be described within and between intervention groups and their relationship to the primary and secondary outcomes will be examined.

Weight will be measured at the biennial clinic visits following the same standardized protocol that has been used throughout Look AHEAD.

Physical activity will be assessed by accelerometry. Physical activity and sleep data are obtained over a 24-hour period and are summarized in two ways: duration (time in minutes) and intensity of movement (threshold of activity count/min). Participants will be instructed to wear the accelerometer for a period of seven days, including one weekend day, for a period of 24 hours per day.

The sample size for this Look AHEAD Extension substudy will be approximately 1800 individuals currently active Look AHEAD -C and participated in the accelerometry sub studies in the past. The Central Reading Center for the accelerometry data will receive and process these data and transmit summary scores to the coordinating center.

In addition, all participants will complete the Paffenbarger Physical Activity Questionnaire (Paffenbarger 1978) to assess leisure time activity. This questionnaire was administered to the same subgroup described above at baseline, year 1 and year 4 , and to all Look AHEAD participants at year 8.

Fat and lean mass, bone density and bone mineral content will be assessed by DXA in a subset of 800 participants at five Look AHEAD sites (Baton Rouge, Boston-MGH, Houston, Los Angeles, and Seattle) who were part of the original Look AHEAD substudy examining these outcomes. The UCSF DXA QA Center was responsible for quality control during the original trial and will continue in this capacity for Look AHEAD Extension. Scans will be sent to the UCSF DXA QA Center for quality review of acquisition, and incorporation into a centralized database of DXA results. UCSF will provide a standard protocol to the densitometer sites, training in the specific study procedures for the DXA technicians, and certification of the technicians as qualified for Look AHEAD Extension scanning. DXA results will be provided to the participants. In addition, UCSF will notify the clinical site if a total hip, femoral neck or lumbar spine BMD T-score is below -2.5, and the clinical site will alert the participant. Quality control will include careful attention to machine cross calibration. Longitudinal changes in densitometer performance will be monitored using spine and whole body phantoms.

Cognitive assessment Among participants who consent, the 30-45 min cognitive battery used in the Look AHEAD Continuation (Rapp, 2017) will be repeated. It includes validated measures of attention and concentration, verbal learning and memory, processing speed, executive function, and global cognitive functioning,

Cognitive Impairment. Cognitive impairment (dementia and mild cognitive impairment) will be centrally adjudicated with the same protocol as used in the Look AHEAD Continuation (Espeland, 2017). Adjudication will be based on all available data for individuals whose scores on the Modified Mini Mental State Exam fall below age- and education-specific cut points. This triggers telephone administration of the Functional Assessment Questionnaire to a proxy, identified by the participant to query functional status in instrumental activities of daily living. Additional cases of cognitive impairment will be ascertained through interviews of proxies for participants who died or can no longer answer questions about their health or functioning .

Lab Substudy. The Lab Substudy will be conducted after the end of participant follow-up to identify factors associated with cognitive resilience and mechanisms that explain any differential responses to ILI on cognitive function and cognitive impairment. It will be based on stored bio-specimens collected at Look AHEAD baseline, year 10, and during the Look AHEAD Extension: no additional specimen collection is required. Assays will be conducted to determine plasma/serum levels of analytes related to angiogenesis (leptin, apelin, VEGF), inflammation (IL-6, CRP, adiponectin), and sex hormones (testosterone, estradiol).

1.4.4 Schedule for Ascertaining Outcomes

Study measures will be obtained during the Look AHEAD Extension at clinic exams and at six month phone contacts. Participants will be invited to attend two clinic examinations at an interval of approximately two years. All clinic visits will involve a blood draw, physical and anthropometric measures, physical function measures, questionnaires, and interviews for study outcomes. In addition, the second clinic visit will include waist circumference measures and the cognitive assessment among participants who consent. Some participants will also be asked to participate in the DXA and/or accelerometry sub-study. All participants will receive six month phone calls for study outcomes. The list of study measures and frequency of collection is shown in Table 1.

1.4.5 Table 1. Study Measures and Time Points for Data Collection in the Look AHEAD Extension

Table 1. Study measures and time points for data collection in the Look AHEAD Extension			
	EXAM 1 (2016-2018)	EXAM 2 (2018-2020)	SIX MONTH PHONE CALLS
Laboratory Measures			
HbA1c	X	X	
Serum Creatinine	X	X	
Stored Plasma, Serum and Whole Blood	X	X	
Physical Measures			
Seated BP & Pulse	X	X	
Weight, Height	X	X	
Waist Circumference		X	
Foot exam for neuropathy	X	X	
Outcomes/Events Interview			
Hospitalizations (& discharge summaries)	X	X	X
Outpatient Visits	X	X	X
Major Health Events	X	X	X
Falls	X	X	X
Renal Replacement Therapy	X	X	X
Amputations	X	X	X
Mortality (death certificates and other records)	X	X	X
Questionnaires			
Participant Contact Form & Proxy Identification	X	X	X
Michigan Neuropathy Screening Instrument	X	X	
Medications	X	X	
SF-36	X	X	
PHQ-9	X	X	
EuroQual (Feeling) Thermometer	X	X	
Loneliness Questionnaire	X		
Paffenbarger Physical Activity	X	X	
Falls Efficacy Scale International	X	X	
Resilience Questionnaire	X		
Pittsburgh Fatigability Scale	X		
Pepper Assessment Tool for Disability (PAT-D)	X	X	
Physical Function and Abilities Questionnaire	X	X	
Sleep Questionnaire	X	X	
Cognitive Function Battery			
Interviewer Administered Battery (45 min)		X	
Digit Symbol Coding Test		X	
Rey Auditory Verbal Learning Test		X	
Modified MiniMental State Exam		X	

Trails Making Test Parts A&B		X	
Modified Stroop Color-Word Test		X	
Functional Assesment Questionnaire (as needed)		X	
Dementia Questionnaire (as needed)		X	
Physical Function			
400-m Walk/alternate 4 meter walk	X	X	
Grip Strength	X	X	
Short Physical Performance Battery (SPPB)	X	X	
Sub studies			
DXA (selected sites)	X		
Accelerometry (selected sites)	X		

1.5 STATISTICAL CONSIDERATIONS

Details of the design, power, and statistical analysis plan are provided in the Statistical Analysis Plan (Appendix 2). Here are summarized the analytical approaches to the two primary aims of the Look AHEAD Extension Study.

Specific Aim 1 is to test the hypothesis: The hazard rates for total mortality will differ between intervention groups across follow-up. Mortality will be adjudicated from death certificates, recent hospitalization records (discharge summaries only), outcomes interviews, and National Death Index (NDI) search. All data collected since randomization will be included. Time to death from any cause will be measured from the time of randomization. Follow-up time for participants who remain event free will be calculated as the time in years from randomization to their last available visit. The primary analysis of the all-cause mortality will be proportional hazards regression with stratification for clinical sites, mirroring the analysis of the trial's primary composite cardiovascular disease outcome. Significance for the intervention effect will be based on the likelihood ratio test. Hazard ratios and 95% confidence intervals will be constructed from the fitted models. The proportional hazard assumption will be examined using log/log plots of survival (e.g. Lagakos, 1984) and alternative models may be used as sensitivity analyses, if necessary. In addition, Kaplan-Meier plots will be used to present the survival curves by intervention.

Specific Aim 2 is to test the hypothesis: the cumulative mean (discounted) total health care costs post-intervention will differ between intervention groups. As described in the protocol synopsis, health care costs during the intervention phase of the Look AHEAD have been published (Espeland, 2104). We have continued to collect these data post-intervention (i.e. after 9/2012) and Specific Aim 2 is based on these data as collected through 7/2020. Each participant's annual costs for hospitalizations, outpatient care, medications, and rehabilitation/nursing home stays will be tallied and divided by follow-up times to obtain observed costs per year. Weighted analysis of covariance will be used to compare intervention groups, with analytical weights proportional to participants' lengths of follow-up. Clinic, the sole stratification factor in randomization, will be used as a covariate. To accumulate costs post-intervention, annual estimates will be discounted at 3% per year and summed and bootstrapping will be used for confidence intervals of accumulated mean costs. We will also

generate accumulated mean costs across the full span of follow-up (i.e. since randomization) for descriptive purposes.

1.6 STUDY ORGANIZATION

The organizational structure of the Look AHEAD Extension is patterned after the successful structure of the previous phases of Look AHEAD. The Steering Committee is the main governing body, at which each clinic, the coordinating center and NIH have one vote: it meets at least twice a year, in person, by telephone conference call, webinar, or other means according to available technology. The Executive Committee is comprised of the Study Chair and Co-chair, coordinating center representatives, and NIDDK representative(s): it meets weekly, as needed, by phone to ensure efficient progress and attend to day-to-day issues.

The Adjudication Committee is comprised of physician scientists who will meet regularly to adjudicate mortality and cause of death. The Ancillary Study Committee reviews all proposals for ancillary studies to evaluate burden to the participants and study. Studies approved by the committee are then forwarded to the Steering Committee for a full vote. Clinic Operations and Quality Control Committee monitors clinic and central unit performance. They work closely with the coordinating center to produce and review reports of study data quality. The Program Coordinators Committee is comprised of the Program Coordinator at each clinic, who meet regularly to discuss study operations and to troubleshoot issues. The Publications and Presentations Committee follows a structured set of policies regarding the approval of abstracts, manuscripts and study presentations. It meets regularly to move the scientific products of Look AHEAD rapidly into the scientific literature. Manuscripts approved by the Publications and Presentations committee are forwarded to the Steering Committee for a full vote. The Retention Committee monitors study-wide and site specific retention, providing strategies to maximize retention throughout the trial. The Safety Committee reviews safety events, as needed, and any clinic-related serious adverse event.

1.7 QUALITY CONTROL

The Look AHEAD Extension will continue the successful quality assurance program of the trial that includes extensive manuals, central training, certification/recertification, special educational workshops (as needed), monitoring, and reporting. The web-based data management, reporting, and document archive is an extraordinary resource for maintaining exceptional quality control.

In addition, the Clinic Operations and Quality Control Committee composed of study staff and investigators with support from the coordinating center, has been active since the beginning of Look AHEAD. The committee works in concert to oversee the standardized measurement protocols for collecting data during clinic visits and interviews. The committee will oversee and recommend any revisions to, or further development of, study and sub-study data collection forms, develop guidelines for and oversee central units (e.g., central laboratory and reading centers), review and monitor quality control related to study and sub-study measures, and report on quality control to the study group. This committee also reviews the certification of clinic staff and assists with training and certification/recertification of study staff on measurement protocols. Any problems identified with laboratory and reading centers or clinic performance is addressed with remediation plans.

Quality Control at the Clinical Centers

The Look AHEAD Extension Manual of Procedures specifies quality control activities that will be carried out at each of the Clinical Centers to assure consistent, high quality data across sites. These activities include: certification/recertification of clinic staff in data collection procedures; monitoring of regular equipment calibration and maintenance; regular observation and monitoring of clinical procedures, including specimen collection; review of all questionnaires and data collection forms prior to data entry and before the participant leaves the Clinical Center; performing monthly quality control checks in the centralized data entry system to randomly check source documents against actual data entry; and regular monitoring by the Project Coordinator to assure that Clinical Center procedures are being carried out properly and with consideration for the Look AHEAD Extension participant.

Further assurance of consistent, high quality data across Clinical Centers is provided by the quality control checks built into the web-based centralized data entry system, which allows authorized users to access clinic and participant information for the purpose of entering and editing study data. At entry, data are immediately validated against sets of validation rules.

Quality Control at the Central Units

There are three central units that will participate in data analysis and quality control in the Look AHEAD Extension: the Central Laboratory, the DXA Reading Center, and the Accelerometry Reading Center. Each of these central units employs their own quality control metrics and will report regularly to the Clinic Operations and Quality Control Committee. The Committee will also request certain metrics from each unit.

Central units transmit data to the coordinating center on a monthly basis following a schedule established for previous phases in Look AHEAD. The process involves uploading data directly to the secure Look AHEAD website, where staff is immediately notified of a new data file and a set of standard quality control and cleaning processes are initiated. Once cleaned, data are merged with the master database.

Performance Reports

Throughout Look AHEAD Extension, the coordinating center, the Executive Committee, Clinic Operations and Quality Control Committee and the Retention Committee will monitor the performance of the clinical sites. The coordinating center produces performance reports summarizing on-going ancillary studies, clinic operations, data entry quality control, retention, physical function, outcomes and protocol performance. These reports are available on the password-protected Look AHEAD website. Additional reports are developed, as needed based on requests from the DSMB, the Steering Committee and associated subcommittees.

The Clinical Operations and Quality Control Committee works closely with the coordinating center to regularly produce and review a one-page report card, which provides site-specific data and study-wide targets for data quality. Elements include retention, rate of form completion and data entry, delays in laboratory shipments, and time to submission of study outcomes packets. Sites that underperform are identified and remediation work is initiated first by the coordinating center staff then by the Clinical Operations and Quality Control Committee. Sites are also praised for strong performance based on results of the report card.

Staff Training and Site Visits

Central training for clinic personnel will be organized and conducted early in the first year of the Look AHEAD Extension. Certification and recertification are mandatory to assure that staff have clear understanding of the protocol and for standardization. Annual refresher training/certification sessions will be conducted in conjunction with Steering Committee meetings or using webinars. Cognitive training and certification of staff will take place prior to the second clinic visit. Training sessions contribute significantly to high-quality data collection by providing opportunities for learning skills and promoting camaraderie and problem solving. Look AHEAD has had success with a "train the trainer" model.

Based on clinic performance monitoring, the coordinating center with NIDDK and other study personnel, may visit a Clinical Center to promote communication, answer questions, and ensure that study procedures are understood and carried out correctly. The site visit program will provide a mechanism to encourage the effective and standardized delivery of recruitment and retention efforts, and the collection of appropriate and valid data within each of the Look AHEAD Extension clinic sites. Site visits may also be performed if consistent departures from the Protocol and Manual of Procedures are detected. The decision for these site visits will rest with the Executive Committee.

1.8 CENTRALIZED DATA MANAGEMENT SYSTEM

The Look AHEAD Extension study features an integrated web-based system for managing operations and capturing data. At entry, data are immediately validated against sets of validation rules. Some of these rules identify errors that must be corrected immediately. Other rules for less critical concerns present validation warnings for review, which are saved to the database for later reconciliation and tracked with reminders and reports. Data are immediately available in alert/tracking systems and dynamic reports based on relational databases. No records are ever deleted, all changes produce audit trails, and back-ups are created hourly. This provides a high degree of integrity, detail, and flexibility in responding to unexpected study needs related to report generation, auditing, and monitoring. A comprehensive security program is in place that integrates policy and practice.

The system allows authorized users to access clinic and participant information for the purpose of entering and editing study data. Only authorized users may access and enter/update information regarding participants' study data. The application maintains audit logs which identify the activity of each user at all times while logged into the system.

1.9 CONFIDENTIALITY

Great precaution will be taken in the Look AHEAD Extension to maintain the confidentiality of all participants. Confidentiality of data will be maintained by using research identification (ID) numbers that uniquely identify each individual. Participants' names will not be used as identifiers on any data collection forms, specimens, or databases; only the Look AHEAD research ID will be used. Hardcopies of individual participants' research records will be kept in a locked room at each Look AHEAD Extension Clinical Center. The file that links participants' names and demographic information with their research ID numbers will be kept in a separate room and will be stored in a locked file cabinet that opens with a unique key different from that used for all

other filing cabinets. Only authorized clinic staff will have access to these files, and they will be asked to sign a document certifying that they agree to maintain the confidentiality of the information. After the Look AHEAD Extension is completed, local data will be stored with that of other completed studies in a secure storage area following all applicable regulations for the storage and maintenance of research data. De-identified databases (limited to participants who consent) will be prepared periodically for NIH archives.

Participants will be asked to consent to having their Protected Health information (PHI) shared with and electronically transferred to the coordinating center at Wake Forest School of Medicine. Participants are not required to consent to this sharing of information; their decision about sharing this information will not affect their participation in the Look AHEAD Extension. Section 3d. "Informed Consent" describes the potential use of these data, including recovery in the event of a major disaster, searches of national databases such as the National Death Index (NDI) or Centers for Medicare and Medicaid Services (CMS) or, in the event that future funding is not available for the clinics to contact their participants, this information would be used to allow direct contact by the coordinating center with the participant. For participants who consent to having their PHI shared with and electronically transferred to the coordinating center at Wake Forest School of Medicine, these identifiers will be collected and stored in the electronic database. Using a role-based security model, user access is tailored by user group (e.g., clinic staff, programmer, database manager). Access for Clinical Centers is restricted so that clinic staff have access only to their own clinic information.

1.10 SAFETY MANAGEMENT

The potential risks to individuals participating in this non-intervention phase of Look AHEAD are very few.

Physical function assessments

Protocols for tests of physical function have been chosen to maximize safety. Staff performing these measures will be trained and certified on proper conduct of the tests. To minimize the risk of falling, the area where the activity will take place will be as free of clutter and distractions as possible. Other steps to minimize risks include: (1) safely escorting participants to chairs located along the walking course should they become unsteady; (2) walking with them at a close distance for close supervision; and, (3) being at their side should they need assistance. There is a risk that participants may experience muscle soreness or discomfort as a result of the physical performance testing procedures. An emergency plan of action will be in place at each site to address injury or emergency situations.

Blood draw and blood pressure measurement

Staff will be trained in obtaining measurements in order to minimize risks.

Participants will receive reports with the results of Look AHEAD Extension measurements (weight, body mass index, blood pressure, GFR, serum creatinine, and HbA1c). Those sites performing DXA will also provide reports on those results. Reports include explanations as to what is considered normal or abnormal, and if they authorize it, a copy of their results will be sent to their primary care provider (PCP). Participants with abnormalities needing medical

management will be referred to their PCP. The following are Look AHEAD Extension alerts and the action required by study staff.

ALERT	ACTION
Blood pressure (mm Hg)	
SBP≥170 or DBP≥100	Clinic staff will inform the participant during the clinic visit and write to the participant's physician * within one week; they will note the alert in the participant's chart.
SBP≥200 or DBP≥120	Emergency action (see footnote #)
ALERT	**ACTION**
eGFR (ml/min/1.73m^2, CKD-Epi equation)	
First study eGFR and none of the conditions below	eGFR letter A* (see Appendix).
<60	Clinic staff will note the alert in the participant's chart and send the central lab report, eGFR letter B*. If this is the first occurrence of eGFR<60, send the PCP letter and central lab report to the participant's PCP within one week, and send the NIDDK brochure to participant within one week.
≥60 but ≥30% drop from last study eGFR	As above, but send eGFR letter C*.
<15	As above, but send eGFR letter D* within one week.
HbA1c ≥12%	Note the alert in the participant's chart and send central lab report to participant and PCP within one week.
Cumulative BMD decreases **Visit 48 to Look AHEAD –E visit >15%** **Visit 96 to Look AHEAD –E visit > 10%** **for spine or hip**	Repeat scan according to Excessive Bone Loss Procedures, Chapter 12. If excessive bone loss is confirmed by DXA Reading Center, follow procedures in Section 12.3.1 of the MOP for informing participant and PCP. Send the BMD alert letter, appendix E*.
PHQ-9 Questionnaire	
If total score ≥15 but <20	Staff should talk to participant, and encourage participant to seek additional follow-up and/or evaluation. No intervention or letter.
if total score is ≥20	Anyone with a score of 20 or greater, regardless of suicidal ideation, should be encouraged to talk with their doctor or mental

	health professional "because you seem to be experiencing some significant symptoms of depression. I think your doctor could help you feel better." In the absence of suicidal ideation, they can be asked to notify you after they've had a chance to see their doctor or LA staff can call to follow-up on the patient a couple of weeks later.
If question 9, (Q9. "Thoughts that you would be better off dead or of hurting yourself in some way") is answered greater than 0, regardless of the total PHQ-9 score	Emergency action (see footnote [#]).

*Send letters to physicians only if the participant has consented to informing his/her physician.

[#]Emergency action: This will be clinic specific, depending on the physical location and staffing of each clinic. It may involve evaluation by a study clinician (e.g., doctoral level clinical psychologist, physician, nurse, or physician's assistant for suicidal ideation), staff escorting the participant to an emergency room, sending the participant to an emergency room or physician's office by taxi or ambulance, or other such action.

For individuals who express concern about cognitive abilities, clinic sites will have a resource list available but should be encouraged to contact their PCP.

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Appendix A: Model Consent Form

A.1 MODEL Informed Consent Document

Look AHEAD (Action for Health in Diabetes) Extension Study

Introduction

You are invited to be in a research study called Look AHEAD-E. This study is only for people who took part in the original Look AHEAD study. Research studies are designed to gain scientific knowledge that may help other people in the future. You are being asked to take part in this study because you have type 2 diabetes and you have been in the Look AHEAD studies. Your participation is voluntary. Please take your time in making your decision as to whether or not you wish to participate. Please ask your study doctor or the study staff to explain any words or information contained in this informed consent that you do not understand. You may also discuss the study with your friends and family.

Why Is This Study Being Done?

The purpose of this study is to continue to follow you and to help us understand the *long-term* effects of weight change on overall health. During the original Look AHEAD study, participants were assigned by chance to be in either the Intensive Lifestyle Intervention group or the Diabetes Support and Education group. We are no longer providing these separate programs; but, we want to know whether these programs have long-term effects on your health.

There are many aspects to overall health. These include heart attacks and strokes, complications of diabetes, psychological health, and quality of life. We focused on these aspects of health in the early phases of Look AHEAD and have continued to do so in the Look AHEAD Continuation. In Look AHEAD-E we now want to look at some other areas of health. These include your physical function (your strength and ability to walk a set distance). We will also continue to follow the changes in your weight, your level of physical activity, your use of medications, hospitalizations, and your overall health. Continuing to follow you over time will allow us to determine whether there are long-term benefits or risks of weight loss for each of these different aspects of health.

How Many People Will Take Part in the Study?

We expect about 3,800 current Look AHEAD participants at nineteen clinical sites across the United States to continue in this study. Look AHEAD-E will involve approximately (*insert number)* participants at this research site.

What Is Involved in the Study?

If you take part in this study you will be asked to sign this consent form and answer some questions about your understanding of what we will be doing in the study. If you have trouble understanding the consent form, you may choose to have a friend or family member help you understand the form and help you decide whether to participate, or we may ask you to have a friend or family member help you with the consent process. If you decide to participate in Look AHEAD-E, you will be contacted by phone every six months to answer questions about your health. You will be asked to come into the clinic for two clinic visits during the next five years of Look AHEAD-E. Some individuals will be asked to come to the clinic a third time to again measure your physical function or to undergo a DXA exam to measure their body composition.

Some will be asked to wear a small device – like a pager or wrist watch – to measure physical activity and sleep. The tests and procedures that are part of Look AHEAD-E are described below.

Social Event

You will be invited to attend social events during Look AHEAD-E, and you may be invited to bring your spouse or a friend. The activities may include a lunch or dinner and some type of social activity. The purpose of social events is to thank you for your participation in Look AHEAD-E, and to provide an opportunity for visiting with fellow participants and research staff.

Telephone Calls

You will be contacted by study staff on the phone every six months to answer questions about your general health, medical conditions, the quality of your life, and any hospitalizations and outpatient visits you have had. If you have had a hospitalization, the study staff will ask your permission to obtain a discharge summary or medical records. Each call will probably take about 10 - 45 minutes depending on how many health problems you report.

Questionnaires

You will be mailed a package of questionnaires for your visit and asked to return them by mail or bring them to your clinic visit. These questionnaires are similar to those asked in the past and include questions on thoughts and feelings, diabetes and its complications, physical activity, behaviors, eating habits and medical events. The questionnaires will take about 30 minutes to complete.

Clinic Visit

You will come into the clinic for two visits over the next five years. Some individuals may be asked to complete additional visits for a DXA exam or to repeat the walking test. Each clinic visit will last about two hours. A clinic visit will normally be completed as one visit; however, there may be times where it would be divided into two visits. Cognitive testing will be done once either during the second clinic visit, or the last two years of the study. If you are fasting for this visit, you will be able to have something to eat and drink after your blood is drawn. The following tests will be done:

<u>Physical Measures</u>

We will measure your height, weight and waist circumference and take your blood pressure. You will have a brief foot exam (when a tuning fork is placed on your foot and the staff record the vibrations), , and neuropathy test (during which the staff will place an instrument similar to fishing line against several areas of the foot and ask you to tell them when you feel it). We will ask you to provide a blood sample and about 5 teaspoons of blood will be taken from a vein. We can send copies of your test results to your personal physician. Even if you do not wish to have any of your medical information sent to your physician, you can still be a part of this research study.

Physical Function Tests and Measures of Physical Activity

Staff will ask you to perform some tasks that include: standing up from a seated position in a chair 5 times in a row, standing in 4 different positions to assess your balance, walking 400 meters or less with staff (about 5 minutes or like walking around the block), and gripping a device with your hands. Some Look AHEAD-E participants will be asked to wear a small device (called an accelerometer) to measure their activity levels by recording movement.

Cognitive Function Measures

Cognitive function testing will be done once during the second clinic visit or during the last two years of the study second clinic visit. Staff will ask you some questions about your memory and thinking skills, concentration, and your ability to do certain physical tasks such as drawing lines or circles. This interview may be recorded on audiotape (voices only) and sent to the Coordinating Center at Wake Forest. This is being done as a quality control measure to make sure the Look AHEAD staff is administering tests in a standardized way. These recordings will not identify you in any way and they will be destroyed when the study is over. You may request the recording be stopped at any time during the course of the research study. You should also understand that you will not be able to inspect, review, or approve the audiotapes before they are used in this study. Previously collected stored samples will be used for tests related to cognitive functioning. You will be asked to provide the name(s) of family members or close friends to serve as a proxy. After your visit, the staff may call your proxy to collect additional information on your health and functioning.

Stored Blood Samples

We are requesting your permission to store your blood samples at a central laboratory for future research. There have been many advances in the ways in which blood can be studied. Many researchers are focusing on ways to predict diseases based on what is found in a person's blood. We are asking your permission to allow your stored blood samples to be studied by Look AHEAD researchers as well as outside researchers that have been approved by the Look AHEAD study or NIDDK. Look AHEAD provides these samples without personal identifying information, such as your name, address, or Social Security number. All research on your samples will be done only by individuals and organizations that meet NIDDK standards. This means that research proposals will undergo careful review by Look AHEAD or NIDDK, or by an NIDDK review group, or by Institutional Review Boards. Researchers will be required to treat the data or samples as strictly confidential, and agree not to share data or samples with other parties. Your blood samples will be stored at a central site listed under a code number. The samples will be stored for as long as they are useful for research.

Interviews

Staff will ask you some questions on your thoughts and feelings, your overall health, hypoglycemia (low blood glucose), physical activity, and medical events.

Other Medical Tests

In addition to what is described above, some people will be asked to complete other medical tests that require a third visit. These additional medical tests are voluntary, and will only be done on individuals who had the test done previously.

For example, Look AHEAD-E participants at some sites will be asked to participate in a test that measures the distribution of fat in their bodies and the density of their bones with a low dose radiology machine called a DXA (dual energy x-ray absorptiometry).

Some individuals may be asked to return to the clinic for an additional 400 meter walking test.

How Long Will I Be in the Study?

You will be in the study through December 31, 2022. We may also call you up until December 31, 2027 to see if you would like to join another study connected with Look AHEAD. You may stop taking part in the study at any time. You will not be penalized and you will not lose any benefits if you decide to stop taking part in the study. If you decide to stop taking part in the study, we ask you to discuss this decision with the investigators or study staff.

What Are the Risks of the Study?

The risk of harm or discomfort that may happen as a result of taking part in Look AHEAD-E is not expected to be more than in daily life or from routine physical or psychological examinations or tests.

Risks of Blood Draw

While rare, the risks of drawing blood for the study include the possibilities of brief pain, becoming faint during the blood draw, or developing a bruise or bump following the blood draw, and there is a slight risk of infection at the site where blood was drawn.

Risks of Blood Pressure Measurement

You may experience temporary discomfort during blood pressure recordings due to the pressure of the blood pressure cuff on your arm.

Risks of Physical Function Tests

Risks and side effects associated with the physical performance-based testing (the walking test, balance tests, rising from a chair) includes the risk of losing your balance and falling. In rare instances persons doing the walking test will experience leg or chest pain, heart palpitations, shortness of breath or light headedness. In very rare situations exercise can result in heart attack or sudden death. We will minimize this risk by: (1) safely helping you to chairs located along the walking course should you become unsteady, (2) walking with you at a close distance, and, (3) being at your side should you need assistance. There is a risk that you may have muscle soreness or discomfort as a result of the physical function tests.

Risks of Cognitive Function Tests

There are no risks associated with the memory-testing portion of the study. If you are uncomfortable with a question or task you may decline to answer or stop the task.

Risks of DXA Exam

The DXA exam uses a small amount of X-ray radiation, so there is a very slight risk of radiation exposure. The radiation exposure is comparable to what you would get if you were in the sunshine for 3 hours or if you took a flight from California to New York.

Other Risks

Taking part in this research study may involve providing information that you consider confidential or private. In addition, there is a slight risk of a breach of confidentiality. We will do our best to protect your confidential information. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe. A monitoring committee, an independent group of experts, will be reviewing the data from this research throughout the study. You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

Are There Benefits to Taking Part in the Study?

There may be no direct benefit to you from this study. You will receive regular medical tests relating to diabetes and its complications. You will be notified of any concerns from your study results so you may discuss them with your doctor or if you provide permission, we can share the information with your doctor. This information about your health problems may be of benefit to you. We hope the information learned from this study will benefit other people in the future.

What Other Choices Are There?

This is not a treatment study. Your alternative is to not participate in this study.

What About My Health Information?

In this research study, any new information we collect from you and/or information we get from your medical records or other facilities about your health or behaviors is considered Protected Health Information. By taking part in this research study, your protected health information, as well as other information that directly identifies you, may be used and disclosed. Information that identifies you includes, but is not limited to, such things as your name, address, telephone number, and date of birth. Your protected health information includes all information about you which is collected or created during the study for research purposes. It also includes your protected health information that is related to this study and that is maintained in your medical records at this clinic and at other places such as other hospitals and clinics where you may have received medical care. Examples of your protected health information include your health history, your family health history, how you respond to study activities or procedures, laboratory and other test results, medical images, and information from study visits, phone calls, surveys, and physical examinations. In all cases, only those study personnel and federal sponsors who have a need to see the information will be given access to the information. In addition, when the data are analyzed and published, there will be no information included that would identify individual participants.

We will make every effort to keep your Protected Health Information private. We will store records of your Protected Health Information in a cabinet in a locked office or on a password protected computer. Also, according to the rules governing research procedures at add your institution here, by agreeing to participate in the study, you grant permission for information about you obtained during the study to be made available to:

- The investigator and members of their study team,
- Authorities at add your institution here including the Institutional Review Board (IRB) that independently reviews studies to assure adequate protection of research participants, as required by federal regulations,
- The Federal Office of Human Research Protections (OHRP) and other government agencies that oversee the safely of human subjects.
- Other participating researchers including staff at other medical centers, laboratories, reading centers, repositories, data coordinating centers, and institutions involved with the Look AHEAD Study and its ancillary studies, including the Wake Forest School of Medicine,
- National Institutes of Health, including the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute on Aging (NIA),and the Center for Disease Control and Prevention (CDC).

Those listed above will have access to the information you provide in this interview and any information in your research file. Some of these people, agencies, and businesses may further disclose your health information. If disclosed by them, your health information may no longer be covered by federal or state privacy regulations. Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This information may be used by other researchers. You will not be directly identified in any publication or presentation that may result from this study.

To help us further protect your privacy, the investigators have obtained a Confidentiality Certificate from the Department of Health and Human Services (DHHS). With this Certificate, the investigators cannot be forced (for example by court subpoena) to disclose research information that may identify you in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings. Disclosure will be necessary, however, upon request of DHHS for audit or program evaluation purposes.

In addition, we are asking that you agree to have your Protected Health information shared with and electronically transferred to the Coordinating Center at Wake Forest School of Medicine to ensure the success of the study. The reasons for transferring your personal identifiers to the Coordinating Center are:

1) The information would be used at the Coordinating Center in the event of natural or other major disaster affecting a clinical site (for example, if a clinic were destroyed by a hurricane or tornado, the Coordinating Center would be able to provide contact information for you to the clinics so that they could reach you).

2) This information would be used to allow direct contact with you, by telephone or mail, for the following purposes: to invite you to take part in another study that is connected to Look AHEAD-E; to conduct the study outcomes interview; to conduct other types of interviews, e.g., to inquire about current health status or body weight, or to update contact information on designated friends and family member.

3) The information would be used to allow searches of national databases such as the Centers for Medicare and Medicaid Services (CMS) and the National Death Index

(NDI) for the purpose of determining your health, assessing medical and hospitalization visits and vital status. These would require that the Coordinating Center have access to names, addresses, birth dates, social security number, and/or Medicare number.

When you sign this consent and authorization form, you authorize or give permission for the use of your health information as described in the consent form. You can revoke or take away your authorization to use and disclose your health information at any time. You do this by sending a written notice to the investigator in charge of the study at the following address:

Principal Investigator Name

Address

City, State, ZIP

If you withdraw your consent, you will not be able to be in this study. If you withdraw your consent, no new health information that identifies you will be gathered after that date. Your health information that has already been gathered may still be used and disclosed to others.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for at least six years after the study is finished. At that time, any research information not already in your medical record will either be destroyed or it will be de-identified. This authorization does not expire. You will not be able to obtain a copy of your Protected Health Information in the research records until all activities in the study are completely finished.

What Are the Costs?

There are no costs to you for taking part in this study. All study costs will be paid for by the study. Costs for your regular medical care, which are not related to this study, will be your own responsibility.

Will You Be Paid for Participating?

You will be paid $100 for the completing each of the two in-person study clinic visits and $25 per outcomes phone calls during Look AHEAD-E. If an additional visit is required to repeat the walking test or if you complete a DXA exam, you will be paid an additional $25 for each test.

Who is Sponsoring this Study?

This study is being sponsored by the National Institutes of Health, including the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute on Aging (NIA), and the Center for Disease Control and Prevention (CDC). These agencies are part of the U.S. Federal Government. The sponsor is providing money or other support to help conduct this study. The researchers do not, however, hold a direct financial interest in the sponsor or in what is being studied.

What Are My Rights as a Research Study Participant?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or

loss of benefits to which you are entitled. The investigators also have the right to stop your participation in the study at any time.

Who Do I Call if I Have Questions or Problems?

For questions about the study or in the event of a research-related injury, contact the study investigator, *Name* at *telephone number (also include after-hours number)*.

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, or you would like to discuss problems or concerns, have questions, or want to offer input, or you want to obtain additional information, you should contact the Chair of the IRB at *[insert phone number here].*

You will be given a copy of this signed consent form.

Signatures

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

I agree to participate in Look AHEAD-E. [ ] Yes [ ] No

If you have agreed to participate in the Look AHEAD-E, we ask that you to consider agreeing to the following. If you do not agree to these, you will still be able to participate in Look AHEAD-E.

I agree to participate in the cognitive portion of the study. [ ] Yes [ ] No

I agree to have you send important medical findings from my study tests/exams to my personal physician. [ ] Yes [ ] No

I agree to the audio recording of my cognitive tests. [ ] Yes [ ] No

I agree to share my data with participating researchers including staff at other medical centers, laboratories, reading centers, repositories, data coordinating centers, outside researchers and institutions involved with the Look AHEAD Study and its ancillary studies, including Wake Forest School of Medicine. [ ] Yes [ ] No

I agree to provide the names of family members or close friends so that staff at my clinical site may contact them to ask additional questions about my health and functioning if necessary. Also, if my health problems ever make it hard for me to answer questions for myself, the staff at my clinical site may contact these people to ask questions on my behalf. [ ] Yes [ ] No

I agree to allow the staff at the clinical site or the Coordinating Center at Wake Forest University Health Sciences to contact me before December 31, 2027 for reasons such as: to inquire about

current health status or body weight or to update contact information on designated friends and family member or to join a future research study. [ ] Yes [ ] No

I agree to allow the study to store my blood sample with a code number for any kind of future research. [ ] Yes [ ] No

I agree to provide my social security number and Medicare number so that the Look AHEAD Coordinating Center at the Wake Forest School of Medicine may search national databases for information about my health and vital status any time before December 31, 2027.

[ ] Yes [ ] No

I agree to allow other groups approved by the Look AHEAD investigators to use my contact information to get in touch with me for reasons such as: to see if I would like to join another study connected with Look AHEAD, to inquire about current health status or body weight, or to update contact information on designated friends and family member and to search national databases for health information about me before December 31, 2027. [ ] Yes [ ] No

Subject Name (Printed):_____

Subject Signature: _____

Date: _____Time:_____ am pm

Person Obtaining Consent: _____

Date: _____ Time: _____ am pm

The following should be included if you are recruiting subjects who cannot provide informed consent (for example due to diminished mental capacity):

Legally Authorized Representative Name (Print):_____

The above named Legally Authorized Representative has legal authority to act for the research subject.

Legal Representative Signature: _____

Date: _____ Time: _____ am pm

Documentation that a copy of this Informed Consent was given to the research participant is a Federal requirement. Prior to making a copy of the signed and dated

Informed Consent, please check all appropriate boxes, as applicable, to indicate that a copy was provided to:

☐ **Study Volunteer** ☐ **Medical Record** ☐ **Researcher**

☐ **Other (Specify)**

A.2 MODEL Verbal Informed Consent Document & HIPAA Authorization
Look AHEAD (Action for Health in Diabetes) Extension Study Look AHEAD-E

This is intended as a model script to be read to participants, which you can tailor according to your local IRB requirements.

MODEL Look AHEAD Extension

I am calling to complete the medical outcomes interview for the Look AHEAD Extension study, also called Look AHEAD-E. You already consented to participate in the Look AHEAD study and you may have completed a Look AHEAD Continuation visit. The questions I will ask you on the phone are almost the same questions that you have answered in Look AHEAD for the past 11-13 years. The questions are about your general health, medical conditions, the quality of your life, and any hospitalizations and outpatient visits you have had. If you have had a hospitalization, I will ask your permission to obtain medical records. This call will probably take about 10 - 45 minutes depending on how many health problems you report. You will be paid $25 for this phone call in the form of a gift card mailed to you. We will continue to call you for these phone visits every six months through July 31, 2022. We may also call you up until December 31, 2027 to see if you would like to join another study connected with Look AHEAD.

The Look AHEAD researchers will have access to information that you provide in this phone interview and all the information already collected in your Look AHEAD file.

Research Purpose

The purpose of this phone interview is to continue to collect information regarding the long term effects of weight change on overall health. There are many aspects of overall health. These include heart attacks and strokes, complications of diabetes, mobility and disability, psychological health, and quality of life. The questions we will ask you relate to your doctor's visits, medical tests, and/or hospitalizations that you may have had since your last outcomes interview. Please note that the health information that may be used and disclosed include answers to the questions that you provide and information already included in your research file.

Benefits

There may be no direct benefit to you through your participation in the study. We hope the information learned from this study will benefit other people in the future.

Confidentiality

Although every effort will be made to protect the confidentiality of your records, absolute confidentiality cannot be guaranteed.

Also, according to the rules governing research procedures at add your institution here, by agreeing to participate in the study, you grant permission for information about you obtained during the study to be made available to:

- The investigator and members of their study team;

- Authorities at add your institution here including the Institutional Review Board (IRB) that independently reviews studies to assure adequate protection of research participants, as required by federal regulations;
- The Federal Office of Human Research Protections (OHRP) and other government agencies that oversee the safety of human subjects;
- Other participating researchers including staff at other medical centers, laboratories, reading centers, repositories, data coordinating centers, and institutions involved with the Look AHEAD Study and its ancillary studies, including the Wake Forest School of Medicine.
- National Institutes of Health, including the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute on Aging (NIA),and the Center for Disease Control and Prevention (CDC).

Those named above will have access to the information you provide in this interview and any information in your research file.

To help us further protect your privacy, the investigators have obtained a Confidentiality Certificate from the Department of Health and Human Services (DHHS).

With this Certificate, the investigators cannot be forced (for example by court subpoena) to disclose research information that may identify you in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings. Disclosure will be necessary, however, upon request of DHHS for audit or program evaluation purposes. If your health information is disclosed to a third party, federal privacy law may no longer protect it from further disclosure.

Please note that you may change your mind and revoke "take back" this authorization at any time for any reason. To revoke this authorization you must contact the Principal Investigator put PI name / phone and address here. However, even if you revoke this authorization, the researchers may continue to use and disclose the information already collected, however new information will not be collected for this research purpose.

Use of this information which is your HIPAA authorization does not have an expiration date.

Your decision to participate is voluntary and your treatment or payment or eligibility for benefits will not be conditioned upon your decision to participate in this research.

Who Do I call if I have questions or problems?

If you have any questions or concerns about this study, you may contact put local PI and phone number here (###) ###-####.

You do not have to participate in the research study. You can decide not to participate at any time. If you would like Look AHEAD staff to stop contacting you at any time, please call the Look AHEAD Project Coordinator _____ at (###) ###-####. Your treatment at Local Institution will not be affected by your decision to participate. If you have any questions about your rights as a research subject, you can contact the Institutional Review Board at ###-###-#### or visit the website at put local IRB website here.

A copy of this information sheet will be mailed to you.

Documentation that a copy of this Informed Consent was given to the research participant is a Federal requirement. Prior to making a copy of the signed and dated Informed Consent, please check all appropriate boxes, as applicable, to indicate that a copy was provided to:

☐ **Study Volunteer** ☐ **Medical Record** ☐ **Researcher**

☐ **Other (Specify)**

APPENDIX B:

The Action for Health in Diabetes (Look AHEAD) Extension

Statistical Analysis Plan

Version 1.0

December 14, 2015

Contents

1.0 Introduction and Background

The Action for Health in Diabetes Extension (LA-E) builds on the success of Look AHEAD (LA) in producing and maintaining significant differences in weight loss over 10 years in participants who were randomly assigned to intensive lifestyle intervention (ILI) or its comparison condition of diabetes support and education (DSE). Even though the lifestyle intervention in LA ended in September 2012 due to futility in the primary outcome (fatal and non-fatal myocardial infarction and stroke, hospitalization for angina), follow-up continues into the post-intervention phase of the trial – the Look AHEAD Continuation (LA-C) – through the end of 2015. We continue to observe legacy effects of the intervention on many health outcomes related to diabetes and aging. Of the original randomized 5145 participants, we anticipate following 3800 participants in LA-E (i.e. over 80% of the surviving cohort and 96% of those currently active). We propose to follow these participants with biennial clinic visits and 6-month outcomes phone calls through 4.5 years.

2.0 Study Aims

The **primary** aims of LA-E are to test the hypotheses that, among obese and overweight adults with type 2 diabetes, random assignment to an average of 10 years of ILI relative to DSE has long term legacy effects on:

1. Increased lifespan.

2. Reduced health care costs.

The **secondary aims** of LA-E test the hypotheses that ILI relative to DSE will have long-term beneficial effects on key dimensions of healthy aging.

3. Less frailty.

4. Reduced diabetic microvascular complications.

5. Improved quality of life.

The **tertiary aim** is to

6. Describe the long-term trajectories of a) weight, b) physical activity, c) fat and lean mass, and d) bone density within and between the intervention groups and examine how these are related to outcomes defined by the primary and secondary aims.

Using both existing and newly collected data, we will examine predictors of outcomes (e.g. genetics), interrelationships among outcomes (e.g. association of renal disease and mortality), and differences among important subgroups including history of cardiovascular disease. The goals of LA-E are distinct from those addressed in the original LA or LA-C and focus on critical domains of later life health, each of which has clear individual and societal importance. Launching a trial de novo to examine the long-term health consequences of weight loss on later life health would be cost-prohibitive; continued follow-up of these participants provides a cost-

effective means to examine the long-term consequences of lifestyle intervention in older overweight individuals with type 2 diabetes.

3.0 Study Schedule

Exhibit 1 shows the measures that are proposed for LA-E and the frequency of assessment.

Exhibit1. Measurement Schedule for the Look AHEAD Extension		**Frequency**	**Staff Time**
Measurements			
Blood Draw:	HbA1c; Serum creatinine; Serum & plasma storage	Biennial exams	10 mins
Physical measures:	Seated blood pressure & pulse; Weight; height; waist girth; Neuropathy monofilament, reflexes, vibration tuning fork test	Biennial exams	30 mins
Body composition:	DXA (5 clinics; N=800)	First exam only	Separate Visit
Physical activity:	Accelerometry (8 clinics; N=1800)	First exam only	15 mins
Physical function:	Pepper Assessment Tool for Disability (PAT-D); Short Physical Performance Battery (SPPB); Grip Strength; 400 meter walk	Biennial exams	45 mins
Questionnaires/Interviews			
Health events:	Outcomes/Events Interview and ; Falls	Outcomes 6 mos; Falls: Biennial Exams	5-40 mins
	Medication Inventory	Clinic Vist	
Psychosocial:	Brief Resilience Questionnaire; Fall Self-Efficacy Scale International; Loneliness; Fatigue	Biennial exams	15 mins
Quality of life/Other:	SF-36; Feeling Thermometer; Patient Health Questionnaire; Paffenbarger; Sleep	Biennial exams	10 mins

Two clinic exams will occur for each participant based on an even numbered year following the LA randomization. In addition, participants will continue to receive telephone calls at 6 month intervals to assess outcomes. The LA-E clinical battery and completing forms will require approximately 2 hours and will be completed in a single clinic visit. Those individuals completing a DXA scan will require an additional visit.

4.0 GENERAL APPROACH

4.1 Intention to treat and type 1 error. In keeping with LA's original clinical trial design, we intend to use an intention-to-treat approach in analyses. Much of the clinical impact of LA-E comes from its broader study of health outcomes related to weight loss, diabetes, and aging. Its aims are distinct from those addressed earlier in LA or LA-C, and have been selected to add breadth and context. For this reason, we have not proposed controlling the type 1 error across all LA-E outcomes simultaneously. This approach to type 1 error in secondary and exploratory endpoints is consistent with that described by Moyé, who writes: "*The role of analyses carried out on secondary endpoints is to provide support for the conclusions drawn from the trial's primary endpoint….If they are endpoints that are related to the primary endpoint, they can add additional persuasive force to the argument for the beneficial effect of therapy, a force that is bolstered by the reliability of their effect size estimates*" [Moyé, 2010, p115]. Our analysis of individual outcomes, however, will account for several potential sources of inflation to the type 1 error for repeated testing of hypotheses related to each outcome.

LA's primary composite outcome was formally monitored by the trial's DSMB, and to be significant the test statistic for a difference between intervention groups would have had to exceed an adjusted critical value. Although the secondary composite outcomes and total mortality were not formally monitored, differences between intervention groups were reviewed along with the primary outcome, so that some adjustment for interim monitoring is appropriate. Group sequential testing was done using an O'Brien-Fleming-type boundary. Since this is a very conservative approach to sequential testing, the final critical value was only moderately increased, from ±1.96 to approximately ±2.1, so that the impact of interim monitoring on type 1 error is relatively small. Outcomes other than cardiovascular disease events and mortality would not have stopped the trial for efficacy, and so are not affected by the interim monitoring.

We do not expect to halt LA-E or halt collection of any outcomes during the extension in response to emerging differences between intervention groups, so that we do not anticipate any formal monitoring, with one exception. It is possible that the study group might feel compelled to publish an important difference in total mortality were it to become highly significant before the end of the extension. For this reason the power calculation for total mortality assumed continued interim monitoring. Since this monitoring will be implemented as an extension of the monitoring that took place during the intervention phase, the impact on the type 1 error for testing of effects on total mortality will be modest. The final decision on monitoring will be based on recommendations from our Data and Safety Monitoring Board (DSMB). As an example of how this might be approached for other outcomes, we discuss how the analysis for microvascular events may also be adjusted for interim monitoring (Section 5.4).

A more appreciable effect on the type 1 error comes from having selected some of the more promising but non-significant trends for special attention during LA-E. As noted above, our primary aim for total mortality has been collected during LA and LA-C and reported to the DSMB. For this, some adjustment for "playing the winner" has been incorporated in the power computations, and is formally included in analysis plans. For our other primary outcome, health care costs, the LA-E hypothesis is restricted to post-intervention data, and thus is distinct from the cost data we have presented for the intervention phase of LA [Espeland, 2014] and we do not make such an adjustment.

4.2 Differential retention and mortality. Retention in LA has been very high and well balanced between the two intervention groups. Currently, there is a slight imbalance in the

number of deaths, with an excess of about 40 in the DSE group. If this imbalance increases over time, it may be necessary to explore mortality as an informative source of missing data.

4.3 An overview of analytic methods and assumptions in calculations of statistical power. For statistical methods, most of the outcomes and hypotheses we expect to collect and test can be analyzed using standard approaches of survival analysis, generalized linear models (i.e. logistic regression, Poisson regression, negative binomial regression), generalized estimating equations (GEE) models for binary data, and mixed-effects models for continuous data.

In the sections below, we will describe some specific analysis plans for outcomes addressing our primary aims (total mortality, health care costs) and for a number of the outcomes addressing our secondary aims (frailty, diabetic microvascular complications, and quality of life). We will also describe our approach to supporting analyses, exploration of possible mechanisms for observed effects, our tertiary aim, and to identification of effect modification or subgroup effects.

Many of the outcomes we will analyze will be defined by the incidence of an event. The main comparisons of intervention groups with respect to the distribution of time until the first post-randomization occurrence of an event will be based on survival analyses. This approach is useful in that it allows for varying lengths of follow-up among participants and for comparisons to be made over the entire course of the follow-up period. To compare intervention arms, we will use a Mantel-Haenszel test with unit weighting, stratified by clinical center. This test is equivalent to a log-rank test and, if the proportional hazards assumption is warranted, to a Cox proportional hazards model. To incorporate covariates into survival models, proportional hazards models will be used. The proportional hazards assumption for the intervention effect will be assessed by examining Schoenfeld residuals plotted against time and by including covariate by time interactions in the model. Outcomes subject to competing risks for which loss-to-follow-up for one time-to-event endpoint may be a result of death or other competing risks [Putter, 2007; Byersman, 2012] will be analyzed using the flexible approach described in Scheike and Zhang [Sheike, 2008] implemented in the R timereg package [Sheike, 2011] which generalizes the approach of Fine and Gray [Fine,1999] for directly modeling the cause-specific subdistribution hazard function.

When repeated outcomes are available, continuous outcomes will be analyzed using linear mixed effects models to estimate the intervention effects. Count data (e.g., number of hospitalizations) will be analyzed using Poisson or negative-binomial regression, for which the natural log of the follow-up time will be included in models as an offset term. Generalized linear models, including generalized estimating equations (GEE) for repeated measures, will be used to analyze binary outcomes with a logit link function.

For each specific aim, we clearly identify the timeframe for analyses.

- For some outcomes (e.g. mortality, renal replacement therapy) inference involves data collected through the full span of LA, LA-C, and LA-E follow-up. It is necessary to have the full span of follow-up to have adequate power for these outcomes. We will, in supporting analyses, estimate intervention effects during the intervention phase and post-intervention phases of follow-up, but the primary comparisons will span these two time periods.

- Other outcomes (e.g. costs, SF-36) have been featured in publications from the intervention phase of the trial (prior to 9/2012 in LA). For these, LA-E aims and principal inferences are based on data collected post-intervention and we project to have sufficient power for these comparisons. In supporting analyses, we will also portray data by intervention assignment from the time of randomization, but this will be for descriptive purposes.
- Some outcomes (e.g. frailty) have not been measured previously in LA , so that inference is based solely on LA-E data.

In projecting statistical power, we have made the following assumptions. For mortality, we have assumed that the percentage of individuals who we are unable to track with respect to mortality would accrue at 1%/yr. We have also assumed that the inability to establish mortality status on participants who were actively followed will also additionally accrue at 1%/yr. For general data collection, we assume that lost follow-up will accrue at 2%/yr (note that throughout the first 12 years of LA, lost follow-up accrued at 1.2%/yr). We also project that we will continue to obtain clinic-based measures on >95% of participants who are currently active (i.e. who are not lost to follow-up for general data collection).

4.4 Missing data.

While retention during LA and LA-C has been balanced between intervention groups, missing data is always a concern for analyses. They are inevitable and statistical methods must take this into account in order to draw valid conclusions. Information collected during the study related to reasons that values are missing will be helpful in examining assumptions about missing data, e.g., whether data are missing completely at random, missing at random, or non-ignorably missing. In general, our analytical plans follow the recommendations of the 2010 National Academy of Sciences report regarding the treatment of missing data in clinical trials [National Research Council, 2010]. To identify factors that provide information as to the probability of missing outcomes, we will first compare the baseline characteristics of participants who do and do not have specific follow-up measures. Sensitivity analyses to determine how conclusions from primary outcome models may be affected by missing data initially will be performed by including covariates predictive of missing observations in such models. Such sensitivity analyses are intended as a conservative reexamination of data to explore whether reasonable assumptions placed on missing data might alter an observed finding, but primary consideration will be given to the original analysis of the aim.

The linear mixed effects model fitted by maximum likelihood estimation is unbiased if missing data are unrelated to outcomes, i.e., if the data are considered missing at random or missing completely at random. Nevertheless, because it is not always known whether missing data are ignorable and because missing observations have the potential to alter the results of analyses, the pattern of missing data and dropouts will be examined between the two treatment arms. We will also examine whether the outcome is related to missingness by using logistic regression models to determine if the outcome measure at the follow-up times preceding the missed visit predicts that the next value is missing and if baseline values predict monotone missing outcomes (i.e. non-intermittent). If there are no systematic differences between those with and without missing data, the data will be considered to be observed (and missed) at random.

When missing outcomes are dependent on unobserved outcomes, potentially biased estimates of intervention effects due to differential missingness may occur. If this situation is suspected,

then for continuous outcomes a multiple imputation approach will be developed that uses various underlying distributional assumptions for the missing observations within the imputation procedure to evaluate if overall conclusions from analyses change based on reasonable assumptions for the underlying distribution of the missing outcomes. Alternatively, selection models, or shared parameter random effects models, will be fit, and sensitivity analyses will be performed to check the robustness of study conclusions. For survival analyses, there will be right censoring of follow-up time; however, some individuals drop out without having complete follow-up. For these analyses, inverse probability weighting will be used to perform sensitivity analyses of the primary results relative to assumptions about those that dropped out.

5.0 Analytical Plan For Specific Aims

5.1 Specific Aim 1 (primary) is to test the hypothesis: The hazard rates for total mortality will differ between intervention groups across follow-up. Mortality will be adjudicated from death certificates, recent hospitalization records (discharge summaries only), outcomes interviews, and National Death Index (NDI) search. All data collected since randomization will be included. Time to death from any cause will be measured from the time of randomization. Follow-up time for participants who remain event free will be calculated as the time in years from randomization to their last available visit. The primary analysis of the all-cause mortality will be proportional hazards regression with stratification for clinical sites, mirroring the analysis of the trial's primary composite cardiovascular disease outcome. Significance for the intervention effect will be based on the likelihood ratio test. Hazard ratio (HR) and 95% confidence intervals will be constructed from the fitted models. The proportional hazard assumption will be examined using log/log plots of survival [e.g. Lagakos, 1984] and alternative models may be used as sensitivity analyses, if necessary. For example, we have experience in applying parametric Weibull models [Lawless, 2003] to the LA mortality data. In addition, Kaplan-Meier plots will be used to present the survival curves by intervention.

Supporting analyses: We will test whether the hazard rates during the intervention and post-intervention phases of the trial differ. Cause-specific mortality rates will be calculated and compared. We will also compare the expected disability-free survival rates between the ILI and DSE participants, using data from the PAT-D disability index. There are several approaches we will explore with these data to project expected disability-free survival [Izmirlian, 2000; Jagger, 2007; Imai, 2007]. Our analyses will take advantage of the LA-C/LA-E PAT-D disability index collection and will project transitions from disability to recovery and from recovery to disability and from both states to death. The concept that total life expectancy can be decomposed into disabled and non-disabled life expectancy (i.e. active life expectancy) for a given age has developed over the past few decades [Katz, 1983; Branch, 1991; Guralnik, 1993; Laditka, 1998; Ferucci, 1999; Izmirlian, 2000]. More recently, a strong case has been made that a relevant public health consideration from a cost perspective is life expectancy free of disability [Olshansky, 2009] and, in particular, free of mobility disability [Keeler, 2010]. From an outcome perspective of a clinical trial, and as pointed out by Izmirlian,et al (2000), life table methods for determining age-specific constructs such as expected disability-free survival [Katz, 1983; Branch, 1991] do not easily lend themselves to hypothesis testing, such as one would desire in a clinical trial setting. As such, Izmirlian et al. developed regression-based Markov chain models [Izmirlian, 2000]. These models allow estimation of multiple parameters describing transition probabilities in/out of multiple states, yet can be difficult to interpret when trying to summarize the effect of an intervention for increasing disability-free survival time as they use multiple parameters to describe transitions between states. We have experience applying these types of

models to disability data from the Lifestyle Interventions and Independence for Seniors [LIFE] study using the R msm and ELECT packages [van den Hout, 2013; Jackson, 2011]. We plan to apply these multi-state survival modeling techniques to LA, and believe that through use of these methods, our overall understanding of the effect of the intervention on disability and mortality will be enhanced.

Subgroup analyses: Pre-specified subgroup comparisons include sex, history of cardiovascular disease, race/ethnicity, and age. We will report tests of interactions to assess the consistency of differences between intervention groups for each of these subgroups.

Power: Because total mortality has been monitored over time and was selected from among a larger set of events contributing to the LA primary and secondary composite outcomes, some adjustment of the type 1 error should be made to avoid making a spurious claim on the effect of ILI on death rates. A conditional power calculation that uses the number of deaths in the DSE cohort as a measure of information is equivalent to treating LA as an events-driven study of total mortality. Based on the current mortality rate and the assumptions on follow-up rates (Section 4.3), we project that we will ascertain 509 deaths in the DSE arm by 7/2020 (date of the last LA-E contact). These projections take into account the increasing hazard of mortality and the expectations that 3800 participants will agree to be followed when LA-E begins in February of 2016 and that vital status will become permanently unknown on 1% of the cohort per year. In this conditional power calculation, we have assumed that the final critical value for testing the intervention effect will be 2.6, corresponding to a nominal p-value of 0.01, instead of 1.96 (i.e. the common unadjusted two-sided alpha=0.05). This more conservative critical value tests the intervention effect with an adjustment for our history of testing for an intervention effect on total mortality since May of 2007 (at the request of the DSMB), as well as annual interim analyses during LA-E. The conditional power for a final p-value of 0.01 with a 20% intervention effect in future data is 88%.

5.2 Specific Aim 2 (primary) is to test the hypothesis: the cumulative mean (discounted) total health care costs post-intervention will differ between intervention groups. As described in the protocol synopsis, health care costs during the intervention phase of the LA trial have been published [Espeland, 2104]. We have continued to collect these data post-intervention (i.e. after 9/2012) and Specific Aim 2 is based on these data as collected through 7/2020. Each participant's annual costs for hospitalizations, outpatient care, medications, and rehabilitation/nursing home stays will be tallied and divided by follow-up times to obtain observed costs per year. Weighted analysis of covariance will be used to compare intervention groups, with analytical weights proportional to participants' lengths of follow-up. Clinic, the sole stratification factor in randomization, will be used as a covariate. To accumulate costs post-intervention, annual estimates will be discounted at 3% per year and summed and bootstrapping will be used for confidence intervals of accumulated mean costs. We will also generate accumulated mean costs across the full span of follow-up (i.e. since randomization) for descriptive purposes.

Supporting analyses: We will also report whether differences in the separate components of health care costs (hospitalizations, inpatient, medications, other) differ between arms. Other supporting outcomes will be the annual rates of hospitalizations, medication use (by previously reported classes), nursing home stays, and rehabilitation center stays.

Subgroup analyses: Pre-specified subgroup comparisons include sex, history of cardiovascular disease, race/ethnicity, and age. We will report tests of interactions to assess the consistency of differences between intervention groups for each of these subgroups.

Power: As noted earlier, LA-E plans to follow 3,800 participants through 2020, with regular collection of data towards estimating medical care costs. The hypothesis for this aim also draws from health care costs from the 279 participants who provided data during the post-intervention follow-up but who are not expected to be followed in LA-E. This provides us a range from 1-8 years of post-intervention cost data. Based on the enrollment/retention assumptions (Section 4.3), we estimated the distribution of these follow-up times and used study data and the proposed analytical approach to estimate the standard error for the inference we describe above: this resulted in a standard error of $196/yr for the difference between intervention groups. Thus, we project (2-sided 0.05 alpha) 80% power to detect a mean difference in annual total health care costs of $549/yr. We note that the difference during the intervention phase of LA was $595/yr and increased with the age of participants (i.e. was $864/yr for participants aged 65-76 at LA entry) [Espeland, 2014].

5.3 Specific Aim 3 (secondary) is to test the hypothesis: among obese and overweight adults with type 2 diabetes, random assignment to an average of 10 years of ILI relative to DSE will lower the prevalence of frailty seen during LA-E.

Frailty is the primary outcome for this aim and is a new aim because it has not been measured prior to LA-E. It will be assessed using the Fried criteria [Fried, 2001] developed during the Cardiovascular Health Study**.** Frailty classification is based on the presence of five frailty characteristics: 1) walking speed standardized based on median height and sex, 2) grip strength standardized based on body mass index (BMI) and sex, 3) energy expenditure standardized based on sex, 4) exhaustion based on self-report, and 5) weight loss of 10 lbs or more in the last year without trying or intending to (based on self-report). Walking speed will be assessed using the timed short walk included in the Short Physical Performance Battery (SPPB) and grip strength. Energy expenditure will be based on kcal/week of energy derived from the Paffenbarger physical activity questionnaire. Exhaustion will be assessed using the question from the Geriatric Depression Scale, “Do you feel full of energy?.” Weight loss will be assessed by self-report. (We acknowledge that this is a difficult item to interpret for the LA cohort, and will also examine the impact on a construct without this item.) Based on these assessments, frailty will be classified into three stages: non-frail (no frailty characteristics present), pre-frail (1 or 2 frailty characteristics present), and frail (3 or more frailty characteristics present). Our primary analysis will classify a person as having prevalent frailty if they are classified as frail during either of the LA-E visits. The proportion of participants experiencing any frailty will be compared between randomized groups using logistic regression, with clinic site, sex, and time from randomization to classification of frailty or the last non-frail classification as covariates. Odds ratios and 95% confidence intervals will be used to summarize the relative effect of the intervention on frailty.

Supporting analyses: include persistent major mobility disability (PMMD) based on repeated assessments of the adjudicated 400-m walk, sensitivity analyses for frailty and PMMD, falls, fractures, SPPB, grip strength, and Pepper Assessment Tool for Disability (PAT-D).

PMMD is considered present when an individual fails to complete two successive 400-m walks [Newman, 2006; Pahor, 2014]. Death after an initial MMD determination will also be considered

PMMD. Additionally, information used in the adjudication of MMD (i.e. self- or proxy report of inability to walk across a small room without the assistance of another person) in the absence of 400-m walk data will be collected every 6-months via telephone and will be used to ascertain PMMD. We will define PMMD based on the sequence of 400-m walks from LA-C (one) and LA-E (twice). In addition, those who failed the 400-m walk for the first time at their last scheduled LA-E clinic visit and who are not adjudicated as persistent failures will return 6 months later for a repeat assessment to establish persistence. The proportion of participants experiencing any PMMD will be compared using logistic regression models. The basic model will include an indicator variable for intervention assignment, follow-up time with covariate adjustment for sex and clinical site. Follow-up time for PMMD will be considered as the time until the initial MMD failure or last successful completion of the 400-m walk for those without PMMD. Odds ratios and 95%CI will be used to summarize the relative effect of the intervention on PMMD.

Several **sensitivity analyses** will be performed for both frailty and PMMD: 1) covariates found to be predictive of missing outcomes will be entered into the logistic regression models to explore the effect of covariate dependent missingness on inference; 2) for the PMMD analysis, cases adjudicated as probable or possible MMD will be included as MMD cases to determine how robust the conclusions about the effect of the intervention on PMMD are to this broader classification of mobility disability, 3) for frailty, analyses will also be performed to compare the proportions not frail versus pre-frail or frail in each group, 4) multi-state survival models (PMMD) or transitional models for categorical outcomes will be used to compare the probability of transitions into and out of outcome states between participants randomized to the two intervention groups. Two absorbing states will be death and loss to follow-up. We will specifically evaluate the effect of the intervention on recovery from MMD or frailty. Recovery is defined as restoring the ability to complete a 400-m walk test after experiencing a MMD outcome or no longer being classified as frail. This evaluation will be accomplished by applying multi-state survival models to the disability and survival state data using the R msm and ELECT packages [van den Hout, 2013; Jackson, 2011] or using Proc Genmod of SAS™ to fit transitional models.

Annual collection of the self-reported number of **falls** was initiated at year 8 of LA and continued in LA-C. In combination with the additional data collected every 6 months in LA-E, we will compare the average proportion of participants who reported at least one fall over time between DSE and ILI since year 8. The basic model will include an indicator variable for intervention assignment, follow-up time, and the interaction between the intervention and follow-up time while adjusting for clinic centers. The model will use generalized estimating equations (GEE), a logit link, a binomial variance, and include compound symmetry covariance to account for the correlations among repeated measures. A contrast, incorporating a robust variance estimate to account for potentially mis-specified covariance, will be used to test for the significance of the overall intervention effect across follow-up. In supporting analyses, we will also use the total number of falls reported as a dependent variable in negative binomial regression models. The basic model will include an indicator variable for intervention assignment, clinic centers as covariates, and the log follow-up time as an offset. Robust standard errors will be used for hypothesis testing. The average number of falls will be estimated for DSE and ILI. We will also examine the CI for the dispersion parameter. If there is evidence that a dispersion parameter is not necessary, we will resort to a Poisson regression model.

In addition to actual falls, a self-reported concern about falling will be assessed using a 16-item **Fall Self-Efficacy Scale International (FES-I)** at the two clinic visits in LA-E. Each item ranges from 1 to 4, representing 'not at all concerned' to 'very concerned' [Yardley, 2005]. The total FES-I score will be compared between DSE and ILI using linear mixed effects models. The basic model will include an indicator variable for intervention assignment, follow-up time, and the interaction between the intervention and follow-up time while adjusting for clinic centers. The covariance between repeated measures will be characterized with an unstructured covariance structure and a contrast will be used to test for the significance of the overall intervention effect across follow-up.

SPPB was developed to measure lower-extremity physical function as reflected in balance, gait speed, strength and endurance; and is comprised of the ability to stand with feet together in the side-by-side, semi-tandem, and tandem positions, time to walk 8-feet, and time to rise from a chair and return to the seated position 5 times [Guralnik, 1993]. The SPPB was modestly expanded to minimize ceiling effects of the SPPB when used in younger, more well-functioning populations: the holding time of the standing balance tasks was increased to 30 seconds and a single leg stand added [Simonsick, 2001]. The component scores on the expanded SPPB are calculated as the ratio of observed performance to the best possible performance and summed to provide a continuous total score. In addition, **grip strength** will be measured twice in each hand to the nearest 2 kg using an isometric Hydraulic Hand Dynamometer (Jamar, Bolingbrook, IL), and the value from the stronger hand will be used. An additional analysis of physical function will be performed from the 19-item version of the **Pepper Assessment Tool for Disability (PAT-D).** The overall PAT-D score will be the mean of the 19 items. Disability scores from the 3 subscales will also be calculated: the basic Activities of Daily Living (ADL) with 7 items, the mobility disability score with 8 items, and the instrumental ADL score with 6 items.

All these physical function measures were collected once during LA-C and will be measured twice in LA-E. The average post-intervention difference between DSE and ILI will be compared using linear mixed effects models. The basic model will include an indicator variable for intervention assignment, a follow-up time effect (3 levels), and the interaction between the intervention and follow-up time while adjusting for clinic centers. The covariance between repeated measures will be characterized with an unstructured covariance structure and a linear contrast will be used to test for the significance of the overall intervention effect across follow-up.

Subgroup analyses: Pre-specified subgroup comparisons include sex, history of cardiovascular disease, race/ethnicity, and age. We will report tests of interactions to assess the consistency of differences between intervention groups for each of these subgroups.

Power: If 3800 participants are enrolled in LA-E and 8% in the DSE group will be classified as frail during LA-E, we project 80% power to detect an odds ratio of 0.70 (two-sided 0.05 type 1 error). Note that our preliminary data with a somewhat limited definition of frailty provide support for these assumptions: observed OR=0.75 [95% CI 0.57, 0.98] and 6.4% prevalence in the DSE group.

As noted earlier, LA-E plans to follow 3,800 participants through 2020, with collection of MMD data on two occasions, 2 years apart. If we assume 12.7% of the DSE group experience PMMD, a two-sided 0.05 probability of Type I error, and 1900 active participants in each group are followed for MMD, LA-E will have approximately 80% power to detect a 25% reduction in the

odds of PMMD in the ILI group compared to the DSE group. This percent relative reduction is consistent with what was observed in the LIFE [Pahor, 2014] trial (physical activity vs successful aging interventions) where the physical activity group had a 28% reduction in the hazard rate for PMMD.

5.4 Specific Aim 4 (secondary) is to test the hypothesis: the time until first occurrence of end stage renal disease (RRT or death from nephropathy) post-randomization will differ between intervention groups.

The primary outcome for diabetic nephropathy will be the first occurrence of **end stage renal disease (ESRD)**, defined as renal replacement therapy (RRT) or death from nephropathy. Information on outpatient and inpatient dialysis has been a crucial part of data collection since the beginning of the LA trial and has been collected every 6 months throughout. Renal transplants have been captured throughout follow-up, as well. This will continue in LA-E. The distribution of time to first occurrence of ESRD will be compared between ILI and DSE using survival analyses as described for total mortality (Section 5.1). Because data on ESRD will continue to be collected every six months in LA-E (as it was in LA and LA-C), censoring and follow-up times will cluster around these six month time points even though we will use the dates of the participant encounter to calculate follow-up time. Because 6-month intervals are fairly short and regular in length throughout follow-up, we will follow the commonly accepted recommendations [Leung, 1997] and will not complicate the analysis by considering interval censoring. All data since randomization will be used for analysis.

Supporting analyses include other measures of diabetic nephropathy and neuropathy and sensitivity analyses accounting for competing risk of death.

Supporting outcomes related to diabetic nephropathy will be derived from serum creatinine. Serum creatinine was collected annually from baseline to year 4 and biannually thereafter in LA and LA-C. **Estimated Glomerular filtration rate (eGFR)** will be calculated based on CKD-Epi equation [Levey, 2009]. Renal outcomes for supporting analyses will be the **doubling of serum creatinine from baseline** and **serum creatinine $\geq$2.5 mg/dl**. These will be analyzed as time until first occurrence of an event. Because death censors the occurrence of renal events, we will conduct a sensitivity analysis to examine these renal outcomes (including ESRD) accounting for the competing risk of death. We will create an indicator variable to distinguish between three different states: participants who experienced a particular renal event, participants who died before experiencing a particular renal event, and participants who were censored at their last available follow-up visit. We will fit a Cox model to estimate type-specific hazard ratio treating the participants who died without experiencing a particular event as censored. Alternatively, we will model the cumulative incidence function and estimate the subdistribution hazard ratio. The cumulative incidence function will be plotted for DSE and ILI.

We will also compare the average level of eGFR over time between DSE and ILI using linear mixed effects models. The basic model will include an indicator variable for intervention assignment, follow-up time, and the interaction between the intervention and follow-up time while adjusting for clinic centers and baseline eGFR. Least square means will be plotted to portray the trend over time. The average post-randomization levels of the overall eGFR for DSE and ILI will be estimated and compared using linear contrasts. The difference in average score between DSE and ILI at a particular visit will also be compared using linear contrasts. The covariance between repeated measures will first be characterized with an unstructured

covariance structure. If the model does not converge, we will explore simpler covariance structures such as compound symmetry. Akaike information criterion (AIC) will be used to aid in selection of an appropriate covariance structure.

Diabetic neuropathy will be measured by **Michigan Neuropathy Screening Instrument (MNSI)**. It includes two separate assessments: a 15-item questionnaire and a lower extremity examination. The **MNSI questionnaire score** will be the sum of fifteen items (with items 7 and 13 reverse coded) and range from 0 to 15. The score will be dichotomized with ≥4 being abnormal [Herman, 2012]. MNSI questionnaire was administered in LA annually and in LA-C and will be collected at the two clinical visits in LA-E. All data collected since randomization will be included. The presence of MNSI≥4 will be analyzed using logistic regression models appropriate for repeated binary outcomes. The model will use GEE, a logit link, and a binomial variance. Given the large number of repeated measures, we will use an exchangeable correlation matrix and a robust covariance estimate. The basic model will include baseline presence of MNSI≥4, an indicator variable for intervention assignment, follow-up time, and the interaction between the intervention and follow-up time while adjusting for clinic centers. Significance for the intervention effect will be based on the likelihood ratio test. Overall odds ratio and 95% confidence intervals will be constructed from the fitted models. The difference in average proportion of participants with MNSI≥ 4 between DSE and ILI at a particular visit will be compared using linear contrasts.

The clinical exam component of the MNSI was added in LA-C and will be repeated at the two clinical visits in LA-E, leading to a maximum of three measurements on the MNSI exams for an individual. The **MNSI exam score** will be the sum of eight items (four on each foot) that inspect abnormality in appearance, ulcer, ankle reflexes, and vibration sensation. The score will range from 0 to 8, with higher scores indicating potential neuropathy. Additionally, we will incorporate a participant's **amputation** history into deriving the MNSI exam scores. We will use linear mixed effects models to test the intervention effect. The basic model will include an indicator variable for intervention assignment, follow-up time, and the interaction between the intervention and follow-up time while adjusting for clinic centers. The covariance between repeated measures will be characterized with an unstructured covariance structure. We will also assess the intervention effect on prevalence of MNSI exam score of ≥2.5 [Feldman, 1994] using generalized estimating equations. In LA-C (once) and again In LA-E (twice), we will perform the **monofilament test** to examine touch sensitivity on all participants. The reduction or absence of light touch sensation to monofilament will be defined as <8 of 10 applications detected in either foot.

Diabetic retinopathy will be measured by self-reported history of **laser treatment, diagnosis of retinopathy, and cataract extraction**. This information has been collected every 6 months since the beginning of LA and will continue in LA-E. The distribution of time to first occurrence of laser treatment on the back of the eyes will be compared between ILI and DSE using survival analyses described for total mortality.

Subgroup analyses: Pre-specified subgroup comparisons include sex, history of cardiovascular disease, race/ethnicity, and age. We will report tests of interactions to assess the consistency of differences between intervention groups for each of these subgroups.

Power: We project 80% conditional power to detect a 18% reduction in the rate of ILI participants experiencing ESRD compared to DSE (alpha=0.05, two-sided log rank tests). These conditional power calculations use a boundary value of 2.1: this allows for a moderate

number of interim analyses during the LA-E, should the DSMB require this. If no interim monitoring is required, that boundary level is 1.96 and the power is slightly greater.

5.5 Specific Aim 5 (Secondary) is to test the hypothesis: The mean SF-36 score over time during the post-intervention phase will differ between intervention groups.

We will use the **Medical Outcomes Study Short Form 36 (SF-36),** a self-report health-related quality of life (HRQoL) measure with well-documented psychometric properties across a wide range of clinical and nonclinical populations [McHorney, 1994] for this aim. The primary outcome will be the overall score derived from eight domains in SF-36 (US mean = 50, SD = 10), with higher scores indicating more favorable health-related quality of life. SF-36 was administered twice annually for the first 4 years and annually thereafter. These data have been published for the intervention phase of LA. Therefore, the LA-E hypothesis is restricted to post-intervention follow-up data, including data from LA-C (once) and LA-E (twice). We will use similar linear mixed effects models to compare mean scores between DSE and ILI.

Supporting analyses. These include the eight separate domains of SF-36, the Feeling Thermometer (FT), SF-6D, latent class analysis of self-reported physical function, late life depression, loneliness, resilience, and fatigue. We will also generate figures of mean differences in the SF-36 score over the full course of follow-up.

In addition, we will examine two preference-based quality of life measures: **Feeling Thermometer (FT)** and **SF-6D**. The FT and SF-6D serve as direct and indirect preference-based assessment methods for general health status, respectively. FT scores range from 0, representing the worst possible health, to 100, representing the best possible health. The raw FT scores will be divided by 100 so that its scale will be similar to that of SF-6D. The SF-6D scores will be derived from SF-36 based on six multilevel dimensions of health: physical functioning, role participation, social functioning, pain, mental health, and vitality.

During LA, we used discrete hidden Markov modeling to classify participants according to self-reported physical functioning based on their patterns of SF-36 responses [Ip, 2010; Zhang, 2010; Rejeski, 2012]. We will repeat this analysis on post-intervention data and for the full span of follow-up. In this novel approach, six questions from the SF-36 (vigorous activities; moderate activities; climb one flight of stairs; bending, kneeling, or stooping; walking more than a mile; and walking 100 yards) will be used to set up the physical function profile. The hidden Markov model conceptualizes the level of physical function as two distinct but parallel processes, a sequence of multiple indicators of self-reported function driven by an underlying sequence of latent states (classes of functional abilities—note the hidden Markov model approach differs from how we will estimate disability-free survival to support Aim 1, in which the states are observed and are not estimated latent classes). We assume that the state at time “t+1” depends only on the state at time “t” and not on the history before “t.” The number and structure of the states is assumed to be constant across time. We will use Bayesian information criterion (BIC) as a goodness of fit measure to help determine the number of states in a best-fitting model. As a result, prevalence of each state of functional ability at each time point can be estimated and compared between DSE and ILI groups. We will also estimate the transition probabilities from one state to another across consecutive time points. The confidence intervals of the lifetime estimates will be estimated using Monte Carlo simulation, in which we will repeatedly draw age- and sex-specific estimates from the underlying parametric distributions based on our data.

Another aspect of quality of health is **late life depression** assessed by **Patient Health Questionnaire-9 (PHQ-9).** PHQ-9 is a nine-item questionnaire with each item scored from 0 to 3. The sum of the nine items will provide a 0 to 27 severity score, with ≥10 indicating clinically significant depression. PHQ-9 was collected in LA-C and we will have two additional measurements from LA-E. Both the overall score and the prevalence of PHQ-9 ≥10 will be compared between DSE and ILI. In LA-E we propose to include several additional questionnaires that relate to aspects of quality of life that are of particular relevance to aging adults, namely loneliness, social isolation, resilience, and fatigability. Loneliness will be assessed by the **Three-Item Loneliness Scale** and the 20-item **Revised UCLA Loneliness Scale**. Each item in the Three-Item Loneliness Scale is scored from 1 to 3 [Hughes, 2004]. The summary score will range from 3 to 9, with higher score indicating higher level of loneliness. Each item in the Revised UCLA Loneliness Scale ranges from 1 to 4. Appropriate items will be reverse coded while computing the total score. Resilience will be assessed by a 6-item **Brief Resilience Scale (BRS)**. Responses vary from 1-5 for all six items. The final score will be calculated by dividing the total sum by the total number of questions answered. The 10-item **Pittsburgh Fatigability Scale for Older Adults** captures activities that span sedentary to high intensity of particular relevance to older adults [Glynn, 2015]. Linear mixed effects models will be applied to the scores from these questionnaires. In addition to comparing the overall mean scores between DSE and ILI on these measures, we will also examine the distribution of these scores and identify appropriate categorizations in the situation that the scores are highly skewed.

Subgroup analyses: Pre-specified subgroup comparisons include sex, history of cardiovascular disease, race/ethnicity, and age. We will report tests of interactions to assess the consistency of differences between intervention groups for each of these subgroups.

Power: We used the distribution of expected follow-up times and longitudinal sequences of SF-36 scores to project the standard error that would be available to detect mean differences between intervention groups on post-intervention SF-36 scores (i.e. difference from baseline), arriving an estimate of 0.027 SD units. This provides 90% power to detect an overall mean difference of 0.088 SD units. At year 10 during the intervention phase, the mean difference was 0.106, thus we project >90% power to detect a difference over time even if it wanes post-intervention.

5.6 Specific Aim 6 (tertiary) is to describe the long-term trajectories of a) weight, b) physical activity, c) fat and lean mass, and d) bone density within and between the intervention groups and examine how these are related to outcomes, including those defined by the primary and secondary aims.

Weight change has been monitored annually throughout the study. We will summarize the patterns of weight loss and regain using both continuous measures [e.g. Espeland, 2009; Neiberg, 2012] and categorical measures with clinically meaningful cutoffs. **Body composition and bone density** will be assessed objectively using **dual X-ray absorptiometry**. This will be collected at the first clinic visit in LA-E on all participants who have previous measurements at baseline and one or more post baseline time points (a total of approximately 800 participants from 5 sites). We will calculate change in total and regional (e.g., arm, leg, and trunk) fat mass and lean mass. We will also calculate change in whole body and regional (e.g., hip, arm, leg, trunk, spine, pelvis) bone mineral content (BMC) and bone mineral density (BMD). Longitudinal trajectories for the continuous outcomes between DSE and ILI will be compared using linear mixed effects models. Ordinal outcomes (e.g., weight change categories) will be compared

using generalized linear models with a cumulative logit link function and a binomial error term. **Physical activity** will be assessed objectively using **accelerometry** on a subset of participants. This will be collected at the first clinic visit on all LA-E participants who have previous measurements (from substudies at years 0, 1, 4 at the Baltimore, Baton Rouge, Denver, Houston, Memphis, Minneapolis, Philadelphia, and Providence sties and years 8 and 10 at the Pittsburgh site). The total sample size for this sub-study will be approximately 1,800 individuals. We note that the RT3 accelerometer was used in LA. However, this technology is outdated. LA-E will use an alternative device (wrist actigraph), which provides 24-hr physical activity and sleep information. A cross-validation study will be conducted to allow us to compare the RT3 and the wrist actigraph prior to implementation study-wide. This will allow for the development of a calibration factor to be established in the event that there are differences in the activity counts between the two devices. Summary scores for the accelerometry data will be based on recommendations from the American College of Sports Medicine and the American Heart Association [Haskell, 2007]. Moderate intensity physical activity will be defined as ≥3 METs per minute, where METs per minute is metabolic equivalents (METs) per minute and will be obtained by dividing the estimated total energy expenditure per minute by the estimated resting energy expenditure. Vigorous intensity physical activity will be defined as ≥6 METs per minute. Bouts of activity will be defined as ≥10 minutes in duration. Summary measures include (but not limited to) bouts per day, minutes per bout, METs per minute, and total METs for moderate/vigorous physical activity will be compared between DSE and ILI using linear mixed effect models. Data from the accelerometry will also be used to determine time spent in sedentary activities (<1.5 METs per minute) and sleep. All these measures will be considered as potential mediators and used in mediation analyses. Physical activity will also be assessed with the **Paffenbarger** questionnaire on all participants. We will use linear mixed effects models to compare longitudinal trends between intervention groups.

Use of mediation analytical techniques in a randomized trial setting has traditionally required the assumption that the mediation factor is randomly assigned to individuals (i.e., the sequential ignorability assumption), making such analyses unprotected from unmeasured confounders, which can lead to biased inferences [Lynch, 2008]. Two approaches that have been proposed to investigate causal mediation in a randomized trial context are structural mean models [Robins, 1994; Ten Have, 2004; Ten Have, 2007] and principal stratification [Frangakis, 2004; Frangakis, 2002]. More recently, Imai, Tingley and colleagues provided an R package (mediation) to allow design-based mediation inference (i.e. it does not require the sequential ignorability assumption) in a wide variety of settings, including allowing for multiple mediators [Imai, 2013ab; Tingley, 2014]. To explore the hypotheses under this aim, we will determine how approaches within these families of causal mediation models can be used to assess how post-randomization levels of body composition, bone density, physical activity and weight may be account for the indirect effects of the intervention on outcomes (including PMMD and frailty) within the framework of the models used to measure the direct effect of the intervention on these outcomes.

Supporting analyses: LA provides many other measures that may inform mediation analyses, including trajectories of physical function, waist circumference, CVD risk factors, and medication use. We will also examine how events (e.g. fractures) influence subsequent outcomes.

5.7 Additional Analyses.

The rich LA databases offer the opportunity to explore many additional analyses. Data on genetics, cognitive function, medications, and many biomarkers are available to examine

associations these have with LA-E outcomes. A range of modelling approaches will be used to describe longitudinal trajectories of measures and to compare these between intervention groups. We are interested in examining whether there are patterns of responses and will use multivariate approaches to describe clusters of responses. As noted above, we are experienced with using latent variable approaches such as hidden Markov modeling to assist with this. The prevalence of cognitive impairment will be assessed using logistic regression and the incidence rates from the Look AHEAD Continuation to the Extension will be computed.

We are able to create constructs such as active life expectancy [e.g. Manton, 2008], healthy life expectancies [Molla, 2008], disability-free life expectancy [Andrade, 2010], and multimorbidity transition rates [Kadam, 2013] that can expand the exploration of long-term intervention effects on novel outcomes.

5.8 Study Monitoring.

The progress of LA-E and the study's potential of attaining its goals will be regularly evaluated by the Data and Safety Monitoring Board (DSMB). This committee will review and provide feedback to the NIDDK on the overall performance of the study group, including its success with respect to goals for recruitment, retention, safety, and data quality.

Recruitment and retention We will provide summary data on re-enrollment in terms of number of informed consent documents signed for each site and overall. Retention will be monitored continuously throughout LA-E. We will provide summary data on failure to obtain required exams/follow-up visits on time and the number of consent withdrawal and inability to contact the participants for each site and overall. These summary data will also be presented to the DSMB committee by intervention assignment and by age group. This will assure early recognition of inadequate performance and identify reasons for inadequate performance in each clinical site and in the study overall.

Safety Two types of safety events will be reported in LA- E. The first type that will be reported are events or problems that are unexpected or unanticipated; and possibly, probably, or definitely related to participation in the study; and are fatal, life threatening, or serious. An example of this would be an accident that happened in the clinic such as a serious fall. The second type that will be reported are events or problems that may not be serious but are events or problems that are unexpected or unanticipated; and possibly, probably, or definitely related to participation in the study and not serious, but suggest greater risk or harm to study participants than was previously known or recognized. Examples of this would include a Breach of Confidentiality or information that indicates a change to the risks or benefits of participating in the study.

We will summarize all adverse event (AEs) and serious adverse events (SAEs) for each system organ class by intervention assignment and CVD history. The number of participants and percentage reporting an event will be compared between DSE and ILI using either chi-square tests or Fisher’s exact tests (when expected cell counts are small). The incidence rates of an event between DSE and ILI will be compared using likelihood ratio method. At each DSMB meeting, the committee will review data on adverse events and other safety issues to make an overall recommendation to the NIH concerning the safety of continuing LA-E. Consistent with NIH policy, each LA-E Principal Investigator will receive a report summarizing the DSMB review of the adverse event data. Principal Investigators are responsible for providing this report to the IRB at their institution.

6.0 References

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